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SPECIAL ISSUE REVIEWS-A PEER REVIEWED FORUM

Cancer Models in *Caenorhabditis elegans*

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Although now dogma, the idea that nonvertebrate organisms such as yeast, worms, and flies could inform, and in some cases even revolutionize, our understanding of oncogenesis in humans was not immediately obvious. Aided by the conservative nature of evolution and the persistence of a cohort of devoted researchers, the role of model organisms as a key tool in solving the cancer problem has, however, become widely accepted. In this review, we focus on the nematode *Caenorhabditis elegans* and its diverse and sometimes surprising contributions to our understanding of the tumorigenic process. Specifically, we discuss findings in the worm that address a well-defined set of processes known to be deregulated in cancer cells including cell cycle progression, growth factor signaling, terminal differentiation, apoptosis, the maintenance of genome stability, and developmental mechanisms relevant to invasion and metastasis. ***Developmental Dynamics 239:1413–1448, 2010.*** **© 2010 Wiley-Liss, Inc.**

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Caenorhabditis elegans AS A MODEL ORGANISM FOR STUDYING CANCER

Extensive research into the underlying basis of cancer has led to the general consensus that alterations in a defined set of biological activities are required for cells to attain a fully malignant state (Thompson et al., 1989; Renan, 1993; Kinzler and Vogelstein, 1996; Hanahan and Weinberg, 2000; Hahn and Weinberg, 2002a,b). Key traits associated with oncogenic transformation include cell cycle deregulation, independence from growth factor signaling, immortalization, metastasis and invasion, avoidance of apoptosis and immune surveillance, genomic instability, and the induction of angiogenesis. Although virtually all malignant cancers acquire most or all of these defined characteristics during the course of their progression, the particular spectrum of mutations leading to these standardized traits can vary dramatically among different types of cancers. This fact alone is responsible for increasing the complexity of cancer biology by orders of magnitude. Importantly, the collective insights required to attain a comprehensive picture of the oncogenic process will necessitate the use of many complementary approaches. It is in this context that model organisms can continue to make their mark.

C. elegans is a free-living soil nematode that is approximately 1 mm in length. As the first metazoan to have had its genome sequenced, *C. elegans* has benefited greatly from both classical genetic and modern functional genomic approaches. Several characteristics of the worm make it highly amenable for cancer research. *C. elegans* has a completely characterized and essentially invariant somatic cell lineage, thereby facilitating the analysis of phenotypes that disrupt normal proliferation and patterning (Sulston and Horvitz, 1977; Sulston et al., 1983). In addition, *C. elegans* is transparent throughout all stages of development, allowing for the direct visualization of all cells, including their divisions and movements. Both forward and reverse genetics are well established and straightforward, allowing for the comprehensive analysis of genetic pathways and protein functions. Finally, and quite critically, many human genes and pathways involved in cancer are highly conserved in *C. elegans*. Indeed, these regulatory networks are often easier to parse in *C. elegans*, as the gene families involved contain fewer members, thus reducing the likelihood for genetic redundancy. Examples of this include the pRb and p53 tumor suppressors, which are estimated to be directly or indirectly compromised in

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nearly all human cancers (Hunter and Pines, 1994; Sherr, 2000, 2004; Nevins, 2001; Sherr and McCormick, 2002; Yamasaki, 2003; Bindra and Glazer, 2006; Knudsen and Knudsen, 2006). The pRb and p53 gene families contain three members each in mammals, whereas *C. elegans* contains only a single member of each family, LIN-35/pRb and CEP-1/p53, respectively (Lu and Horvitz, 1998; Mulligan and Jacks, 1998; Chen, 1999; Kaelin, 1999; Derry et al., 2001).

Perhaps surprisingly, of the acquired malignant characteristics listed above, the large majority can be addressed quite directly by studies in *C. elegans*. In this review, we will attempt to touch upon most of these areas, although the relative depth of coverage will vary somewhat among subjects. Our goal is to provide a comprehensive description of the contributions of worm research to cancer biology and to serve as a starting point for readers to delve more deeply into the primary literature and more-specialized reviews that address these subject areas.

CELL CYCLE DEREGULATION AND CANCER

Most mammalian cells receive a variety of antiproliferative signals from the extracellular environment. These can lead to either transient arrest or permanent withdrawal from the cell cycle and terminal differentiation (Zetterberg et al., 1995; Sun et al., 2007; Nishikawa et al., 2008). Thus, for tumorigenesis to occur, cancer cells must develop the ability to evade the influence of negative growth signals to remain in a state that is permissible for continuous proliferation. Most typically, this is accomplished by acquiring mutations in genes that regulate cell cycle entry and progression. Importantly, many of the core components of the cell cycle network are conserved from yeast to mammals. In the established model, cell cycle progression is driven by the physical association of cyclin proteins with small serine/threonine kinases known as cyclin-dependent kinases (CDKs; Bird, 2003). This interaction confers activity on the CDKs and allows them to phosphorylate several downstream targets (Bird, 2003). One of the most critical CDK substrates involved in the G1-to-S phase progression is pRb (Blomen and Boonstra, 2007). When in a relatively under-phosphorylated state, pRb blocks the ability of "activating" E2F-family transcription factors to promote the expression of genes required for S phase entry. Simultaneously, this hypophosphorylated form of pRb (or its family members p107 and p130; collectively termed the pocket proteins), also associates with distinct set of "inhibitory" E2F-family members to directly mediate the transcriptional repression of E2F targets (Schafer, 1998). CDK-dependent phosphorylation of pRb alleviates both inhibitory activities by inducing the dissociation of hyperphosphorylated pRb from E2Fs, thereby allowing S phase to proceed (Stevaux and Dyson, 2002).

As the regulation of cell cycle control is critical for proper growth and development, CDKs are subjected to extremely tight regulatory control. Some of the mechanisms involved include the controlled expression and degradation of cyclins (Bird, 2003), the expression of cyclin-dependent kinase inhibitors (CKIs), which block cyclin-CDK activity (Sherr and Roberts, 1999), targeted degradation of cell cycle regulatory proteins by the proteasome (van Leuken et al., 2008; Kitagawa et al., 2009), and the phosphorylation and dephosphorylation of key sites on CDKs by other regulatory protein kinases (Kellogg, 2003; Lolli and Johnson, 2005; Queralt and Uhlmann, 2008; Lavecchia et al., 2009).

Importantly, most human cell cycle genes have orthologs in *C. elegans*, and their functions have generally been shown to be well conserved (van den Heuvel, 2005a,b). Notably, mutations in many of the genes involved in controlling the expression, activity, and degradation of the cyclin-CDK complexes lead to hyperproliferation of postembryonic cell lineages (Table 1). Two noteworthy characteristics are shared by these genes. First, virtually all of them are involved specifically in G1/S progression. This is also consistent with a relative lack of mutations that have been reported to lead to embryonic hyperproliferation, as embryonic cycles largely bypass G1 phase (Edgar and McGhee, 1988). Second, all of the known hyperproliferation-inducing mutations affect genes that directly or indirectly regulate the abundance or activity of G1/S cyclin-CDK complexes, indicating that the G1/S transition is the most critical step in controlling cell division in *C. elegans*. This is similar to the case in human cancers, where alterations in cyclin D, CDK4, and $p16^{INK4A}$ are detected more frequently than mutations in genes that regulate other cell cycle events (Sherr, 1996). Although evidence to date has not directly shown that overexpression of G1/S cyclin-CDK complexes can induce hyperproliferation in *C. elegans*, their loss does lead to a reduction in cell numbers (Park and Krause, 1999; Fay and Han, 2000; Boxem and van den Heuvel, 2001).

CKIs REGULATE CELL CYCLE QUIESCENCE

Two families of mammalian CKIs promote terminal differentiation and cell cycle exit (Matsuoka et al., 1995; Parker et al., 1995; Casaccia-Bonnefil et al., 1997). One, the INK4 family, which is composed of $p16^{INK4a}$, $p15^{INK4b}$, $p18^{INK4c}$, and $p19^{INK4d}$, does not appear to be conserved in *C. elegans*. The other, the human Cip/Kip family, consisting of $p21^{Cip1}$, $p27^{Kip1}$, and $p57^{Kip2}$ (Sherr and Roberts, 1999; Besson et al., 2008), has a pair of orthologs in *C. elegans*, CKI-1 and CKI-2, which share equal similarity to $p21^{Cip1}$ and $p27^{Kip1}$ (van den Heuvel, 2005a). Homozygous null $p27^{Kip1}$ mice exhibit several striking phenotypes, including gigantism, multiorgan cell hyperproliferation, and increased rates of cancer (Fero et al., 1996; Nakayama et al., 1996; Fero et al., 1998). In addition, $p57^{Kip2}$ has been implicated in tumorigenesis in humans (Hatada et al., 1996a,b; Matsuoka et al., 1996; Thompson et al., 1996).

In *C. elegans*, homozygous *cki-1*(*gk132*) deletion mutants exhibit embryonic lethality, whereas heterozygotes display weak hyperproliferation of vulval precursor cells (VPCs), a set of larval blast cells from which the vulva is derived (Saito et al., 2004; Buck et al., 2009). Strikingly, RNAi of *cki-1* results in excessive proliferation of other postembryonic tissues, including in the hypodermis, vulva, and somatic gonad (Hong et al., 1998). In contrast, homozygous *cki-2*(*ok2105*) mutants, as well as *cki-2(RNAi)*, display only weak hyperproliferation in VPCs (Buck et al., 2009), although double RNAi of *cki-1*

TABLE 1. *C. elegans* Hyperplasia-Associated Genes

Common name	Worm gene	Mammalian ortholog	Affected tissue(s)
cdc-14	C17G10.4	Cdc14	Hypodermis[1], VPCs[1]
cdc-25.1(gf)	K06A5.7	Cdc25A	Intestine[2,3]
cdk-8	F39H11.3	Cdk8	VPCs[4]
cki-1	T05A6.1	Cip/Kip family	Hypodermis[5], VPCs[5], DTC[5], Germ cells[5], Intestine[6], Multiple[6,7,8,a], Multiple[7,8,b]
cki-2	T05A6.2	Cip/Kip family	VPCs[6], Multiple[6,7,8,c], Multiple[7,8,d]
cpb-1	C40H1.1	CBP/p300	Embryonic cells[9]
cul-1	D2045.6	Cul1	All postembryonic blast cells[10]
dpl-1	T23G7.1	DP	Intestine[8,e]
efl-1	Y102A5C.18	E2F4, E2F5	Intestine[8,e]
fzr-1	ZK1307.6	Cdh1/Hct1/FZR	Intestine[11], Multiple[11,f]
let-7	C05G5.6	Let7	Hypodermis[12]
lin-1	C37F5.1	Ets	VPCs[4]
lin-4	F59G1.6	miR-125	Hypodermis[13], Intestine[13], Sex myoblasts[13], VPCs[13]
lin-14	T25C12.1	None known	Hypodermis[14], Intestine[14], Sex myoblasts[14], VPCs[14]
lin-23	K10B2.1	βTRCP	All postembryonic blast cells[15]
lin-29	W03C9.4	None known	Hypodermal seam cells[14]
lin-31	K10G6.1	FoxB1	VPCs[4]
lin-35	C32F10.2	Retinoblastoma, p107, p130	Intestine[16,17], Multiple[7,8,e], Multiple[11,g]
lin-36	F44B9.6	None known	Intestine[8,e]
mdt-1.1/sop-3	Y71F9B.10	None Known	VPCs[4]
mdt-12/dpy-22	F47A4.2	TRAP230	VPCs[4]
mdt-13/let-19	K08F8.6	TRAP240	VPCs[4]
mdt-23/sur-2	F39B2.4	MED23	VPCs[4]
skr-1	F46A9.5	$p19^{Skp1}$	All postembryonic blast cells[18]
skr-2	F46A9.4	$p19^{Skp1}$	All postembryonic blast cells[18]

[a]in combination with *cki-2*; [b]in combination with *cki-2* and *lin-35*; [c]in combination with *cki-1*; [d]in combination with *cki-1* and *lin-35*; [e]in combination with *cki-1/2*; [f]in combination with *lin-35*; [g]in combination with *fzr-1*; [1](Saito et al., 2004); [2](Clucas et al., 2002); [3](Kostic and Roy, 2002); [4](Clayton et al., 2008); [5](Hong et al., 1998); [6](Buck et al., 2009); [7](Boxem and van den Heuvel, 2001); [8](Boxem and van den Heuvel, 2002); [9](Shi and Mello, 1998); [10](Kipreos et al., 1996); [11](Fay et al., 2002); [12](Reinhart et al., 2000); [13](Chalfie et al., 1981); [14](Ambros and Horvitz, 1984); [15](Kipreos et al., 2000); [16](Grishok and Sharp, 2005); [17](Ouellet and Roy, 2007); [18](Nayak et al., 2002).

and *cki-2* leads to intestinal cell hyperproliferation, indicating that these genes are partially redundant in their functions. Furthermore, overexpression of either CKI-1 or CKI-2 triggers cell cycle arrest (Hong et al., 1998; Fukuyama et al., 2003), indicating that CKI-1 and CKI-2 are sufficient to induce cell cycle quiescence.

Notably, the excess vulval cells that are generated in *cki-1(RNAi)* animals result from the precocious division of normally quiescent VPCs during early larval development, indicating that developmental timing is also misregulated in *cki-1* mutants (Hong et al., 1998). Although it is generally believed that cell cycle control must be intimately coordinated with developmental-stage progression, direct links between these two processes have generally been lacking. Thus, a unique facet to the analysis of the *C. elegans* CKI orthologs has been the identification of proteins that regulate the timing of CKI-1 expression (Fig. 1). Two such regulators, LIN-14 and LIN-29, positively regulate expression of *cki-1* in VPC and hypodermal lineages, respectively (Hong et al., 1998). LIN-14 and LIN-29 belong to the heterochronic group of proteins, which are involved in the global regulation of developmental timing during postembryonic development (Moss, 2007). Notably, mutations in *lin-14* and *lin-29* also cause supernumerary cell divisions, as cell division patterns that are characteristic of early developmental events are typically reiterated multiple times (Ambros and Horvitz, 1984). Thus, in the absence of LIN-14 or LIN-29 activity, CKI-1 expression is reduced, resulting in the premature termination of G0 quiescence and ectopic divisions within several postembryonic lineages. Using a clever genetic screen, Saito and colleagues identified two additional *cki-1* transcriptional regulators, *lin-1*/Ets and *lin-31*/FoxB1 (Clayton et al., 2008). Ets family transcription factors have important roles in proliferation and differentiation during development and have been suggested as targets for cancer therapies

(Hahne et al., 2008). Although LIN-29 and LIN-14 do not have obvious orthologs in humans and little is known about the role of mammalian FoxB1, the regulation of *cki-1* by these transcription factors suggests that further investigation is justified.

Mammalian CKI proteins are also posttranslationally regulated. For example, phosphorylation of CKI family members by Akt alters their subcellular localization and affinity for particular targets, as well as triggering their degradation (Montagnoli et al., 1999; Fujita et al., 2002; Liang et al., 2002). It is not currently known whether the *C. elegans* Akt co-orthologs AKT-1/2 directly phosphorylate CKI-1/2. AKT-1/2 does, however, inhibit DAF-16/FOXO activity by phosphorylation, and DAF-16/FOXO is required for the transcription of *cki-1* during the L1 larval stage (Ogg et al., 1997; Henderson and Johnson, 2001; Baugh and Sternberg, 2006). Therefore, in nutrient-deprived *daf-16*/FOXO mutants, CKI-1 levels are insufficient to mediate the normal pattern of starvation-induced cell division arrest (Baugh and Sternberg, 2006). Notably, this mechanism provides a direct link between food availability, sensed by the insulin signaling pathway, and cell cycle control.

Phosphorylational control of CKI-1 in *C. elegans* is also suggested by the observation that the CDC-14/Cdc14 protein phosphatase is required for the stabilization of CKI-1 expression (Saito et al., 2004). Inhibition of CDC-14 activity leads to the hyperproliferation of VPCs, intestinal nuclei, and hypodermal cells (Saito et al., 2004). Furthermore, overexpression of CDC-14 in wild-type leads to a reduction in the normal number of intestinal cells in a CKI-1–dependent manner. These results suggest that in *C. elegans*, CDC-14 is critical for promoting cellular quiescence through the maintenance of CKI-1 stability (Fig. 1). It is also worth noting that, although *Saccharomyces cerevisae cdc14* was originally implicated in controlling transit through mitosis, a recent report suggests that CDC14 may also function in G1/S regulation in other organisms (Dulev et al., 2009).

PHOSPHORYLATION REGULATES CDK ACTIVITY

As mentioned above, CDK phosphorylation is a well-conserved means for regulating cell cycle progression in many systems (Fattaey and Booher, 1997; Schmitt and Nebreda, 2002; Kellogg, 2003; Han et al., 2005; Burrows et al., 2006). Inhibitory phosphorylation of CDKs is carried out by members of the Wee1/Myt1 family of protein kinases. Acting in opposition to Wee1/Myt1 are the CDC25 family of protein phosphatases, which remove inhibitory phosphate groups from CDKs, thereby promoting cell division (Boutros et al., 2007). In *C. elegans*, the best-studied member of the Wee1 family is *wee-1.3*, which is actively transcribed throughout development. Putative null alleles of *wee-1.3* lead to embryonic lethality, suggesting a general role in cell cycle regulation (Lamitina and L'Hernault, 2002). One well-established target of WEE-1.3 is the *C. elegans* CDK-1/cyclin B complex, thus directly implicating WEE-1.3 in the control of the G2/M transition (Burrows et al., 2006).

Although no hyperproliferation defects have been reported for *wee-1.3* loss-of-function mutants (or for other *C. elegans* Wee1 homologs), postembryonic intestinal hyperplasia has been observed in strains containing gain-of-function (gf) mutations in *cdc-25.1* (Clucas et al., 2002; Kostic and Roy, 2002). Of interest, although *cdc-25.1(gf)* mutants do not exhibit hyperproliferation outside of the intestinal lineage, loss of function of CDC-25.1 activity leads to pleiotropic defects including a widespread failure in cell proliferation. Thus, although CDC-25.1 appears to play an important role in cell cycle progression in multiple tissues, the intestine may be particularly sensitive to perturbations in this pathway. Additionally, *cdc-25.1(gf)* alleles result in reduced rates of protein turnover by altering internal phosphodegron sequences that are targeted by the LIN-23/βTRCP ubiquitin-ligase complex (Hebeisen and Roy, 2008).

Ubiquitin-Mediated Proteolysis and Cell Cycle Control

Protein degradation through ubiquitin-mediated proteolysis is known to play an important role in regulating the expression of cyclins, CKIs, and many other cell cycle proteins in mammals (Hochstrasser, 1995). Initial insight into the role of ubiquitin-mediated proteolysis in *C. elegans* cell cycle control began with the characterization of *cul-1* mutants, which display extensive hyperplasia of the hypodermis, vulva, uterus, and sex muscles (Kipreos et al., 1996). CUL-1 has served as the founding member of the *C. elegans* cullin protein family, which is conserved from yeast to humans. A second gene, *lin-23*/βTRCP, was identified through mutations that conferred similar hyperproliferation defects to those of *cul-1* (Kipreos et al., 2000). Both *lin-23* and *cul-1* mutants show normal embryonic development but undergo hyperplasia beginning in larval stages. However, in contrast to *cki-1* and *cdc-14* mutants, which initiate cell divisions precociously, excess cells in *lin-23* and *cul-1* mutants occur not as a result of premature cell cycle entry but instead because of an inability to exit the cell cycle in response to normal developmental cues (Kipreos et al., 1996, 2000; Hong et al., 1998; Saito et al., 2004).

In mammals, βTRCP and Cul1, together with $p19^{Skp1}$ and the RING Box protein Rbx1, function as an E3 ubiquitin-ligase complex (termed SCF). Mammalian SCF complexes catalyze the ubiquitylation, and subsequent destruction, of several proteins that are critical for proper cell cycle regulation, including CDC25A; $p27^{Kip1}$; cyclins A, B, D, and E; Emi1; and Wee1 (Yu et al., 1998b; Carrano et al., 1999; Dealy et al., 1999; Sutterluty et al., 1999; Tsvetkov et al., 1999; Nakayama et al., 2000; Busino et al., 2003; Guardavaccaro et al., 2003; Margottin-Goguet et al., 2003; Watanabe et al., 2004). Likewise, *C. elegans* SCF complex components have been implicated in the degradation of CDC-25.1 and CYE-1/cyclin E (Fay et al., 2002; Hebeisen and Roy, 2008). Consistent with this, mutations in two worm homologs of $p19^{Skp1}$, *skr-1* and *skr-2*, lead to the hyperproliferation of multiple postembryonic lineages (Nayak et al., 2002). Although *C. elegans* RBX-1 and RBX-2 have roles in multiple aspects of mitotic and meiotic progression, no hyperproliferation phenotypes have been detected in mutants (Sasagawa et al., 2003). In addition to cell cycle control, both the worm and mammalian SCF complexes regulate additional targets that may be relevant to tumorigenesis, including the Wnt pathway member and cell adhesion component β-catenin (Fuchs et al., 1999; Hart et al., 1999; Latres et al.,

1999; Winston et al., 1999; Dreier et al., 2005). Furthermore, SCF-related E3 complexes target additional cell cycle regulators. For example, CKI-1 is a target for ubiquitylation by an E3 ubiquitin-ligase complex involving CUL-4/Cul4 and DDB-1/DDB1 in *C. elegans* (Kim et al., 2007), which is consistent with a similar reported activity in *Drosophila* and humans (Bondar et al., 2006; Higa et al., 2006; Li et al., 2006).

pRb IS A PHYLOGENETICALLY CONSERVED CELL CYCLE REGULATOR

One of the most widespread events leading to oncogenesis in humans is the loss of G1/S regulation resulting from the inactivation of pRb (Weinberg, 1995). Loss of pRb activity can occur through either direct mutations within the *RB1* locus or by alterations to other loci that result in the functional inactivation of pRb. Mutations in this latter class include loss of function of the INK4 family of CKIs or the amplification and overexpression of Cyclin D and Cdk4 family members (Sherr, 1996; Nevins, 2001). *C. elegans*, with its single pocket protein family member, LIN-35, provides a streamlined system for deciphering pRb family functions within the context of an intact developing organism. In addition, the *C. elegans* genome encodes two bona fide E2F family members (EFL-1 and EFL-2) and one E2F dimerization partner, DPL-1/DP; mammals contain eight E2Fs and two DP family proteins (La Thangue, 1994; Yamasaki, 1998; Ceol and Horvitz, 2001; Page et al., 2001; DeGregori and Johnson, 2006; van den Heuvel and Dyson, 2008). This minimalistic, but complete, pathway configuration lowers the potential for intragene family functional redundancy. For example, in mammals, pRb, p107, and p130 have significant functional overlap, thereby complicating the analysis of both the collective and individual activities of these paralogs (Cobrinik et al., 1996; Lee et al., 1996; Mulligan and Jacks, 1998; Robanus-Maandag et al., 1998; Sage et al., 2000; Dannenberg et al., 2004).

Despite the fact that many cell cycle-related genes are misregulated following loss of LIN-35 activity, *lin-35* null single mutants are viable and display only minimal cell proliferation defects (Lu and Horvitz, 1998; Kirienko and Fay, 2007; Ouellet and Roy, 2007). For this reason, the great majority of cell cycle functions ascribed to LIN-35 have resulted from the analysis of compound mutants. For example, whereas both *lin-35* and *fzr-1*/Cdh1 single mutants exhibit only weak hyperproliferation of the intestine, *lin-35; fzr-1* double mutants display pronounced hyperplasia in multiple lineages (Fay et al., 2002). This synthetic phenotype is thought to result from an inability to negatively regulate G1 cyclins through either transcriptional repression by means of LIN-35–EFL-1 or at the level of protein stability through FZR-1, which functions as a specificity component of the anaphase-promoting-complex (APC) E3 ubiquitin-ligase (Schwab et al., 1997; Sigrist and Lehner, 1997; Visintin et al., 1997; Fay et al., 2002). Likewise, inhibition of *lin-35* activity enhances hyperproliferation in *cki-1/cki-2 (RNAi)*, *cdc-14*, and *lin-31* mutants (Boxem and van den Heuvel, 2001; Saito et al., 2004). Hyperproliferation in these latter examples is likely due to the cumulative effects of inactivating multiple pathways that inhibit the G1/S transition. Loss of *lin-35* can also suppress developmental defects in *cyd-1*/cyclin D and *cdk-4*/Cdk4 mutants, which is consistent with its role as a downstream target of these factors in mammals (Boxem and van den Heuvel, 2001).

It is worth noting that LIN-35/Rb also carries out several functions that are distinct from its role in cell cycle control. These include promoting germline apoptosis (Grote and Conradt, 2006; Reddien et al., 2007; Schertel and Conradt, 2007), inhibiting ectopic growth factor signaling (Lu and Horvitz, 1998), and preventing the expression of germline traits in somatic cells (Wang et al., 2005; Kirienko and Fay, 2007). In addition, LIN-35 redundantly controls organ morphogenesis (Fay et al., 2003; Bender et al., 2007; Mani and Fay, 2009), cell fate specification (Bender et al., 2004a), maintenance of organ homeostasis (Kirienko et al., 2008), and other developmental processes essential for fertility and viability (Cui et al., 2004; Cardoso et al., 2005; Chesney et al., 2006; Ceron et al., 2007). LIN-35 also plays a role in controlling ribosome biogenesis (Voutev et al., 2006), promoting the expression of transgenes (Hsieh et al., 1999), and inhibiting the RNAi response in somatic tissues (Wang et al., 2005; Lehner et al., 2006). Notably, many of these reported functions have correlates with some of the proposed tumor-suppressing functions of mammalian pocket proteins. Thus, the role of pRb family members in repressing malignant transformation may extend well beyond cell cycle regulation (Fig. 2).

NOVEL CELL CYCLE REGULATORS

Although the roles and activities of many hyperplasia-associated genes in *C. elegans* and mammals are well defined and can be traced to specific cell cycle functions, critical mechanistic details for others are still lacking. For example, the mammalian Cdk8 protein, a component of the conserved Mediator subcomplex (Akoulitchev et al., 2000), functions generically in target gene repression (Kobor and Greenblatt, 2002; Knuesel et al., 2009a,b). CDK-8, along with several other members of the Mediator complex, including MDT-13, is required in *C. elegans* for the maintenance of cell cycle quiescence in VPCs (Clayton et al., 2008). It is unclear why loss of the Mediator complex components leads to ectopic divisions, as expression of CKI-1 and G1 cyclins are not altered in *mdt-13* mutants (Clayton et al., 2008). Nevertheless, these findings suggest that additional means of cell cycle control remain to be identified through further studies in *C. elegans*.

GROWTH SIGNAL SELF-SUFFICIENCY

As discussed above, the core machinery and molecular mechanisms controlling cell cycle progression are highly conserved between mammals and *C. elegans*, making direct comparisons straightforward. The signals that trigger cell proliferation, on the other hand, are quite different. In mammals, mitogenic factors (MFs; also referred to as growth factors) are generally required to initiate exit from the quiescent state. Most often, these signals are conveyed from the exterior of the cell through receptor tyrosine kinases (RTKs), leading to the activation of intracellular

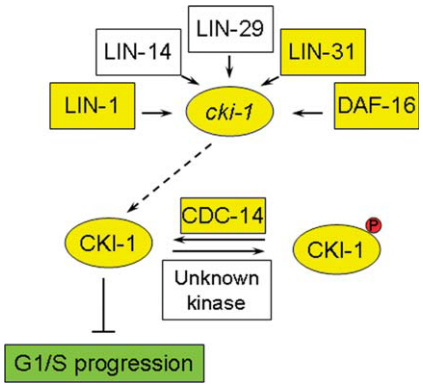

Fig. 1. Regulation of CKI-1. Model of factors controlling the expression and activity of CKI-1. LIN-1, LIN-14, LIN-29, LIN-31, and DAF-16 promote transcription of *cki-1*, whereas CDC-14 is thought to stabilize CKI-1 protein through removal of an inhibitory phosphate. The antagonist of the CDC-14 protein phosphatase, a presumed kinase, is unknown in *C. elegans*. Yellow shading indicates the existence of human orthologs. Dashed arrow indicates translation of *cki-1* mRNA into protein.

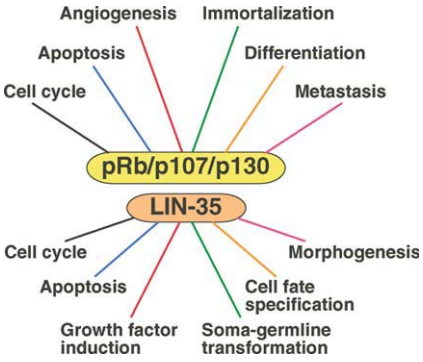

Fig. 2. Pocket protein functions are phylogenetically conserved. Comparison of the reported functions for mammalian pocket proteins in tumor suppression and the known functions of the sole *C. elegans* pocket protein ortholog, LIN-35/pRb. Identically colored lines correspond to related or analogous functions.

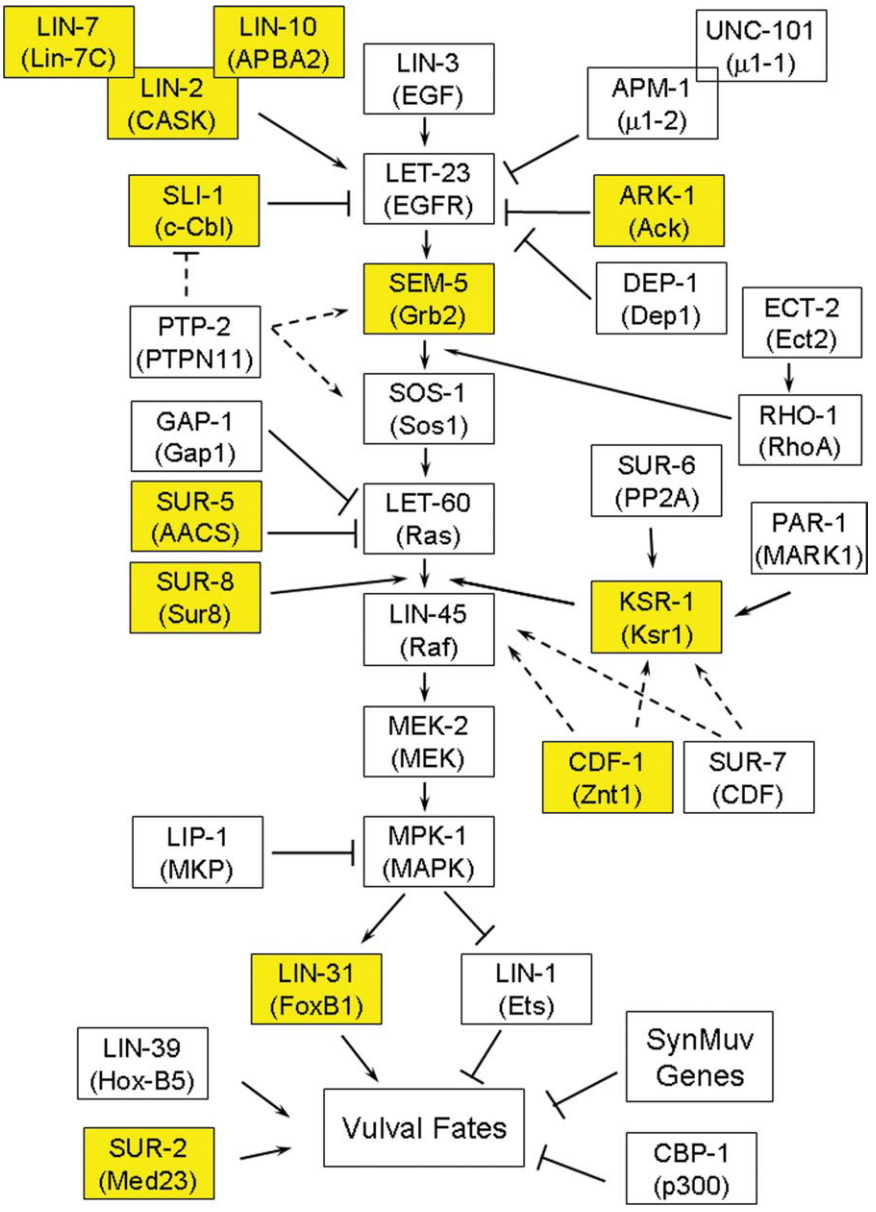

Fig. 3.

signaling pathways and changes in gene expression (Hanahan and Weinberg, 2000). As these pathways are required for the promotion of cell division in mammals, it is not surprising that alterations in growth factor signaling components are commonly observed in tumors. These include mutations that lead to the autonomous production of MFs by cancerous cells (Andrae et al., 2008; Palumbo et al., 2008), overexpression or constitutive activation of growth factor receptors or their downstream signaling components (Kaleko et al., 1990; Cappellen et al., 1999; Ono and Kuwano, 2006; Palumbo et al., 2008; Acevedo et al., 2009; Werner and Bruchim, 2009; Zahorowska et al., 2009), and the expression of variant extracellular matrix-associated proteins that influence signaling strength (Wilkins-Port and Higgins, 2007; Dydensborg et al., 2009).

C. elegans, as previously mentioned, has an invariant somatic cell lineage (Sulston and Horvitz, 1977; Sulston et al., 1983). In addition, growth in adult worms occurs by cell expansion rather than cell division, a process largely dependent upon endoreduplication events in the expanding cells (Flemming et al., 2000; Lozano et al., 2006). Furthermore, cell proliferation per se is not dependent on growth factor signaling. Rather, these pathways are used instead to regulate developmental events such as the induction of specific cell fates and the coordination of cell migration events. In addition, growth factor signaling pathways are used in *C. elegans* to respond to environmental challenges, such as starvation, stress, and infection by pathogens (Johnson et al., 2002; Kim et al., 2002, 2004; Garsin et al., 2003; Troemel et al., 2006; Hu, 2007). Despite its apparent lack of involvement in cell proliferation control, there are nevertheless compelling reasons to study growth factor signaling in *C. elegans*, as the components of

these pathways are often conserved, even if their specific biological functions are not. More generally, *C. elegans* has provided seminal insights into the regulation of many canonical signaling pathways connected to tumorigenesis including Delta-Notch, Wnt, insulin growth factor (IGF), and epidermal growth factor (EGF; Joneson and Bar-Sagi, 1997; Polakis, 1999; Waltzer and Bienz, 1999; Brown, 2001; Lustig and Behrens, 2003; Weng et al., 2004; Dunn et al., 2005; Dhillon et al., 2007; Bolos et al., 2007, 2009; Khavari and Rinn, 2007; Leicht et al., 2007; Samani et al., 2007; Frasca et al., 2008; Pollak, 2008; Thurston and Kitajewski, 2008; Werner and Bruchim, 2009). For illustrative purposes, we will focus here on the contributions of *C. elegans* research toward elucidating conserved components of EGF signaling, as many of these factors have subsequently been demonstrated to play a role in human tumorigenesis.

The EGFR-Ras-MAPK pathway is thought to be mutated in approximately one-fifth of human cancers (Montagut and Settleman, 2009). Notably, mutations that lead to enhanced activity of the *C. elegans* Ras ortholog, LET-60, occur at identical residues to those found in constitutively activated Ras from human tumors (Ferguson and Horvitz, 1985; Bos, 1989; Beitel et al., 1990). As described below, several distinct strategies have been used to identify novel components of this pathway in *C. elegans*, although most are based on forward-genetic approaches. The most well-studied phenotypes associated with *C. elegans* EGF signaling are those that affect the specification of vulval tissue (Sundaram, 2006). The development of the vulva is induced in response to signaling from the somatic gonad anchor cell, which secretes an EGF-like signal, LIN-3, which binds to the LET-23/EGFR receptor on the surface of VPCs (Hill and Sternberg, 1992). This signal triggers the activation of a canonical Ras-MAPK cascade that results in the specification of three vulval cell progenitors, which then undergo stereotypical divisions and morphogenetic events to form the mature organ. In addition, coordinated signaling through the Delta-Notch and Wnt pathways is also required to further refine vulval fates and patterning events (Sternberg, 2005). Loss of function in EGFR-Ras-MAPK signaling leads to a reduction in or absence of vulval tissue in the adult, such that gravid hermaphrodites cannot lay eggs [the Vulvaless (Vul) or Egg laying defective (Egl) phenotype]. Conversely, gain of function in EGFR-Ras-MAPK activity leads to an over-production of vulval tissue, causing a multivulval (Muv) phenotype. Importantly, both phenotypes are straightforward to score and neither result in inviability.

The complete EGFR-Ras-MAPK pathway involved in vulval cell induction is depicted in Figure 3. Although a significant number of these pathway components were first identified using genetic screens in *C. elegans*, the functions of these proteins are generally conserved across diverse phyla. Many of the core components were identified in simple screens for mutations that cause either Vul or Muv phenotypes. In the case of loss-of-function mutations, the Vul and Muv phenotypes suggested that the affected genes encode positive and negative regulators of the signaling pathway, respectively. More than 20 genes were identified using this approach including LIN-3/EGF, LET-23/EGFR, LET-60/Ras, and the downstream effectors LIN-1/Ets and LIN-31/FoxB1 (Horvitz and Sulston, 1980; Ferguson and Horvitz, 1985). In addition, several pathway modulators were identified in secondary screens for mutations that suppress or enhance loss-of-function alleles of *let-23*/EGFR, *sli-1*/c-Cbl, *lip-1*/MKP, *lin-2*/CASK, and *lin-10*/APBA2. These include SLI-1/c-Cbl itself, UNC-101/AP-1μ1-1, ARK-1/Ack, DEP-1/Dep-1/Scc, and GAP-1/Gap1 (Lee et al., 1994; Jongeward et al., 1995; Sternberg et al., 1995; Yoon et al., 1995; Hajnal et al., 1997; Hopper et al., 2000; Berset et al., 2005).

SLI-1 provides a particularly interesting example, as its mammalian counterpart, c-Cbl, had previously been implicated as a proto-oncogene, although its molecular functions were unknown (Langdon et al., 1989). Mutations in *sli-1* were discovered in screens for mutations that would suppress the Vul phenotype of a *let-23* partial loss-of-

Fig. 3. The EGFR-Ras-MAPK pathway in *C. elegans* vulval development. Activation of the EGFR-Ras-MAPK pathway in *C. elegans* vulval development is initiated when LIN-3/EGF ligand secreted by the gonadal anchor cell (AC) binds to the LET-23/EGFR receptor, causing it to dimerize and undergo autophosphorylation (Aroian et al., 1990; Hill and Sternberg, 1992). This event allows the SEM-5/Grb2 adaptor to bind phosphorylated LET-23 and recruit the SOS-1/Sos1 guanine nucleotide exchange factor (GEF; Clark et al., 1992a; Chang et al., 2000). SOS-1 promotes the exchange of GDP for GTP on the LET-60/Ras GTPase, which in turn activates a protein kinase cascade that includes LIN-45/Raf, MEK-2/MEK, and MPK-1/MAPK/ERK (Han et al., 1993; Sternberg et al., 1993; Lackner et al., 1994; Wu and Han, 1994; Kornfeld et al., 1995a; Wu et al., 1995; Chong et al., 2003). Targets of MPK-1 phosphorylation include the complex of LIN-1/Ets and LIN-31/FoxB1, which dissociates after phosphorylation, thereby allowing activated LIN-31 to promote the acquisition of vulval cell fates (Tan et al., 1998). Additional positive regulators of vulval fates include SUR-2/Med23 and LIN-39/Hox-B5, a member of the homeobox family of proteins (Clark et al., 1993; Singh and Han, 1995). Known negative regulators include members of the SynMuv group of proteins and CBP-1/p300 (Eastburn and Han, 2005; Fay and Yochem, 2007). Pathway modulators include LIN-2/CASK, LIN-7/Lin-7C, and LIN-10/APBA2, which mediate the subcellular localization of LET-23 and UNC-101/AP-1μ1-1 and APM-1/AP-1μ1-2, which promote LET-23 endocytotic recycling (Lee et al., 1994; Sternberg et al., 1995; Kaech et al., 1998; Shim et al., 2000). SLI-1/c-Cbl negatively regulates the pathway by targeting activated LET-23 for internalization and degradation (Rubin et al., 2005; Swaminathan and Tsygankov, 2006). The roles of ARK-1/Ack and DEP-1/Dep1/Scc in inhibiting LET-23 signaling are not yet understood. RHO-1/RhoA and its GEF, ECT-2/Ect2, positively regulate the pathway downstream of SEM-5 (Canevascini et al., 2005). The role of the PTP-2/PTPN11 protein tyrosine phosphatase is not well understood, but it may act at several nodes upstream of LET-60 signaling (Gutch et al., 1998; Chang et al., 2000). LET-60 GTP hydrolysis is stimulated by GAP-1/Gap1 (Hajnal et al., 1997). The putative scaffold proteins KSR-1/Ksr1 and SUR-8/Sur8 are required for robust signaling downstream of LET-60 (Kornfeld et al., 1995b; Sundaram and Han, 1995; Sieburth et al., 1998; Stewart et al., 1999). SUR-5/Sur5/AACS, an aminoacyl CoA synthase, inhibits the pathway at the level of LET-60 through an unknown mechanism (Gu et al., 1998). MPK-1/MAPK/ERK is dephosphorylated by the MAPK phosphatase (MKP) family protein LIP-1/MKP, which renders it inactive (Berset et al., 2005). In addition, KSR-1 activity is regulated in part by zinc ion concentrations that are controlled through CDF-1/Znt1 and SUR-7/CDF, by the SUR-6/PP2A protein serine/threonine phosphatase, and by the PAR-1/MARK1 kinase (Jakubowski and Kornfeld, 1999; Sieburth et al., 1999; Bruinsma et al., 2002; Yoder et al., 2004). Yellow fill indicates proteins that were first implicated in EGFR-Ras-MAPK signaling through studies in *C. elegans*.

function allele (Jongeward et al., 1995). This finding implicated SLI-1/c-Cbl as a negative regulator of LET-23/EGFR signaling, thus suggesting that it may normally function as a tumor suppressor. Both SLI-1 and c-Cbl possess RING finger and SH3 domains, and c-Cbl was subsequently shown to directly bind Grb2, the human ortholog of the SEM-5 adapter (Odai et al., 1995; Yoon et al., 1995). Furthermore, the presence of a RING finger domain suggested a role for SLI-1/c-Cbl in ubiquitin-mediated proteolysis. Consistent with this, c-Cbl was shown to ubiquitylate EGFR in vitro (Levkowitz et al., 1998). Moreover, ubiquitylation of EGFR by c-Cbl occurs following ligand binding and receptor activation (Haglund et al., 2003; Mosesson et al., 2003; Rubin et al., 2005; Swaminathan and Tsygankov, 2006). One model to emerge is that Grb2, when bound to phosphorylated EGFR, recruits c-Cbl for the purpose of degrading the receptor and terminating RTK signaling in a classic negative-feedback loop (Swaminathan and Tsygankov, 2006). Thus, in the absence of c-Cbl, EGFR signaling goes unchecked, thus leading to hyperproliferation.

A second series of suppressor screens sought to identify negative regulators of EGFR-Ras-MAPK signaling based on the ability of mutations to suppress the Muv phenotype. A screen using a *lin-15* Muv background led to the identification of *sem-5*/Grb2, *sos-1*/*let-341*/Sos1, *let-60*/Ras, and *lin-45*/Raf as core determinants of vulval cell fate acquisition (Han et al., 1990; Aroian and Sternberg, 1991; Clark et al., 1992a,b; Han et al., 1993; Hsu et al., 2002), whereas alleles of *let-23*/EGFR, *lin-45*/Raf, *mek-2*/MEK, and *mpk-1*/ERK were identified using gain-of-function *let-60*/Ras alleles (Lackner et al., 1994; Wu and Han, 1994; Kornfeld et al., 1995a; Wu et al., 1995; Hsu et al., 2002). In addition, a large number of noncore pathway regulators, including CDF-1/Znt1, KSR-1/Ksr1, SUR-2/MDT-23/Sur2, SUR-6/PPP2R2A, SUR-7/CDF, and SOC-2/SUR-8/Sur8, were also identified as suppressors of *let-60(gf)* Muv, whereas SUR-5/AACS was identified as a suppressor of a dominant-negative *let-60* Vul allele (Kornfeld et al., 1995b; Singh and Han, 1995; Sundaram and Han, 1995; Gu et al., 1998; Sieburth et al., 1998; Jakubowski and Kornfeld, 1999; Sieburth et al., 1999; Bruinsma et al., 2002; Yoder et al., 2004). Finally, a few important pathway members, including MEK-2/MEK, and the MAPK phosphatase, LIP-1, along with PTP-2/PTPN11 and APM-1/AP-1μ2, were identified by homology searches for EGFR-Ras-MAPK pathway members known in either *C. elegans* or other model organisms (Wu et al., 1995; Gutch et al., 1998; Shim et al., 2000; Berset et al., 2005).

The identification and analysis of KSR-1/Ksr1 exemplifies the ability of genetic screens in *C. elegans* and other model systems to provide novel insights into the regulation of mammalian growth factor signaling pathways (Kornfeld et al., 1995b; Sundaram and Han, 1995; Therrien et al., 1995). Notably, *Drosophila* Ksr/SR3-1 was identified at the same time as the *C. elegans* ortholog, using an analogous screen to study the role of Ras signaling in eye development (Therrien et al., 1995). Furthermore, both reports implicated KSR-1/Ksr in the positive regulation of EGFR-Ras-MAPK signaling. Follow-up studies in mammalian cell lines also indicated that Ksr1 binds to multiple components of Ras-MAPK pathways including MEK2, ERK, and RAF, a finding that has been partially corroborated in *C. elegans* (Michaud et al., 1997; Xing et al., 1997; Denouel-Galy et al., 1998; Joneson et al., 1998; Yu et al., 1998; Stewart et al., 1999). However, overexpression of mammalian Ksr1 was initially reported to stabilize MEK in an inactive form and thus inhibit Ras-mediated transformation in cell culture, suggesting a negative regulatory role in EGFR-Ras-MAPK signaling (Denouel-Galy et al., 1998). Construction of a mouse Ksr1 knockout reconciled this discrepancy, showing that mammalian Ksr1 is required specifically for Ras-mediated transformation, which is consistent with findings in worms and flies (Lozano et al., 2003). The most likely explanation for the incongruity in these reports is that, as a scaffolding protein, Ksr1 expression must be tightly regulated as fluctuations in either direction could potentially lead to the assembly of nonfunctional protein complexes and reduced signaling.

Notably, the functions of the Ras pathway-associated oncogenes CASK, Grb2, Sur2, Sur8, and c-Cbl were first understood in *C. elegans* (Baines, 1996; Hoskins et al., 1996; Kaech et al., 1998; Wang et al., 2002b). In addition, several downstream effectors of the *C. elegans* Ras-MAPK pathway may also be relevant to cancer progression. At least two known targets of this pathway, *lin-1*/Ets and *lin-31*/FoxB1, are involved in maintaining cell cycle quiescence by regulating *cki-1*/CKI (Clayton et al., 2008). Similarly in mammals, Ets transcription factors are targets of Ras-MAPK signaling and regulate $p21^{Cip1}$ (Zhang et al., 2003).

Interestingly, a direct link has been established between the *C. elegans* Ras-MAPK pathway and the LIN-35/pRb tumor suppressor through the study of synthetic multivuvlal (SynMuv) mutants. Two primary classes of SynMuv genes have been described, termed A and B (Ferguson and Horvitz, 1985; Fay and Yochem, 2007; van den Heuvel and Dyson, 2008). Whereas in general, single mutations in either A or B class genes fail to display vulval induction defects, when combined, class A–B double mutants show a highly penetrant Muv phenotype. Molecular cloning of the class B genes identified LIN-35, along with several conserved transcriptional regulators including EFL-1/E2F, DPL-1/Dp, and HDA-1/histone deacetylase (Lu and Horvitz, 1998; Ceol and Horvitz, 2001). These and other class B members comprise an overlapping set of conserved transcriptional repressor complexes (e.g., NURD, and DRM), which together with the SynMuv class A proteins, inhibit the ectopic expression of *lin-3* in the hypodermis (Cui et al., 2006a). Thus, in class A–B double mutants, exogenous LIN-3 is produced from the hypodermis, leading to the hyper-induction of vulval cell fates and the Muv phenotype (Cui et al., 2006a; Andersen et al., 2008). This link between LIN-35 and growth factor expression in *C. elegans* correlates with findings in mammals where pRb controls the expression of growth factors including VEGF, thus suggesting a novel mode by which pocket proteins may exert their tumor suppressive effects (Gabellini et al., 2006; Chien et al., 2007). It is also worth noting that additional factors identified through studies of SynMuv mutants (e.g., LIN-9), have been subsequently been linked to cancer in humans (Gagrica et al., 2004).

In mammals, many additional growth factors act through Ras-MAPK

signaling including FGF, VEGF, IGF, and PDGF. Correspondingly in *C. elegans*, two FGF ligand orthologs (EGL-17 and LET-756) and their receptor, EGL-15/FGFR, activate Ras-MAPK signaling to control sex myoblast migration, muscle development, neural migration, and osmotic balance (Bulow et al., 2004; Huang and Stern, 2004; Fleming et al., 2005; Dixon et al., 2006). This has led to the suggestion that *C. elegans* can provide a valuable model for noncanonical roles for FGF signaling (Polanska et al., 2009). As *C. elegans* lacks a vascularized circulatory system, studies of vascular endothelial growth factor (VEGF) and its receptors (VEGFR1–3), which are responsible for the angiogenic growth that is necessary for sustained tumorigenesis, seem likely to be out of place. Yet surprisingly, orthologs of these proteins are present in the *C. elegans* genome (Plowman et al., 1999; Popovici et al., 1999; Rikke et al., 2000; Popovici et al., 2002; Tarsitano et al., 2006). Moreover, a putative PDGF/VEGF ortholog, PVF-1, behaves similarly to mammalian VEGF in its ability to dimerize, undergo secretion, and bind at least two mammalian VEGF receptors in heterologous systems (Tarsitano et al., 2006). Furthermore, PVF-1 can activate angiogenesis when expressed in the chicken chorioallantoic membrane and in cultured human umbilical vein endothelial cells (HUVEC; Tarsitano et al., 2006). The four *C. elegans* VEGFR homologs, VER-1–4, are expressed predominantly in neurons and their associated cells, although their functions are currently unclear (Popovici et al., 2002). This expression pattern, however, correlates with the observation that some mammalian angiogenic factors also have a role in neurogenesis, suggesting that some functions of the *C. elegans* VEGF pathway may be phylogenetically conserved (Galvan et al., 2006).

It is also important to note that some differences have been observed between *C. elegans* and mammalian growth factor signaling pathways. For example, the insulin growth factor receptor (IGFR) in mammals signals through a canonical Ras-MAPK pathway. In contrast, the *C. elegans* DAF-2/IGFR pathway functions independently of Ras-MAPK (Sundaram, 2006). Another example is the noncanonical Wnt signaling pathway originally identified in studies of *C. elegans* embryogenesis. In this case, however, the noncanonical Wnt pathway was subsequently shown to be conserved across phyla (Han, 1997; Kuhl et al., 2000; Peifer and Polakis, 2000; Korswagen, 2002; Kuhl, 2002; Veeman et al., 2003). Thus, studies of growth factor signaling pathways in *C. elegans* have been extremely fruitful in identifying both conserved core components and accessory regulators of these pathways and linking their functions to oncogenesis.

THE GERMLINE: TUMORS, IMMORTALITY, GENOME INTEGRITY, AND SURVIVAL

As described in the preceding sections, mutations in several genes associated with cell cycle control can induce somatic cell hyperproliferation defects in *C. elegans*. Such ectopic divisions, however, rarely produce anything resembling a classic tumor. Rather, supernumerary somatic cells undergo quiescence, terminally differentiate, and integrate more or less appropriately into their respective organs. By contrast, mutations leading to excess germline proliferation can result in bona fide tumors. Although generally confined to the gonad, germline tumor cells are mitotically active and fail to differentiate into gametes. As described below, germline tumors can arise through both germline intrinsic (cell autonomous) and somatically based (nonautonomous) mechanisms. In addition, as the only tissue to harbor a population of stem cells throughout adulthood, the *C. elegans* germline provides an opportunity to study mechanisms governing replicative immortality and the maintenance of pluri-potency, both of which are relevant to traits acquired by cancer cells. Finally, the germline is the only tissue capable of undergoing apoptosis in *C. elegans* adults, both in response to damage cues and as part of a normal developmental process. Thus, the germline of *C. elegans* provides a particularly powerful system in which to study several biological phenomena pertinent to malignant transformation.

A BRIEF REVIEW OF GERMLINE PROLIFERATION CONTROL

At hatching, *C. elegans* hermaphrodites contain two primordial germ cells that give rise to independently regulated anterior and posterior germ cell populations in the adult (for detailed reviews, see Hansen and Schedl, 2006; Hubbard, 2007; Kimble and Crittenden, 2007; Byrd and Kimble, 2009). Proliferation of germ cells during larval and adult stages is controlled by the somatic gonad, most notably the distal tip cells (DTCs), which are essential for maintaining a mitotic stem cell niche at the distal terminus of each gonad arm (Kimble and White, 1981; Fig. 4). The DTCs promote mitotic proliferation through a conserved Delta-Notch signaling pathway. Specifically, DTCs express a Delta/Serrate-like transmembrane ligand, LAG-2 (collectively referred to as DSLs; Henderson et al., 1994; Tax et al., 1994), which binds to the GLP-1/Notch receptor located within the plasma membrane of distal germ cells (Crittenden et al., 1994; Henderson et al., 1994; Tax et al., 1994). Activation of GLP-1 by LAG-2 is thought to result in cleavage of the GLP-1 intracellular domain, which then translocates to the nucleus where it interacts with several co-factors to induce the expression of target genes that promote mitosis and inhibit meiosis (Christensen et al., 1996; Doyle et al., 2000; Petcherski and Kimble, 2000; Kovall, 2008).

Although a complete knowledge of GLP-1 downstream effectors is currently lacking, one established target is the Pumilio and FBF (PUF) family member *fbf-2* (Lamont et al., 2004). FBF-2 and its close paralog, FBF-1 (together, termed the FBFs), are both expressed in the distal mitotic region of the germline where GLP-1 is active (Zhang et al., 1997; Lamont et al., 2004). Although mutations that affect individual *fbfs* show minimal defects, germline proliferation is largely abolished after the L4 larval stage in *fbf-1 fbf-2* double mutants, indicating that the FBFs are redundantly required for maintaining the germline stem cell niche in adults (Crittenden et al., 2002). The FBFs function by binding to sequence elements in the 3′UTRs of target mRNAs to inhibit their translation (Zhang et al., 1997; Bernstein et al., 2005). Targets for repression by the FBFs include two additional translational regulators, GLD-1 and GLD-3 (Crittenden et al., 2002; Eckmann et al., 2004; Fig. 5). GLD-3, a Bicaudal-

C family member (Eckmann et al., 2002, 2004), physically associates with the cytoplasmic poly(A) polymerase (PAP), GLD-2 (Wang et al., 2002a). The GLD-2–GLD-3 complex has been suggested to stimulate gene expression by lengthening the poly(A) tails of target mRNAs, resulting in increased stability and translation. Conversely, GLD-1, a maxi-KH/STAR domain RNA-binding protein, acts primarily as a translational repressor (Jones and Schedl, 1995; Lee and Schedl, 2001; Crittenden et al., 2002; Hansen and Schedl, 2006). Also operating in the GLD-1 pathway is NOS-3 and GLD-4, which promote GLD-1 accumulation redundantly with GLD-2–GLD-3 (Fig. 5; Hansen et al., 2004b; Schmid et al., 2009). NOS-3, a homolog of the *Drosophila* Nanos RNA-binding protein, promotes GLD-1 expression at the level of translation and can also physically interact with the FBFs (Kraemer et al., 1999; Hansen et al., 2004b). GLD-4, a cytoplasmic PAP, acts with GLS-1 to promote polyadenylation and increased stability of *gld-1* mRNA (Schmid et al., 2009).

As a result of FBF translational repression, expression of GLD-1 and GLD-3 is inhibited in the distal mitotic niche (Crittenden et al., 2002; Eckmann et al., 2004). GLD-1 and GLD-3 are present at higher levels in cells that lie proximal to the niche, consistent with their role in promoting meiosis (Jones et al., 1996; Eckmann et al., 2004). Moreover, loss of GLP-1 or FBF activity leads to ectopic expression of GLD-1 in the distal portion of the gonad and premature entry of niche cells into meiosis (Crittenden et al., 2002; Hansen et al., 2004b). One known target for repression by GLD-1 is GLP-1(Marin and Evans, 2003), and both GLD-1 and GLD-3 inhibit expression of the FBFs, thus indicating the presence of negative feedback loops (Eckmann et al., 2002; Kimble and Crittenden, 2007; Fig. 5). Many other factors, including a host of additional RNA-binding proteins, have also been implicated in controlling the mitosis-to-meiosis transition (Hansen and Schedl, 2006; Kimble and Crittenden, 2007), but in most cases they will not be discussed here.

It is worth underscoring that the overall picture to have emerged from studies on *C. elegans* germline regulation is one of striking complexity. This is due in part to the presence of numerous feedback loops, the utilization of certain pathway components at multiple nodes in the regulatory network, and the shifting roles of various factors at discrete stages of development. Furthermore, many genes controlling the mitosis-to-meiosis switch are also required for progression through meiosis and for promoting sex-specific germ cell fates. Moreover, germline proliferation is sensitive to environmental conditions. For example, in response to starvation, germ cells in L1 larvae undergo a reversible cell cycle arrest. This arrest is dependent on DAF-18, a PTEN tumor suppressor ortholog, and MDF-1, a MAD family protein required for G2/M checkpoint arrest (Fukuyama et al., 2006; Watanabe et al., 2008). Thus, complex intrinsic mechanisms, as well as external cues, are critical for maintaining proper levels of germ cell proliferation and for controlling the balance between mitosis and meiosis.

GERMLINE TUMORS: INTRINSIC MECHANISMS

Many of the genes controlling germline proliferation and differentiation were first identified in genetic screens for mutations that cause sterility. Further characterization revealed a wide array of phenotypes including the inability of certain mutants to establish or maintain a stem cell niche. Other mutations led to an expansion of the niche and interfered with the ability of germ cells to initiate or complete meiosis. As described below, mutations in this latter class can, under certain conditions, promote the formation of germline tumors. In such cases, gonads become tightly packed with mitotic nuclei that exhibit cellular configurations reminiscent of mammalian tumors. In some instances, excess proliferation leads to severe swelling of the proximal gonad and the release of its contents, which can contribute to premature death (Francis et al., 1995a).

As indicated by the regulatory network depicted in Figure 5, gain-of-function mutations in *glp-1* or loss-of-function mutations in other pathway components, such as the *gld* genes, can shift the balance toward mitotic proliferation. In the case of *glp-1(gf)* mutations, sequence alterations result in constitutive activation of the receptor, which for strong alleles (e.g., *glp-1(oz112gf)*) leads to a complete absence of germline meiosis and the formation of a contiguous germline tumor [Fig. 4; (Berry et al., 1997)]. For weaker *glp-1(gf)* alleles (e.g., *glp-1(ar202gf)*), meiosis and gamete differentiation occur in a relatively normal manner; however, such gonads also contain an ectopic mass of proliferating cells at the proximal terminus (the Pro phenotype; Fig. 4; Pepper et al., 2003a). In the case of *glp-1(ar202gf)* mutants, tumors arise from a population of proximal mitotic germ cells that fail to differentiate, because of the establishment of an ectopic niche (also see below). Deviations from the normal mitotic-to-meiotic spatiotemporal progression also occur for loss-of-function mutations in *gld-1* and *puf-8*; however, in these cases, tumors arise from germ cells that initiate but fail to complete gametogenesis. For example, germ cells in *gld-1* null mutants (heretofore referred to as *gld-1* mutants) initiate meiosis but return to mitosis before completing meiotic prophase (Francis et al., 1995a,b). Likewise, mutations in the PUF family member *puf-8* result in primary spermatocytes that fail to correctly execute reductional meiotic divisions and instead de-differentiate into mitotic cells that form a proximal mass (Subramaniam and Seydoux, 2003).

Analyses of compound mutants have revealed that components of the NOS-3–GLD-1 and GLD-2–GLD-3 pathways function redundantly with respect to promoting meiotic entry and progression (Fig. 5). For example, tumor growth is significantly more pronounced in double mutants of *gld-1* and either *gld-2* or *gld-3* than in *gld-1* single mutants (Kadyk et al., 1997; Eckmann et al., 2004; Hansen et al., 2004a). Moreover, unlike *gld-1* single mutants, germ cells in double mutants generally fail to initiate meiosis and remain constitutively mitotic. As would be expected, other double-mutant combinations that lead to the inhibition of both pathways (e.g., *gld-3; nos-3* and *gld-2 gld-4*) also display "synthetic" tumorous phenotypes (Hansen et al., 2004a,b; Schmid et al., 2009). Conversely, synthetic tumor growth is not observed in *gld-1; nos-3* or *gld-2; gld-3* double mutants, as these combinations disrupt only the activities of the individual pathway branches (Eckmann et al., 2004; Hansen et al., 2004b).

Consistent with NOS-3 and the GLDs functioning downstream of GLP-1, synthetic germline tumors are not suppressed by loss of *glp-1* activity (Kadyk and Kimble, 1998; Eckmann et al., 2004; Hansen et al., 2004b). Of interest, unlike the germlines in strong *glp(gf)* mutants, those in compound mutants (e.g., *gld-1 gld-2*) can still harbor small numbers of meiotic cells (Hansen et al., 2004a). This finding suggests that a third pathway, operating downstream of GLP-1, also contributes to the promotion of meiosis (Fig. 5). We note that the regulatory network described above and in Figure 5 is considerably more complex than we have depicted. For example, contrary to expectations, loss of *fbf* function can suppress synthetic tumor formation in some compound mutants as well as enhance tumor growth in other genetic backgrounds (Eckmann et al., 2004). This latter finding suggests that the FBFs, acting together or individually, may differentially influence outcomes at distinct nodes within the network or at different stages of development.

Several additional germline-intrinsic regulators of the mitosis-to-meiosis switch have also been identified; however, their precise connection to the GLP-1 pathway has yet to be established (Fig. 5). A loss-of-function mutation in *teg-4* was isolated as an enhancer of germline over-proliferation in strains that were heterozygous for the strong *glp-1(oz112gf)* allele (Mantina et al., 2009). Furthermore, a reduction in *teg-4* activity leads to synthetic tumors in *gld-1*, *gld-2*, and *gld-3* mutant backgrounds, indicating that TEG-4 does not function specifically in either the NOS-3–GLD-1 or GLD-2–GLD-3 branches of the pathway. *teg-4* encodes a homolog of human SAP130, a conserved component of the SF3b pre-mRNA splicing complex (Mantina et al., 2009). Thus, TEG-4 may influence germline proliferation and differentiation indirectly, possibly through the expression of one or more downstream targets of GLP-1 signaling. Similarly, mutations in the *mog* genes (*mog-1–6*) produce synthetic germline tumors when combined with mutations in the *gld* genes (*gld-1–3*; Belfiore et al., 2004; Hansen and Schedl, 2006). The molecular identities of the MOGs implicate a role in mRNA processing or metabolism, and genetic epistasis experiments suggest that the MOGs, as well as TEG-4, may function downstream of or in parallel to GLP-1 (Puoti and Kimble, 1999, 2000; Belfiore et al., 2004; Hansen and Schedl, 2006; Mantina et al., 2009).

Roles for epigenetic regulators of germline proliferation are indicated by findings that loss-of-function mutations in *him-17*, which encodes a novel chromatin-associated protein, and *mett-10*, an evolutionarily conserved putative histone methyltransferase, enhance germline over-proliferation in weak *glp-1(gf)* mutants (Reddy and Villeneuve, 2004; Bessler et al., 2007; Dorsett et al., 2009). In addition, certain alleles of *mett-10* cause a partially penetrant tumorous phenotype on their own that can be suppressed by *glp-1(lf)* mutations (Dorsett et al., 2009). Of interest, *mett-10* mRNA levels and METT-10 protein accumulation in nuclei are positively regulated by the dynein motor protein light and heavy chain subunits DLC-1 and DCH-1, which in the case of nuclear import, involves direct binding between DLC-1 and METT-10 (Dorsett and Schedl, 2009). Consistent with this, weak inhibition of *dlc-1* or *dhc-1* strongly enhances the tumorous phenotype of *glp-1(gf)* and *mett-10(lf)* mutants. Genetic and phenotypic data indicate that METT-10 normally promotes meiotic entry and may function either upstream or in parallel to GLP-1 (Dorsett et al., 2009). Additional data suggest that DLC-1–DCH-1 may also promote meiotic entry through an unknown partner of METT-10 (Dorsett and Schedl, 2009). We also note that unlike the situation in *gld-1* mutants, germline tumors associated with mutations in *mett-10*, *him-17*, and *teg-4* are not due to the de-differentiation of meiotic cells but result from prolonged maintenance of the mitotic state (Bessler et al., 2007; Dorsett and Schedl, 2009; Dorsett et al., 2009; Mantina et al., 2009).

Additional insight into the control of germ cell proliferation has come from the identification of mutations that reduce the occurrence or severity of germline tumors. Loss-of-function mutations in either *ego-1* or *atx-2* lead to partial suppression of synthetic tumorous growth in *gld-1 gld-2* double mutants (Maine et al., 2004; Vought et al., 2005). *ego-1* encodes an RNA-directed RNA polymerase that is also required in the RNAi response pathway (Smardon et al., 2000; Vought et al., 2005). *atx-2* encodes an ortholog of mammalian ataxin-2 and has been shown to regulate mRNA metabolism and translation (Kiehl et al., 2000; Ciosk et al., 2004). Based on genetic and molecular evidence, neither EGO-1 nor ATX-2 is likely to function within the GLP-1 pathway, but they may promote germline mitosis through independent mechanisms (Maine et al., 2004; Vought et al., 2005). Simultaneous loss of *puf-8* and *mex-3*, the latter of which encodes a KH-domain RNA-binding protein (Draper et al., 1996), inhibits tumor formation in both *gld-1 gld-2* double mutants and in strong *glp-1* gain-of-function mutants (e.g., *glp-1(oz112gf)*; Ariz et al., 2009). Thus, PUF-8, like the FBFs, can either promote or inhibit tumor formation, depending on the genetic background and developmental context (Subramaniam and Seydoux, 2003; Ariz et al., 2009). Unlike the combined loss of *mex-3* and *puf-8*, inhibition of *atx-2* does not suppress *glp-1(oz112gf)* tumor growth (Maine et al., 2004), suggesting that tumor suppression in these backgrounds may occur by distinct mechanisms. Suppression of tumors in *gld-1 gld-2* mutants also occurs with mutations in the conserved DNA-replication checkpoint gene *clk-2*/TEL2, indicating that correct cell cycle execution is also a requisite for germline tumor growth (Moser et al., 2009).

Intriguingly, mutations that increase longevity can suppress tumor growth and premature death in *gld-1* mutants (Pinkston et al., 2006; Moser et al., 2009). In the case of *daf-2*/IGFR, a component of the *C. elegans* insulin growth factor pathway, the mechanism of tumor suppression is attributable to both decreased germ cell proliferation and increased apoptosis. Mutations in *daf-2* promote germline apoptosis in *gld-1* mutants through a mechanism that requires the functions of DAF-16/FOXO; CEP-1, a protein with homology to p53 family members; and several DNA damage–induced checkpoint genes (Pinkston et al., 2006). In addition, loss of *daf-2* activity reduces the number of actively dividing germ cells in *gld-1* mutants. Similarly, mutations that extend life span by caloric restriction (*eat-2*) and metabolic repression (*clk-1*) reduce *gld-1* germline mitotic

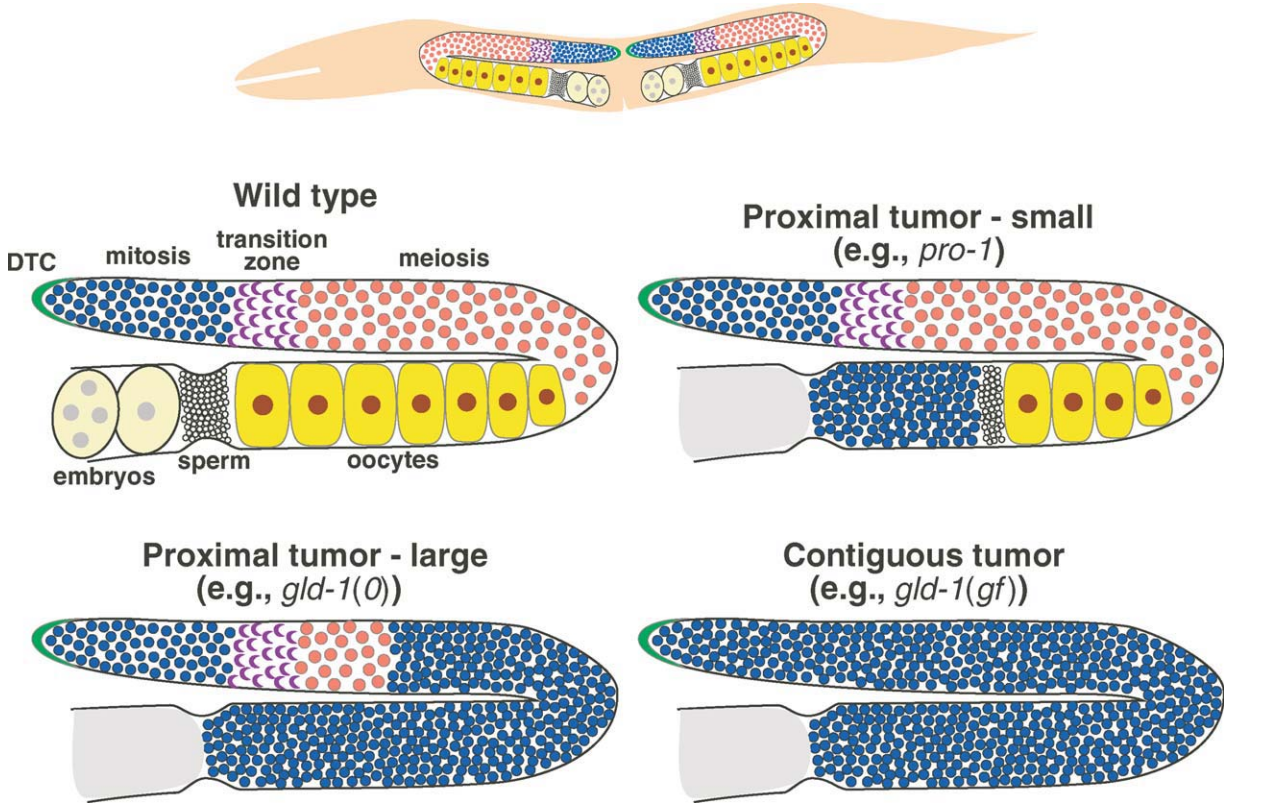

Fig. 4.

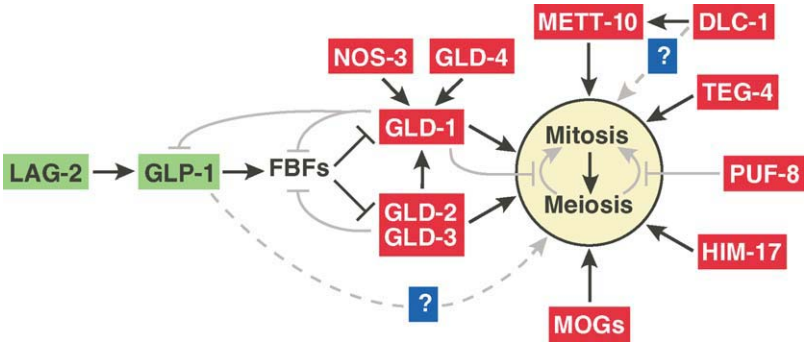

Fig. 5. The regulatory network that controls germ cell proliferation. Increased activity or ectopic expression of proteins in green boxes promotes mitotic proliferation. In the case of *glp-1(gf)* mutants, this results in germline tumor formation. Decreased activity of proteins in red boxes, either alone or in combination, also induces hyperproliferation and tumor formation. For simplicity, only a subset of known germline regulators is shown. In some cases genes depicted to act in parallel to GLP-1, such as TEG-4 and METT-10, may integrate their functions more directly within the GLP-1 pathway. Note the high degree of regulatory cross-talk between the core factors (gray lines). Dashed lines and question marks indicate predicted regulatory connections and missing components, respectively.

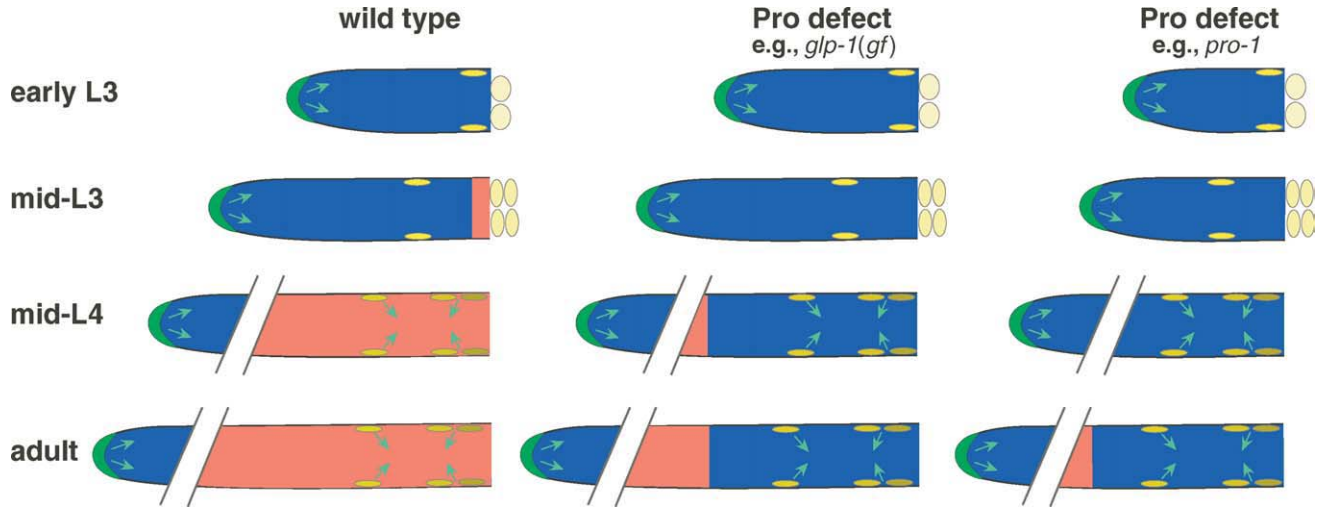

Fig. 6.

proliferation but, unlike *daf-2* mutations, have no effect on *gld-1* germline apoptosis (Pinkston et al., 2006). Curiously, mutations in *daf-2*, *eat-2*, and *clk-2* do not adversely affect germline proliferation in wild-type. This is in contrast to mutations in *ego-1*, *atx-2*, and *mex-3; puf-8*, which suppress germ cell proliferation in both tumorous and wild-type animals (Qiao et al., 1995; Maine et al., 2004; Ariz et al., 2009). More recently, several putative DAF-16 transcriptional targets have been identified that mediate life-span extension and tumor growth suppression in *gld-1; daf-2* mutants (Pinkston-Gosse and Kenyon, 2007). This analysis suggests that both positively and negatively regulated DAF-16 targets contribute to *daf-2*-mediated tumor suppression and that individual targets have specific roles with respect to regulating either proliferation or apoptosis. Given the established role of the DAF-2–DAF-16 pathway in stress response and dietary restriction (Murakami et al., 2000; Kenyon, 2005), these studies provide an additional link between environmental input and germline regulation. This connection is further supported by the finding that inhibition of the *C. elegans* prohibitin orthologs, *phb-1/2*, also suppresses tumor growth in *gld-1* mutants (Artal-Sanz and Tavernarakis, 2009). Loss of *phb-1/2* can extend lifespan under conditions of dietary restriction through the control of fat mobilization and energy metabolism. Notably, overexpression of human prohibitins is associated with several cancers and prohibitins have been suggested as a potential target for cancer therapy (Mishra et al., 2005).

GERMLINE TUMORS: SOMATIC INFLUENCES

As previously discussed, the somatic DTC is required for the establishment of a germline stem cell niche (Kimble and White, 1981). Moreover, the DTC is sufficient for niche induction, as evidenced by experimental manipulations or mutations that lead to the generation of multiple DTCs within a single gonad arm (Kimble and White, 1981; Kipreos et al., 2000; Fay et al., 2002; Kidd et al., 2005; Lam et al., 2006). Furthermore, mutations or manipulations that impede the stereotypical pattern and/or timing of DTC migration during larval development result in abnormal distal-to-proximal patterns of germline proliferation (e.g., Kimble and White, 1981; Blelloch et al., 1999; Nishiwaki, 1999; Tamai and Nishiwaki, 2007). In particular, failure of the DTC to migrate a sufficient distance from the proximal terminus leads to prolonged exposure of proximal germ cells to LAG-2 signaling and can result in tumorigenesis (also see below).

The DTC is not, however, the only somatic cell that influences germ cell proliferation and differentiation. Somatic cells of the proximal gonad can also promote germ cell proliferation and, under certain circumstances, are integral to the genesis of germline tumors. Most prominent among these are the gonadal sheath cells, which form a thin layer surrounding most of the germline (Hirsh et al., 1976; Kimble and Hirsh, 1979; Fig. 6). Each gonad arm in the adult harbors five pairs of sheath cells (Sh1–5), the three most proximal of which (Sh3–5) form a myoepithelial sheet that aids in ovulation (Ward and Carrel, 1979). Laser ablation of sheath cell precursors during larval development leads to pleiotropic germline defects, including a three- to five-fold decrease in the extent of germ cell proliferation, thus demonstrating that somatic gonad cells other than the DTC promote germline mitosis (McCarter et al., 1997). More recently, Sh1, the distal-most sheath cell pair, has been shown to be most critical for this activity (Killian and Hubbard, 2005).

Initial evidence of a role for the proximal somatic gonad in germline tumorigenesis came from cell ablation studies in wild-type and in strains carrying a *lin-12* null mutation, which leads to the formation of proximal tumors (Seydoux et al., 1990). Like *glp-1*, *lin-12* encodes a Notch receptor ortholog that can be activated by LAG-2 (Yochem et al., 1988; Austin and Kimble, 1989; Yochem and Greenwald, 1989; Henderson et al., 1994; Tax et al., 1994). Rather than being expressed in the germline, however, LIN-12 functions in the somatic gonad to control several binary cell-fate decisions (Greenwald, 2005). The ablation studies by Seydoux and colleagues support a model whereby aberrant LAG-2 signal, emanating from the somatic gonad anchor cell (AC), ensues when LIN-12 expression is abolished in somatic cells that lie adjacent to the AC. Thus, rather than binding to LIN-12, its normal target in the proximal somatic gonad, AC-derived LAG-2 activates GLP-1 on neighboring proximal germ cells, thereby promoting

Fig. 4. Hermaphrodite wild-type and tumorous gonads. In wild-type gonads, mitosis is restricted to the distal portion of the germline. In this region, GLP-1/Notch is activated by LAG-2/DSL by means of the somatic distal tip cell (DTC). As divisions occur and mitotic cells move out of range of the LAG-2 signal, GLP-1 becomes inactive and germ cells exit mitosis and enter meiosis (transition zone). Moving further proximally, germ cells transit several stages of meiotic prophase, eventually forming male and female gametes that are used for fertilization. Tumorous gonads contain proliferating mitotic cells at ectopic locations. In the case of strong gain-of-function alleles such as *glp-1* (*oz112gf*), meiosis is completely abolished and mitotic cells are detected throughout the gonad arm, resulting in a contiguous tumor. Loss-of-function mutations in other genes (e.g., *pro-1* and *gld-1*) lead to more-limited tumor formation in the central-to-proximal gonad region.

Fig. 6. A delay in meiotic entry, in combination with somatic gonad signaling, promotes proximal tumor formation. Blue and red indicate mitotic and meiotic germ cell regions, respectively. The green crescent-shaped cell on the left represents the distal tip cell (DTC). Yellow-to-brown flattened oval cells indicate somatic gonad sheath cells; darker shading indicates more proximal sheath cells. The proximal sheath cells depicted in mid-L4 and adult gonads are the Sh3–5 pairs. Rounder proximal cells in early L3 and mid-L3 larvae have not yet completed divisions. Green arrows indicate DSL ligand signaling from the DTC and sheath cells. For simplicity, central portions of mid-L4 and adult gonads are not shown; the missing region is demarcated by parallel lines. Note the delay in the timing of initial meiosis in Pro-defective gonads at the mid-L3 stage. In the case of *glp-1(gf)* mutants (e.g., [*glp-1(ar202)*]), this is due to increased GLP-1 activity that prevents proximal germ cells from exiting mitosis even after moving a sufficient distance from the DTC. Because *pro-1* mutants have reduced mitotic proliferation during early larval development, gonads fail to extend at the normal rate. This results in the prolonged exposure of proximal germ cells to the DTC pro-mitotic signal. Similarly, *hlh-12* mutants, which are defective at DTC migration, also result in continuous ligand exposure. At later developmental stages, these nondifferentiated proximal germ cells are susceptible to stimulation by DSL ligands expressed from the sheath, leading to sustained mitosis and the formation of tumors. This figure is modeled after Killian and Hubbard, 2005.

sustained mitotic proliferation and tumorigenesis.

More recently, several genes affecting ribosome biogenesis have been identified in screens for mutants that develop proximal tumors. Among these are *pro1–3*, which encode orthologs of yeast proteins that regulate ribosome activity at the level of rRNA processing and nucleolar transport (Killian and Hubbard, 2004; Voutev et al., 2006). Furthermore, PRO-1 is specifically required within the sheath cell lineage to inhibit the formation of germline tumors (Killian and Hubbard, 2004). These results indicate that gross disruption of normal metabolic processes within sheath cells can lead to nonautonomous defects in the proximal germline. This conclusion is further supported by the finding that ablation of Sh2–Sh5 can fully revert germline tumorigenesis in *pro-1* mutants (Killian and Hubbard, 2005) and that partial suppression of *pro-1* tumors can also be achieved through secondary mutations that increase pre-rRNA levels (Voutev et al., 2006). Of interest, one of the mutations found to suppress *pro-1* tumors is *lin-35*/Rb, which functions as a negative regulator of POL I rRNA transcription (Hannan et al., 2000; Pelletier et al., 2000; Voutev et al., 2006). In other mutant backgrounds, loss of LIN-35 activity can, however, strongly enhance proximal tumor formation, thus underscoring the influence of genetic context on phenotypic outcome (Fay et al., 2002; Bender et al., 2007).

Given the wide spectrum of germline and somatic genes that have been implicated in proximal tumor formation, one might expect there to be little commonality in the underlying mechanisms of tumorigenesis. This is not, however, the case: through a series of detailed studies, Hubbard and colleagues have successfully uncovered a unifying theme to account for the large majority of proximal tumor phenotypes. Key among their observations is that mutations in either *pro-1*, a somatic factor, or *glp-1(ar202gf)*, a germline intrinsic factor, result in similar temporal delays in the onset of initial meiosis (i.e., the time at which germ cells first exit the mitotic cycle and begin to differentiate; Pepper et al., 2003b; Killian and Hubbard, 2004). This delay leads to a discordance between the developmental ages of the proximal germline and the surrounding somatic gonad (Sh2–Sh5; Fig. 6). According to the model, these developmentally retarded germ cells are then exposed to signals emanating from the maturing proximal sheath, thereby maintaining them in a nondifferentiated mitotic state. This model is supported by results showing that ablation of Sh2–Sh5 can variably suppress proximal tumor formation in *glp-1(ar202gf)*, *puf-8*, and *pro-1* mutants but not in *gld-1* mutants, which are not associated with a delay in the onset of meiosis (Killian and Hubbard, 2005). Also consistent with this model, the induction of synthetic proximal tumors in various compound mutants of *lin-35* (e.g., *lin-35; spr-1, lin-12(RNAi)*) correlates tightly with late-onset meiosis in these germlines (Bender et al., 2007).

Most recently, Hubbard and colleagues have demonstrated a direct role for DSL family ligands in the induction of proximal tumors by the sheath (McGovern et al., 2009). Evidence includes the finding that RNAi or mutations affecting the DSL-encoding genes *apx-1*, *arg-2*, and *dsl-5* can variably suppress tumor formation in *pro-1* and *glp-1(ar202gf)* mutants, as well as in *hlh-12* mutants, which exhibit impaired DTC migration (Tamai and Nishiwaki, 2007; McGovern et al., 2009). This is consistent with previous findings showing that proximal proliferation in *pro-1* mutants requires functional GLP-1 (Killian and Hubbard, 2004). Moreover, simultaneous repression of both *apx-1* and *arg-1* completely suppressed tumor formation in *pro-1* mutants, indicating that the combined activities of *apx-1* and *arg-1* can largely account for the mitosis-promoting activity of the proximal sheath (McGovern et al., 2009). In contrast, inhibition of DSL ligands did not suppress tumor formation in *gld-1* mutants, consistent with previous sheath cell ablation results. Finally, both *apx-1* and *arg-1* are expressed within the proximal sheath lineage. Of interest, disruption of DSL-Notch signaling in adults that harbor proximal tumors led to the differentiation of tumor cells, indicating that continuous signaling is required for tumor maintenance.

To frame their findings in broader terms, the authors invoke the concept of a "latent niche" (McGovern et al., 2009). The latent niche describes a cellular microenvironment that does not normally serve as a niche but that is nevertheless capable of sustaining the proliferation of renewal-competent cells with which it comes in contact. In the case of germline tumors, proximal sheath cells and their progenitors provide a latent niche for nondifferentiated germ cells through DSL-Notch signaling. The authors speculate that the productive seeding of metastatic cancers in humans may occur through the exploitation of latent niches. Intriguingly, tumor promotion by the latent niche would not require additional mutations to arise within either the niche or tumor cells, nor would it require the induction of potential niche cells by the primary tumor. As this proposed mechanism may allow for a greater understanding of tumor metastasis, as well as the potential for directed therapeutic strategies, follow-up work in other systems is clearly warranted.

STEMNESS AND THE MAINTENANCE OF A NONDIFFERENTIATED STATE

Parallels have long been drawn between the characteristics of tumor cells and those of normal stem cells, including their mutual ability to evade terminal differentiation. Although exceptions have been reported, conventional wisdom holds that malignant cells are at most partially differentiated, either because tumor initiation must necessarily precede terminal differentiation, or because the transformation process itself can lead to tumor cell de-differentiation (Daley, 2008). Moreover, patient prognosis, as predicted by histological features, often correlates with the degree of tumor cell differentiation, such that less-differentiated cancers are typically associated with a greater health risk. Several studies have also suggested that a sub-population of tumor cells, termed cancer stem cells (CSCs), comprise the critical self-renewing population of cells within a heterogeneous tumor, although this theory remains controversial (Jordan, 2004; Gupta et al., 2009; Rosen and Jordan, 2009).

The protection of germline totipotency (and other germ cell characteristics) in

C. elegans effectively begins before the first cell division with the asymmetric distribution of germline-specific factors such as P granules, macromolecular particles composed of heterogeneous proteins, and RNAs (Updike and Strome, 2009). Extensive analysis has uncovered several distinct mechanisms that are used at various times to promote survival and prevent future germ cells from undergoing programs of somatic differentiation (for reviews see Seydoux and Schedl, 2001; Shin and Mello, 2003; Strome, 2005; Updike and Strome, 2009). These include the repression of transcriptional elongation in germ cell progenitors by PIE-1, the initiation of epigenetically controlled patterns of gene expression in early germ cells by Polycomb group–related proteins, and the actions of the P granules, which are likely to function at the level of RNA metabolism and mRNA translation.

Although some of the mechanisms initiated during embryonic development are also relevant to germline functions at later stages, less is known about the specific maintenance of germ cell totipotency in adults. Intriguingly, adult germ cells in *mex-3 gld-1* double mutants—and to a lesser extent *gld-1* single mutants—undergo differentiation into a diverse array of cell types, a phenotype that closely resembles human teratomas (Ciosk et al., 2006). That this trans-differentiation process requires the initiation of meiosis is supported by the finding that germ cell differentiation in *mex-3 gld-1* mutants is blocked by the *glp-1(oz112gf)* mutation. Based on computational predictions, germline teratoma formation is likely to involve the translational de-repression of many individual or shared mRNA targets of MEX-3 and GLD-1 (Pagano et al., 2009). Several confirmed targets provide insight into the general categories of factors that are likely to be involved. These include PAL-1, a homeodomain-containing transcription factor that normally promotes muscle cell fates in the embryo and which is translationally repressed by both MEX-3 and GLD-1 (Mori et al., 1988; Draper et al., 1996; Hunter and Kenyon, 1996; Ciosk et al., 2006). Inhibition of *pal-1* largely blocks muscle cell differentiation in *mex-3; gld-1* germlines, indicating that *pal-1* is one of the critical targets for repression by MEX-1 and GLD-1 in teratomas. In addition, *cye-1*/cyclin E, which is required for progression through G1/S, is a target for translational repression by GLD-1 (Fay and Han, 2000; Biedermann et al., 2009). Furthermore, inhibition of *cye-1* by RNAi prevents germ cell trans-differentiation in *gld-1* mutants, demonstrating that re-entry into the mitotic cell cycle is also a critical step in teratoma formation (Biedermann et al., 2009). Finally, the identification of *glp-1* as a target for repression by both GLD-1 and MEX-3 suggests that the deregulation of germline intrinsic factors may also be important in germ cell trans-differentiation (Marin and Evans, 2003; Pagano et al., 2009).

STEMNESS AND IMMORTALITY

Both stem cells and cancer cells possess the capacity for long-term, if not limitless, proliferation. As the sole self-renewing stem cell population in *C. elegans* adults, the germline presents an opportunity for uncovering the mechanisms that inhibit cellular senescence and promote continuous growth and division. One approach to the study of cell immortality in *C. elegans* has been to isolate mutations that give rise to "mortal" germlines (The Mrt phenotype; reviewed by Smelick and Ahmed, 2005). Such mutants become progressively sterile over multiple generations (4–20), most likely in response to the accumulation of structural damage to chromosomes (Ahmed and Hodgkin, 2000; Smelick and Ahmed, 2005). Notably, estimates suggest that >100 independent loci may be required for the maintenance of germline immortality in *C. elegans*, and the full range of mechanisms awaits further exploration (Smelick and Ahmed, 2005).

mrt-2, the first mortal germline mutant to be cloned, encodes a checkpoint protein that is homologous to *S. pombe rad1* (Dean et al., 1998; Ahmed and Hodgkin, 2000). MRT-2 functions in the response to double-stranded DNA breaks and is also required for the faithful replication of telomeres. *mrt-2* mutants exhibit progressive telomere shortening and chromosomal fusions that are characteristic of telomerase-defective mutants in other organisms. Furthermore, loss of function of *hus-1* and *hpr-17*, which encode proteins that associate with MRT-2 family members to promote assembly of the 9-1-1 checkpoint complex, also lead to telomere erosion and progressive sterility, as do mutations that directly or indirectly interfere with telomerase activity (e.g., *trt-1* and *mrt-1*; Hofmann et al., 2002; Meier et al., 2006; Boerckel et al., 2007; Meier et al., 2009). These findings dovetail with studies of mammalian cancer cells, as well as with those of immortalized cells in culture, which are known to select for mutations that activate telomerase. Further analysis of *mrt* mutants may therefore identify novel factors required for telomere maintenance by cancer cells.

As mentioned in the preceding section, chromatin-level transcriptional regulation is critical for the preservation of germline competence. Implicated factors include MES-2/E[Z], MES-6/ESC, and MES-3, which together form a complex related to the Polycomb repressor of *Drosophila* (Holdeman et al., 1998; Korf et al., 1998; Xu et al., 2001a,b; Bender et al., 2004b). This complex blocks inappropriate gene expression in the germline by inhibiting MES-4, a histone H3 methyltransferase that promotes the active chromatin state (Kelly and Fire, 1998; Fong et al., 2002; Bender et al., 2006). Recently, another chromatin modifier, the SPR-5/LSD1 histone demethylase, has been shown to be required for germline immortality (Katz et al., 2009). Similar to *mrt-1* and *mrt-2* mutants, loss of *spr-5* leads to progressive sterility within ~20–30 generations. Unlike *mrt* mutants, *spr-5*-deficient strains do not, however, exhibit telomere shortening or other associated genomic aberrations, such as end-to-end chromosomal fusion and aneuploidy. Furthermore, loss of SPR-5 function correlates with the progressive accumulation of H3K4me2 methylation in germ cells together with an increase in the expression of genes associated with spermatogenesis. Of interest, fertility can be restored to late-generation *spr-5* mutants following a single outcross, indicating that the slow-onset epigenetic changes are nevertheless rapidly reversible. Notably, epigenetic changes are associated with many cancer types and are thought to play important roles in cancer initiation and progression (Daley, 2008; Albert and Helin, 2009; Sharma et al., 2010).

Of interest, several studies have implicated genomic stability as a requirement for germline immortality (Chin and Villeneuve, 2001; Degtyareva et al., 2002; Tijsterman et al., 2002b). One example is MRE-11, a conserved protein that is required for both DNA double-stranded break repair and meiotic crossover (Chin and Villeneuve, 2001). *mre-11* homozygous mutants become sterile after just several generations, despite that fact that meiotic recombination is not required for long-term viability (Zalevsky et al., 1999; Kelly et al., 2000). These results suggest that maintenance of genomic integrity is essential for long-term reproductive capacity. Another example of this phenomenon is the Bergerac strain, a naturally occurring isolate of *C. elegans* that contains several hundred copies of the Tc1 transposon (Emmons et al., 1983; Anderson, 1995; Bessereau, 2006). Like the previously discussed *mrt* mutants, the Bergerac strain exhibits progressive sterility when self-fertilized for multiple generations. In contrast, the Bristol isolate (N2)—the standard *C. elegans* laboratory strain—contains few copies of Tc1, and these are silenced in the germline (Eide and Anderson, 1985; Collins et al., 1987). These observations point to an apparent paradox, as immortality and genomic instability are dual characteristics of tumor cells. Thus, cancer cells may be required to develop mechanisms that maintain immortality while having highly plastic genomes.

REPRESSION OF GERMLINE TRAITS IN THE SOMA

In the preceding sections, we addressed mechanisms required for the promotion of stem cell characteristics in the *C. elegans* germline. An equally relevant line of inquiry, particularly within the context of oncogenesis, is to understand the means by which germ cell traits are normally repressed in the soma. As mentioned above, the partition of soma and germline identities begins in early embryogenesis and involves several mechanisms to ensure the proper asymmetric distribution of germline and somatic cell fate determinants (Gonczy and Rose, 2005). In addition, two pathways have been implicated in the repression of germline gene expression in the somatic tissues of larvae and adults. Notably, one mechanism involves the LIN-35/Rb tumor suppressor; *lin-35* mutants show somatic expression of many germline-specific genes and are systemically RNAi-hypersensitive, a trait associated with germ cells (Wang et al., 2005; Kirienko and Fay, 2007). Correspondingly, components of the nucleosome remodeling and histone deacetylase (NURD) complex, including LET-418/Mi2, HDA-1/HDAC-1, and an associated Zn-finger protein, MEP-1, also exhibit a partial soma-to-germline transformation (Unhavaithaya et al., 2002). Studies in *C. elegans* and other systems have shown that LIN-35/Rb and NURD, together with several additional factors, form a higher-order transcriptional regulatory complex termed DRM/dREAM (reviewed in Fay and Yochem, 2007; van den Heuvel and Dyson, 2008). Moreover, inactivation of several additional DRM-associated components also leads to germline gene expression in the soma (Unhavaithaya et al., 2002; Wang et al., 2005). Of interest, the ectopic expression of germ cell factors in these mutants appears to require the activity of MES-1–4; MRG-1, a chromatin-associated protein; and ISW-1, a chromatin remodeling ATPase (Unhavaithaya et al., 2002; Wang et al., 2005; Cui et al., 2006b; Takasaki et al., 2007). One model to account for these effects is that components of the *C. elegans* DRM and NURD complexes normally antagonize the activities of MES-1–4 and MRG-1 in the soma to prevent the adoption of chromatin patterning states that are permissive for germline gene expression. During embryogenesis, however, PIE-1 physically associates with members of the MEP-1/NURD complex in primordial germ cells to inhibit their activity (Unhavaithaya et al., 2002).

Most recently, it has been shown that somatic cells in long-lived *daf-2*/IGF mutants up-regulate the expression of germline-specific genes (Curran et al., 2009). This effect appears to be due to increased activity of DAF-16/FOXO, which may in some cases act directly on the promoters of germ fate determinants such as PIE-1. Of interest, inhibition of up-regulated germline targets by RNAi can partially revert *daf-2* longevity, suggesting that the acquisition of germ cell traits in the soma may extend lifespan. Consistent with this, inhibition of *isw-1* and *mes-4*, which are required for germline gene misexpression in DRM mutants (Unhavaithaya et al., 2002; Wang et al., 2005; Cui et al., 2006b), also attenuates life-span extension in *daf-2* mutants (Curran et al., 2009). In addition, inactivation of *cct-4* and *cct-6*, which encode components of the cytosolic chaperonin complex, also leads to increased longevity and a partial soma-to-germline transformation (Curran et al., 2009). Nevertheless, the generality of this correlation is currently unclear, as germline genes are not misexpressed in other longevity mutants (e.g., *clk-1* and *eat-2*) and life-span extension is not a general property of mutants that exhibit soma-to-germline transformations (Curran et al., 2009).

LIFE AND DEATH IN THE GERMLINE

The failure to eliminate cells that have accrued genotoxic damage carries with it the risk of allowing malignant transformation to proceed unchecked. Moreover, a hallmark of cancer cells is their ability to evade programmed cell death in response to anti-growth signals, internal checkpoints, and environmentally induced damage or stress. Notably, the phenomenon of programmed cell death was first discovered more than 30 years ago in *C. elegans* as a curious feature of the hard-wired developmental lineage of the soma (Sulston, 1976; Sulston et al., 1983). Follow-up studies led to the identification of many conserved components of the cell death pathway, and the direct roles of their mammalian counterparts in cancer genesis have subsequently been well documented (e.g., Hedgecock et al., 1983; Ellis and Horvitz, 1986; Vaux et al., 1992; reviewed in Reed, 1998; Conradt, 2009).

Somewhat surprisingly, the identification of programmed cell death in the *C. elegans* germline is a relatively recent discovery, following the pioneering work of Hengartner and colleagues (Gumienny et al., 1999l reviewed in Gartner et al., 2008). Two distinct categories of cell death occur in the germline. One, termed "physiological" apoptosis, is part of the normal process that promotes oocyte growth. In contrast to its requirement in the *Drosophila* germline, cell death is not essential for fertility in the *C. elegans* germline (Ellis

and Horvitz, 1986; McCall and Steller, 1998), although apoptosis-defective mutants have reduced fecundity, which correlates with abnormal oocyte production in late adulthood (Gumienny et al., 1999; Andux and Ellis, 2008). The second type, termed "stress-induced" cell death, occurs in response to DNA damage as well as other types of environmental challenges (Gartner et al., 2000, 2008). Moreover, as the only tissue in *C. elegans* to undergo apoptosis in response to genotoxic stress, the germline presents a unique opportunity to study mechanisms that are relevant to the elimination of precancerous and cancerous cells.

Approximately 30 genes have been shown to be required for the induction of germline apoptosis in response to genotoxic stress (Gartner et al., 2008). In addition to core components of the apoptosis pathway, many proteins with established roles in the detection and repair of DNA damage are required for the initiation of germline apoptosis including MRT-2, HUS-1, HPR-17, and CLK-2, which (as described above) have additional roles in germline maintenance (Gartner et al., 2000; Hofmann et al., 2002; Garcia-Muse and Boulton, 2005; Boerckel et al., 2007). A critical downstream target of these checkpoint genes is CEP-1, the sole *C. elegans* ortholog of the mammalian p53/p63/p73 tumor suppressor gene family. CEP-1 is essential for germline apoptosis in response to DNA damage induced by UV light and ionizing radiation as well as meiotic defects that lead to the persistence of double-stranded breaks (Derry et al., 2001, 2007; Schumacher et al., 2001; Garcia-Muse and Boulton, 2005). This latter category includes mutations in the BRCA2 tumor suppressor ortholog, *brc-2*, which is required for the localization of the RAD-51 recombinase to chromosomal break sites (Gartner et al., 2000; Alpi et al., 2003; Martin et al., 2005). Of interest, despite a central role in damage-induced apoptosis, *cep-1* mutants do not show a high incidence in the rate of spontaneous mutations (the Mutator phenotype), indicating that under normal conditions, induction of the apoptotic pathway by CEP-1 plays at most a limited role in the maintenance of genomic integrity [also see below; (Harris et al., 2006)].

In response to signals from upstream DNA-damage sensors, CEP-1 triggers expression of the BH domain-only proteins CED-13 and EGL-1, which physically interact with CED-9/Bcl-2 to promote activation of the CED-3 and CED-4 caspases (Hofmann et al., 2002; Schumacher et al., 2005b; Greiss et al., 2008b; Conradt, 2009). Transcriptome profiling studies also suggest that CEP-1 may regulate several additional targets in response to DNA damage, although a general lack of functional validation along with some significant discrepancies between the two published studies suggest that further analysis will be required to resolve this issue (Derry et al., 2007; Greiss et al., 2008b). Additionally, several factors have been implicated as upstream regulators of CEP-1 activity or expression. CEP-1 pro-apoptotic activity in response to ionizing radiation is antagonized by the ABL-1 kinase, an ortholog of the mammalian c-Abl proto-oncogene (Deng et al., 2004). In contrast, mammalian C-Abl is primarily thought to enhance p53 activity through inhibition of the p53 interactor Mdm2, which does not appear to have an ortholog in *C. elegans* (Levav-Cohen et al., 2005). The AKT/PKB protein kinase family member AKT-1 also inhibits apoptosis, possibly through the direct modification of CEP-1 (Quevedo et al., 2007). In addition, GLD-1 negatively regulates *cep-1* translation through direct interactions with the *cep-1* 3′UTR (Schumacher et al., 2005a). A Skp1/cullin/F-box ubiquitin-ligase complex composed of SKR-1, CUL-1, and FSN-1, has also been implicated in the negative regulation of CEP-1-mediated transcription (Gao et al., 2008). Subsequently, the mammalian FSN-1 ortholog, FBXO45, has been shown to target p73 for degradation, and depletion of FBXO45 activity leads to increased apoptosis (Peschiaroli et al., 2009). Another conserved regulator of apoptosis, APE-1/iASPP, associates with CEP-1/p53 in *C. elegans* and mammals to block its activation (Bergamaschi et al., 2003). As a result, RNAi of *ape-1* in *C. elegans* leads to increased germline apoptosis at levels similar to that observed following DNA damage, that is dependent on CEP-1 activity. Moreover, up-regulation of iASPP is detected in breast carcinomas, and overexpression of iASPP in cooperation with Ras or one of several viral oncoproteins leads to transformation of mammalian cells in culture (Bergamaschi et al., 2003). Recently, PRMT-5, an arginine methyltransferase, has been shown to form a complex with CEP-1 and its conserved transcriptional co-activator, the CBP-1/p300 histone acetyl transferase (Yang et al., 2009). Methylation of CBP-1 by PRMT-1 leads to reduced CEP-1 transcriptional activity and the inhibition of DNA damage-induced apoptosis.

Several pathways also act in parallel to CEP-1 to promote stress-induced germline cell death. SIR-2.1, a *C. elegans* sirtuin family member, is required for the induction of germline apoptosis in response to ionizing radiation and appears to act independently of the CEP-1 pathway (Greiss et al., 2008a). SIR-2.1 translocates from the nucleus to the cytoplasm in cells undergoing apoptosis, where it colocalizes with CED-4, thereby suggesting a possible novel mechanism by which caspase activation may be achieved. Another recently demonstrated means of controlling germline apoptosis in *C. elegans* involves the actions of membrane-associated lipids. Genetic inhibition of sphingolipid metabolism strongly reduces DNA damage-induced apoptosis, which can be restored by providing exogenously synthesized ceramide, a common structural unit in all sphingolipids. Evidence supports a model whereby mitochondrial-localized ceramide facilitates EGL-1-mediated displacement of CED-4 from its inhibitor, CED-9/Bcl-2, thereby activating the caspase cascade. Notably, ceramide has been implicated in controlling several pathological responses in mammals, including cell death, but direct evidence for a mechanism was previously lacking (Gulbins and Li, 2006). *C. elegans* ING-3, a member of the inhibitor of cell growth family of proteins, has also recently been demonstrated to promote germline apoptosis in response to stress (Luo et al., 2009), consistent with previous reports in mammals (Helbing et al., 1997; Nagashima et al., 2003). Based on genetic analysis, ING-3 is likely to act in the same pathway as p53, possibly at the level of chromatin-mediated transcriptional activation. Finally, studies have demonstrated a positive role for LIN-35/Rb and several associated E2F factors in both physiological and stress-induced germline apoptosis as well as in programmed cell death in the soma (Reddien et al., 2007; Schertel and

Conradt, 2007). In the case of physiological germ cell death, LIN-35 may function by inhibiting the expression of CED-9, whereas its role in irradiation-induced apoptotis is unknown but has been suggested to be integrated downstream of or in parallel to EGL-1 and CEP-1 (Schertel and Conradt, 2007).

GENOMIC INSTABILITY

The realization that malignant human cancers require mutations in at least four to six discrete loci led to obvious questions about how multiple mutations could accumulate within a single cell despite the presence of robust DNA repair mechanisms. Several models have been proposed to account for this observation. One is the Mutator Phenotype hypothesis, postulated by Loeb and colleagues, which suggests that the earliest mutations in cancer genesis take place in genes that perform replication and repair functions (Loeb et al., 1974). A second hypothesis, forwarded by Nowell, is that early tumorigenic mutations confer a survival or replicative advantage, which promotes the formation of a rapidly expanding population in which additional mutations can accumulate (Nowell, 1976). Notably, there is support for both hypotheses, suggesting that oncogenesis may proceed through multiple routes (Fearon and Vogelstein, 1990; Eshleman et al., 1995; Perucho, 1996; Tomlinson et al., 1996; Tomlinson and Bodmer, 1999; Chow and Rubin, 2000; Beckman and Loeb, 2006). Regardless, the protection of genomic integrity is a crucial mechanism by which normal cells prevent transmissible changes that lead to transformation.

Aneuploidy is a frequently observed chromosomal aberration in tumors and is thought to occur primarily from errors during mitotic chromosomal pairing and disjunction (Mitelman, 1994; Rew, 1994; Tucker and Preston, 1996). Of interest, the normal process of generating spontaneous males in *C. elegans* populations takes advantage of low-frequency mistakes that arise during meiosis in hermaphrodites. Specifically, males, which are X/O, are generated when one of the two gametes used for fertilization (either sperm or egg), fails to receive a copy of the X chromosome. In contrast, hermaphrodites, which are X/X, are generated in the absence of such errors. By screening for mutants that produce a high incidence of males (the Him phenotype), Brenner and colleagues initially identified mutations in ten loci that directly or indirectly led to a high frequency of X chromosome nondisjunction (Hodgkin et al., 1979). Follow-up work from several groups has identified more than twenty genes that confer this phenotype (Takanami et al., 1998; Aoki et al., 2000; Chin and Villeneuve, 2001; Howe et al., 2001; MacQueen and Villeneuve, 2001; Boulton et al., 2004; Wicky et al., 2004; Phillips et al., 2005; Phillips and Dernburg, 2006). Notably, chromosomal disjunction defects in *him* mutants are generally not specific to the X chromosome but also affect the five autosomes, leading to variable lethality associated with the production of aneuploid progeny (Hodgkin et al., 1979). Examples include HIM-6 (Zetka and Rose, 1995; Wicky et al., 2004), a RecQ family member that is orthologous to the cancer-associated Bloom syndrome helicase; HIM-3, which is necessary for the formation of meiotic synapses and chiasmata (Zetka et al., 1999); and HIM-15/RFS-1/Rad51D, which is responsible for genome stability and telomere maintenance (Yanowitz, 2008). Furthermore, mutations in several genes originally identified in DNA damage response pathways also confer a Him phenotype, including *hus-1*, *cep-1*/p53, *brc-1*/BRCA, *brd-1*/BARD1, and *mre-11*/Mre11 (Chin and Villeneuve, 2001; Derry et al., 2001; Boulton et al., 2004; Gartner et al., 2008).

A heightened susceptibility to DNA damage induced by either environmental insult or endogenous cell cycle processes is also associated with certain familial cancers. One example of the former is xeroderma pigmentosum, which results from mutations in loci that are required for DNA repair following UV exposure (Bergoglio and Magnaldo, 2006; Beck et al., 2008; Gratchev, 2008). Examples of the latter include hereditary nonpolyposis colorectal cancer and BRCA1/2-dependent breast cancers, which correlate with defects in carrying out DNA repair following standard DNA replication and recombination, respectively (Plotz et al., 2006; Abdel-Rahman and Peltomaki, 2008; Powell and Kachnic, 2008; Venkitaraman, 2009). As such, maintaining DNA integrity is a vital and ancient function of all cells, and the genes involved in this process tend to be phylogenetically well conserved. Here again, *C. elegans* has proven instrumental in elucidating the functions of several pathway members. For example, *C. elegans* DOG-1, an ortholog of the cancer-associated helicase BACH1, was first demonstrated to maintain homopolymeric CG tracts in the genome by studies in *C. elegans* (Cheung et al., 2002). Similarly, analysis of *C. elegans* RTEL-1 and its yeast ortholog, Srs2p, helped define the role of human RTEL1 in promoting genomic stability through the inhibition of inappropriate recombination (Lawrence and Christensen, 1979; Barber et al., 2008). In addition, *C. elegans* proteins involved in the repair of double-stranded breaks generated during meiotic recombination have provided an additional avenue for studying the role of genes that function to repair double-stranded breaks in cancer. For example, overexpression of the RAD-51/Rad51 recombinase confers hyperresistance to X-ray irradiation in the gonad (Takanami et al., 2000). This phenotype correlates with the overexpression of Rad51 observed in many cancers, which is associated with an increased resistance of tumor cells to radiation and chemotherapy (Klein, 2008).

Another critical mechanism for maintaining genome stability is the limitation of genomic replication to once per cell division. This restriction is controlled by CDT-1/Cdt1, which licenses a single round of DNA replication by promoting binding of the prereplicative complex (pRC) to origins of replication (Blow and Hodgson, 2002). One of the major players in this process, the conserved ubiquitin-ligase component CUL-4/Cul4, was first identified in *C. elegans*. Inhibition of CUL-4 leads to larval arrest with corresponding increases in DNA ploidy (up to 100C) that result from the apparent re-firing of replication origins (Zhong et al., 2003). Polyploidization in *cul-4(RNAi)* animals is repressed by knocking down levels of CDT-1 (Zhong et al., 2003). Furthermore, in conjunction with DDB-1/DDB1, a conserved protein implicated in DNA repair, CUL-4 targets CDT-1 for ubiquitin-mediated degradation, thereby preventing CDT-1 from re-initiating replication (Zhong et al., 2003). CUL-4 is also required for

the cascade that leads to phosphorylation of the pRC component CDC-6/Cdc6, leading to its export from the nucleus (Kim et al., 2007). This function, together with the degradation of CDT-1, prevents re-replication of the genome and maintains normal ploidy (Kim et al., 2007). Notably, human Cul4 has subsequently been demonstrated to play a similar role in the degradation of Cdt1 following DNA replication (Nishitani et al., 2006) and in response to DNA damage (Higa et al., 2003; Huang and Stern, 2004). In contrast to *C. elegans*, however, the degradation of Cdt1 in humans appears to involve two distinct ubiquitin-ligase complexes, Cul4-DDB1 and SCF^{Skp2}, the latter of which uses Cul1 (Chu and Chang, 1988; Keeney et al., 1993; Li et al., 2003; Kondo et al., 2004; Nishitani et al., 2006; Senga et al., 2006). The role of SCF^{Skp2} in this process may be unique to humans, as it is apparently not conserved in *C. elegans* or mice (Nakayama et al., 2004; Kim and Kipreos, 2007a,b).

Another means of introducing genetic instability is the mobilization of endogenous transposons. All known natural isolates of *C. elegans* possess somatically active Tc1 transposons, which are silenced in the germline of some strains, such as the reference Bristol isolate, N2 (Emmons et al., 1983; Emmons and Yesner, 1984). As active transposons could easily lead to excess mutations, mechanisms to silence transposition should in theory be genetically favored. Indeed, multiple loci repress germline transposase activity (Collins et al., 1987; Mori et al., 1988; Bessereau, 2006). Notably, mutations in several of these genes including *mut-2*, *mut-7*/RNaseD, *mut-14*, *mut-16*, *rde-2*, and *rde-3* also strongly reduce RNAi silencing, suggesting that the RNAi pathway may normally function to ensure transposon silencing (Ketting et al., 1999; Tabara et al., 1999; Tijsterman et al., 2002a; Vastenhouw et al., 2003). It is also worth noting that several of these genes, including *mut-2*, *mut-7*/RNaseD, *rde-2*, and *rde-3* also exhibit a Him phenotype when mutated, suggesting a role for either RNAi or transpositional silencing in normal chromosomal disjunction (Collins et al., 1987; Collins and Anderson, 1994; Ketting et al., 1999; Tabara et al., 1999). This role for RNAi appears to be evolutionarily conserved in taxa as diverse as fruit flies, mice, humans, and plants. For example, transposon silencing in *Drosophila* has been linked to an RNAi-like process known as cosuppression, and plant viruses have developed mechanisms to interfere with cosuppression, which may serve as a primitive form of innate immunity (Anandalakshmi et al., 1998; Beclin et al., 1998; Kasschau and Carrington, 1998; Jensen et al., 1999). Recent evidence suggests that these mechanisms are also at work in mammals, where RNAi-mediated silencing in humans and mice prevents amplification of LINE transposable elements (Watanabe et al., 2006; Yang and Kazazian, 2006). Although it is unclear whether RNAi initially evolved to mediate anti-viral resistance or to restrict transposable element activity, the role of RNAi in maintaining genomic stability is a widespread phenomenon.

WORM MODELS FOR METASTASIS

Nearly 90% of cancer-associated mortality is due to the metastasis of primary cancer cells to secondary sites (Sporn, 1996; Hanahan and Weinberg, 2000). Studies in a variety of model organisms have provided significant insight into the mechanisms underlying tumor metastasis. For example, normal developmental events, including cell migration and morphogenesis, closely parallel events that occur during tumor invasion. In addition, other physiological processes, such as angiogenesis, wound healing, and the immune response, also mirror certain aspects of metastatic progression (Pepper, 1997; Affolter et al., 2003; Yadav et al., 2003). Consistent with this, many genes and pathways that are responsible for conferring invasive and migratory abilities to normal cells have also been implicated in cancer cell metastasis (Kunwar and Lehmann, 2003; Balkwill, 2004; Wang et al., 2004; Yang et al., 2004). Recent advances in the understanding of molecular events that control physiological cell migrations and organogenesis in *C. elegans* have made the worm an attractive system for studying processes related to metastasis. In addition, the existence of *C. elegans* orthologs of many mammalian genes implicated in tumor metastasis suggests that studies in worms will be directly relevant to the understanding of metastasis in higher organisms.

BASICS OF METASTASIS

Cancer metastasis is traditionally divided into several distinct steps (Brodland and Zitelli, 1992; Weinberg, 2008). Initially, a primary cancer cell undergoes intravasation, whereby it alters its shape and adhesion properties and pinches off from the main tumor. Next, traversing local tissues and penetrating basement membranes, it finds its way into the blood or lymphatic systems. Transported passively by the circulatory system to distant sites in the body, the cancer cell undergoes extravasation, whereby it exits the circulation and invades the parenchyma of a new tissue. Successful colonization by the tumor cell within its new location may require further adaptive responses, such as changes to the new environment, which may be mediated by the tumor cell itself (Chambers et al., 2002; Condeelis and Segall, 2003; Fidler, 2003).

One primary example of the close connection between cancer metastasis and normal developmental events is illustrated by studies of epithelial cell migrations during embryogenesis. During this process, epithelial cells that are normally constrained by their attachment to a basement membrane undergo a transition into a mesenchymal-like state (epithelial-to-mesenchymal transition; EMT) before initiating movements. During EMT, the epithelial cells lose many of their characteristic markers including E-cadherin, claudins, desmoplakin, smooth muscle actin, and cytokeratins and instead acquire mesenchymal traits such as expression of N-cadherin, vimentin, and fibronectins (Johnson et al., 1991; Kaiser et al., 1996; Christofori and Semb, 1999). E-cadherin, a ubiquitously expressed cell adhesion molecule, is required for the maintenance of epithelial integrity through homophilic (E-cadherin–E-cadherin) interactions. Notably, loss of E-cadherin in experimental animals confers invasive abilities to epithelial cells, and reduced E-cadherin expression is widely observed in many metastatic cancers (Gotzmann et al., 2002; Thiery, 2002). Additionally, several embryonic transcription factors that induce EMT during embryogenesis

are aberrantly expressed in a variety of human cancer cells, further underscoring the relevance of EMT to cancer pathogenesis (Weinberg, 2008).

Another key property of metastatic cells that has correlates in normal development is the ability to penetrate basement membranes and the surrounding extracellular matrix (ECM). Cancer cells cross the blood or lymphatic basement membranes during intravasation and extravasation. Breaching of basement membranes by migrating cells is also a common occurrence during normal development. Examples include vascular basement membrane invasion by capillary sprouts during the formation of new blood vessels, transit of leukocytes through the perivascular basement membrane at the time of wound healing, and penetration of the endometrial basement membrane by primate trophoblast cells during placental formation (Paku and Paweletz, 1991; Duc-Goiran et al., 1999; Yadav et al., 2003). Additionally, the stromal extracellular matrix undergoes significant remodeling throughout normal development as well as during tumor metastasis. This leads to the activation of integrin signaling cascades that induce altered cell adhesion properties and stimulate the release of cytokines and other chemotactic factors, which promote free cell movement (Leavesley et al., 1993; Abedi and Zachary, 1995; Kinashi and Springer, 1995). Consistent with this, alterations in the expression and activities of integrins occur in metastatic cancers (Hood and Cheresh, 2002; Felding-Habermann, 2003). Matrix metalloproteases (MMPs) also play a crucial role in the remodeling of the extracellular matrix and act on cell surface molecules to alter adhesion properties. In vitro studies using mammalian cell lines show that human MMPs strongly stimulate the invasive capabilities of cancer cells (Egeblad and Werb, 2002). Consistent with this, MMPs are upregulated in a variety of tumors (Arribas et al., 2006).

Although significant advances have been made in recent years toward the understanding of metastatic progression, the underlying mechanisms responsible for EMT, basement membrane invasion, and extracellular matrix remodeling are incompletely understood. This is in part due to difficulties associated with visualizing these events in living animals as well as inherent limitations in the ability to recapitulate these events in vitro. In addition, the presence of functionally redundant paralogs for several genes implicated in mammalian metastasis further complicates this analysis. As discussed below, studies in *C. elegans* are beginning to provide novel insights into how basic processes connected to tumor metastasis are regulated during normal development.

ANCHOR CELL INVASION: A MODEL FOR TUMOR CELL INVASION

In *C. elegans* hermaphrodites, a critical step in the formation of a functional reproductive system involves the establishment of a connection between the vulva and the uterus. Failure to do so leads to reduced fecundity, as this connection is required for both egg laying and mating. During early development, the uterine and the vulval cells develop independently and are well separated by distinct basement membranes. Beginning at the L3 larval stage, the ventral nerve cord (VNC) secretes UNC-6/netrin, which diffuses dorsally toward the anchor cell (AC; Fig. 7). The UNC-6 signal is necessary to direct localization of the UNC-40/netrin receptor to the basal surface of the AC facing the basement membrane (Ziel et al., 2009). In addition, the activity of the integrin heterodimer INA-1–PAT-1 is also required within the AC for the correct localization of UNC-40 (Hagedorn et al., 2009). Polarization of the AC by UNC-6 also leads to the redistribution of filamentous actin (F-actin); phosphotidylinositiol 4,5-bisphosphate; and the cytoskeletal regulators CED-10/Rac1, MIG-2/Rho, and UNC-34, which is an Ena/VASP homolog, to the basal side of the AC, leading to the creation of an invasive membrane domain. Several hours after stimulation of the AC by UNC-6, an unidentified diffusible cue from the proximally located subset of vulval cells, termed primary vulval cells, causes the AC to send out protrusions to breach the basement membrane and fuse with the vulval cells. Several lines of evidence demonstrate that whereas the UNC-6 signal from the VNC prepares the AC for invasion, the signal from the primary vulval cells specifically controls the timing and position of this invasion (Sherwood and Sternberg, 2003; Ziel et al., 2009). Recently, VRK-1, a vaccinia-related kinase, has been proposed to regulate the vulval cue, as loss of VRK-1 activity leads to AC invasion defects that phenocopy ablation of the vulval cells. Moreover, expression of VRK-1 specifically in vulval cells rescues AC invasion defects (Klerkx et al., 2009).

Notably, many of the molecular players identified in AC invasion have also been implicated in mammalian tumor metastasis. For example, pancreatic tumors and cell lines express elevated levels of the Rac1 GTPase (Crnogorac-Jurcevic et al., 2001). Furthermore, Rac1 inhibits the assembly of the E-cadherin/catenin complex in pancreatic carcinoma cells, leading to reduced cell–cell adhesion and enhanced migration through an extracellular matrix (Hage et al., 2009). In fibroblasts and keratocytes, Ena/VASP family proteins control the morphology of membrane protrusions such as filopodia and lamellipodia and influence cell motility by regulating the assembly of the actin-filament network (Bear et al., 2002; Lacayo et al., 2007). Consistent with the localization of UNC-34 and CED-10 to the invading membrane of the AC, the human ortholog of Ena/VASP, Mena, interacts and colocalizes with Rac1 at the lamellipodia of human glioblastoma cells (Higashi et al., 2009). In humans, VRK1 has been postulated to function in cell cycle regulation and has been shown to phosphorylate and stabilize p53, although a connection to tumor metastasis is currently lacking (Lopez-Borges and Lazo, 2000; Santos et al., 2006). Lastly, primary breast cancers show elevated levels of netrins specifically in tumors with metastatic potential, and reducing netrin-1 in vivo leads to decreased metastasis in syngenic mouse models (Fitamant et al., 2008).

Invasion of the basement membrane by the AC is also severely compromised in animals carrying a mutation in *fos-1*, the *C. elegans* ortholog of the FOS proto-oncogene (Sherwood et al., 2005). Although the absence of the FOS-1A isoform does not block the ability of the AC to respond to diffusible cues from the VNC and primary vulval cells to produce a mesenchymal-like protrusion at the basal surface, invasion through

the gonadal basement membrane is strongly impaired. Consistent with this finding, the AC shows elevated levels of FOS-1A preceding the induction of the mesenchymal-like transition and polarization events (Sherwood et al., 2005). Fos proteins are bZIP transcription factors that partner with other bZIP proteins including c-jun to promote transcriptional activation (Chinenov and Kerppola, 2001). Several metastatic tumors such as the squamous cell lung carcinoma and breast and prostate cancers show high expression of various Fos protein family members (Tsuchiya et al., 1993; Serewko et al., 2002; Milde-Langosch et al., 2004). Moreover, ectopic expression of Fos family proteins in cell lines leads to aggressive invasive behavior suggesting a role for this family of proteins in metastasis (Reichmann et al., 1992; Volm et al., 1993; Aoyagi et al., 1998; Zajchowski et al., 2001). Additionally, induction of the *c-fos* oncogene in a mouse mammary cell line induces EMT and causes down-regulation of E-cadherin expression (Eger et al., 2000). Taken together, these findings indicate that Fos proteins have a phylogenetically conserved role in promoting invasive cell behavior, which in the context of oncogenesis can lead to metastasis.

In the AC, *C. elegans* FOS-1A directly activates the transcription of three genes of diverse function: ZMP-1, an MMP, CDH-3, a protocadherin, and HIM-4/hemicentin, a fibulin family extracellular matrix protein. Although ACs of *fos-1* mutants fail to breach the basement membrane, mutations in the direct targets of FOS-1A show only slight delays in the timing of AC invasion. This finding suggests that basement membrane remodeling requires the combined actions of multiple semi-redundant FOS-1A targets or that additional critical targets of FOS-1A remain to be identified (Sherwood, 2006). Though FOS-1A is required for the expression of hemicentin, proper secretion and assembly of this extracellular matrix protein on the invasive side of the AC is controlled by the INA-1–PAT-3 integrin heterodimer (Hagedorn et al., 2009). Regulation of hemicentin accumulation by *C. elegans* integrins is analogous to the regulation of fibronectin deposition, another extracellular matrix protein, by vertebrate integrins. Of interest, members of the fibronectin family of proteins are also overexpressed during the metastasis of human adenocarcinomas (Ramaswamy et al., 2003).

Unlike epithelial cells that loose all their tight junctions while undergoing EMT, the AC remains polarized and stationary. Although netrin and integrin signaling causes major rearrangements at the basal surface, the apical membrane of the AC remains attached to the neighboring uterine cells and retains its epithelial characteristics as indicated by the continued expression of adhesion proteins. The polarized nature of the invading AC is reminiscent of several forms of carcinomas that metastasize en masse, in which invading tumor cells remain attached to one another while simultaneously sending out protrusions. Further analysis of both the cell behaviors and molecular pathways involved in AC invasion are likely to advance our understanding of parallel processes that transpire during tumor metastasis.

DTC MIGRATION: A MODEL FOR THE ROLE OF PROTEASES AND TISSUE MICROENVIRONMENT IN METASTASIS

Although tumor progression is understood to be a multistep process that is driven by genetic changes within the cancer cells, each of these steps is influenced to a great extent by the surrounding microenvironment (Joyce and Pollard, 2009; Mareel et al., 2009). The tumor microenvironment is a mixture of nonmalignant cell types including tumor-associated host cells, fibroblasts, macrophages, leukocytes, and bone marrow-derived progenitor cells. Contributions of the tumor microenvironment to tumor progression come in several forms. Proteases required for cancer cell migration are often released by cells within the microenvironment (as well as by the invasive cells themselves). In addition, cells within the microenvironment secrete growth factors and cytokines that serve as guidance and proliferation signals for metastasizing cells.

The migration of the *C. elegans* distal tip cell (DTC) during gonad development has long been considered an in vivo model for the role of proteases and tissue microenvironments in cell migration (Blelloch and Kimble, 1999; Moerman, 1999; Arribas et al., 2006). The *C. elegans* hermaphrodite gonad consists of two U-shaped arms that connect to the uterus and vulva on the ventral side (Fig. 8). The shape of the gonad is achieved by a tri-phasic migration of the DTCs during larval development. The DTCs are generated in the first larval stage and are positioned adjacently in the ventral mid-section of the body. At the L2 larval stage, the two DTCs initiate migrations in opposite directions along the anterior–posterior axis using the basement membrane of the ventral body wall muscles as a substratum (phase 1). During phase 2, which occurs around the L3 larval stage, the DTCs halt their migration along the ventral side, reorient, and migrate across the lateral epidermal basement membrane toward the dorsal body wall muscles. On reaching the dorsal side, the DTCs once again reorient and migrate toward each other along the dorsal muscle cells thus completing the third phase of the migratory process (Kimble and White, 1981).

Genetic analyses of mutants with DTC migratory defects identified *gon-1* and *mig-17* as essential for normal gonad morphology (Blelloch and Kimble, 1999; Nishiwaki, 1999). GON-1 is a member of the ADAMTS (A disintegrin and metalloprotease with thrombospondin motifs) family of secreted metalloproteases and is expressed at high levels within both migrating DTCs and the adjacent muscle tissues. ADAMTS proteins are thought to remodel the extracellular microenvironment by breaking down the matrix components, which in turn facilitates cellular movement. The absence of GON-1 expression before or after the completion of DTC migration suggests that GON-1 is specifically required during the migratory process. Transgenic strains that express GON-1 specifically in the DTC are able to form an elongated gonad, indicating that expression of GON-1 in the DTC is sufficient for migration. In contrast, strains expressing GON-1 in muscle tissue only are defective for DTC migration. Although expression of GON-1 in muscle tissue is not required for DTC migration, GON-1 muscle expression may promote the development of normal gonad morphology. In humans, ADAMTS-9 and ADAMTS-20 were identified as GON-1 orthologs

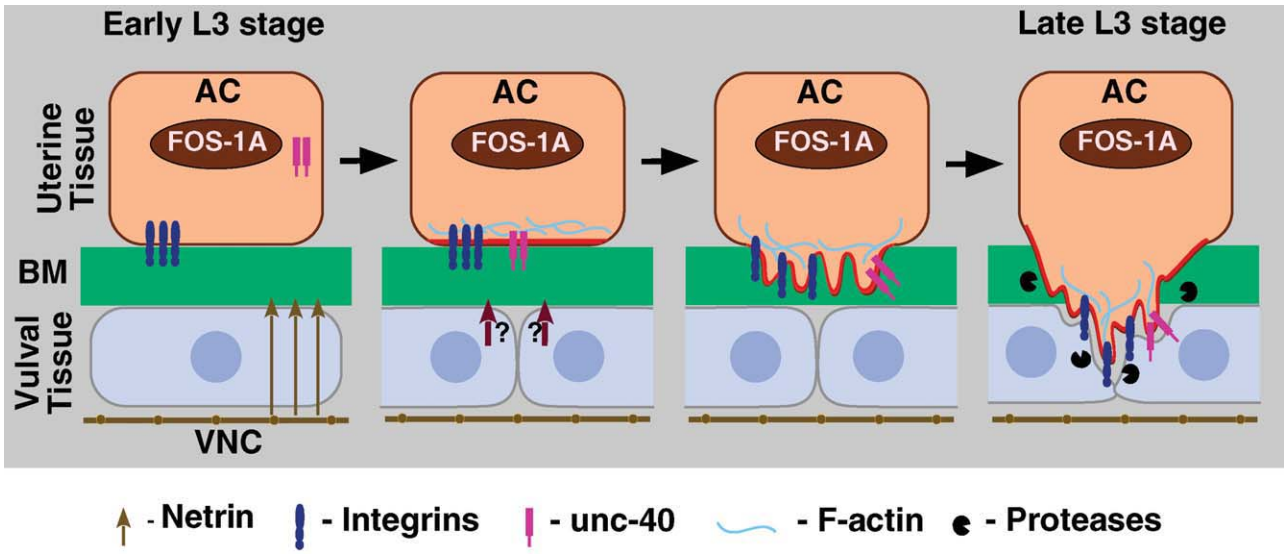

Fig. 7. Schematic of anchor cell (AC) invasion in *C. elegans* hermaphrodites. At the early L3 larval stage, a netrin signal from the ventral nerve cord (VNC) diffuses dorsally to polarize the AC. Polarization (red side of AC) involves the recruitment of UNC-40 by the integrin heterodimer INA-1–PAT-1 as well as redistribution of F-actin and other cytoskeletal modulatory proteins, leading to the creation of an invasive membrane domain. At the mid-L3 larval stage, an unidentified diffusible cue from the primary vulval cells (indicated by question mark), causes the anchor cell to send out protrusions to breach the basement membrane (BM) and penetrate the vulval cells. FOS-1A, which is produced by the AC, facilitates basement membrane removal by activating targets such as MMPs.

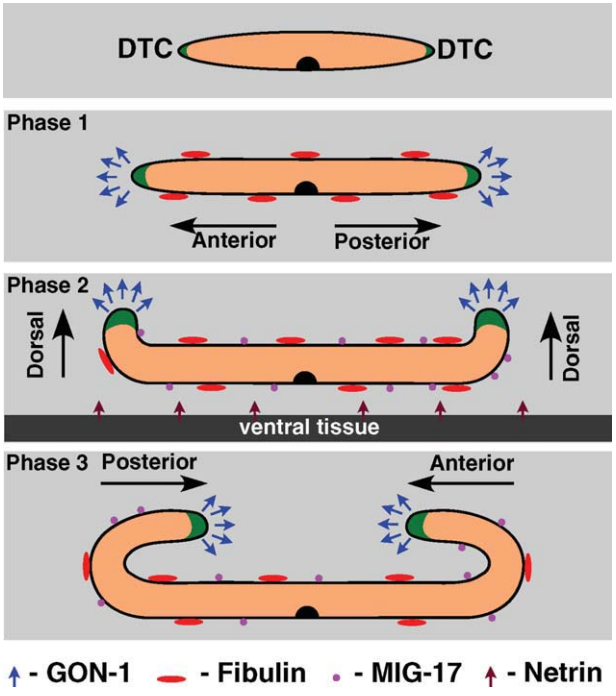

Fig. 8. Schematic of distal tip cells (DTC) migration in *C. elegans* hermaphrodites. Starting at the L2 larval stage, two ventrally located DTC (green) migrate in three distinct phases to attain U-shaped gonadal arms. Black arrows indicate the direction of migration during these phases. GON-1, which is secreted from both migrating DTCs and adjacent muscles (not shown), promotes DTC migration, possibly by degrading FBL-1/fibulin. Phase 2 of migration requires the functions of MIG-17 and UNC-6/netrin, the latter of which transmits a repulsive signal. MIG-17 and FBL-1 localize to the gonad basement membrane.

(Somerville et al., 2003). Notably, ADAMTS-20 is up-regulated in multiple human carcinomas including breast, brain, and colon carcinomas, suggesting a role in tumorigenesis (Llamazares et al., 2003).

MIG-17, another ADAMTS family metalloprotease, functions in the directional guidance of the DTC during phase 2 of migration (Nishiwaki et al., 2000). Expressed and secreted by muscle cells, MIG-17 localizes to the basement membrane of the gonad surface. Mutations that interfere with the metalloprotease activity of MIG-17 or prevent the proper localization of MIG-17 to the gonadal basement membrane specifically disrupt the directionality of DTC migration while not affecting the migratory ability of the DTC per se. The requirement for GON-1 and MIG-17 protease activities in remodeling the ECM during DTC migration is supported by the finding that mutations in fibulin (FBL-1), an ECM component, can strongly suppress the migration defects of *gon-1* and *mig-17* mutants (Hesselson et al., 2004; Kubota et al., 2004). Fibulins are calcium-binding proteins that participate in the regulation of cell migration and have been implicated in malignant transformation (Timpl et al., 2003). Additionally, fibulins show high affinity to other ECM components and to integrin receptors (Kramer, 2005). In *C. elegans*, FBL-1C is an isoform of fibulin that is produced and secreted by the intestinal cells and also localizes to the gonadal basement membrane. Another recently identified ECM protein, MIG-6/ papilin, shows genetic interactions with MIG-17 and functions within the MIG-17

pathway to regulate DTC migration (Kawano et al., 2009).

The ventral-to-dorsal migration of the DTCs is also promoted by a repulsive signal in the form of UNC-6/netrin and its receptors, UNC-5 and UNC-40, as mutations in these genes lead to defects in phase 2 of DTC migration (Leung-Hagesteijn et al., 1992; Chan et al., 1996; Su et al., 2000). Additionally, mutations in *sdn-1*/syndecan enhance phase 2 migration defects observed in *unc-5* mutants. This enhancement by *sdn-1* appears to be due to the deregulation of several signaling pathways in *sdn-1* mutants, as EGL-20/Wnt is mislocalized in *sdn-1* mutants and loss-of-function mutations in *egl-20* or *egl-17*/FGF alleviate DTC migratory defects in *unc-5; sdn-1* double mutants (Schwabiuk et al., 2009). Furthermore, SDN-1 functions in a cell nonautonomous manner, as expression of SDN-1 in either the hypodermis or nervous system is sufficient to rescue DTC migration defects. In addition, the chondroitin biosynthesis pathway member SQV-5 and its cofactor, MIG-22, are also essential for the dorsally guided migration of DTCs (Suzuki et al., 2006). DTC migration defects in *sqv-5* or *mig-22* are efficiently rescued only if SQV-5 or MIG-22 is expressed in both the DTCs and surrounding hypodermis. The process whereby cell migration is aided by factors secreted from the stroma is co-opted by certain malignant cancers in the invasion of surrounding tissues. For example, ADAM9-s, which is secreted by stromal cells, localizes to the surface of colon cancer cells through integrin binding to promote invasion (Mazzocca et al., 2005). Additionally, elimination of stroma-derived MMP-13 in mice significantly impairs both tumor growth and metastasis (Zigrino et al., 2009).

Additional *C. elegans* Models of Metastasis

Several additional *C. elegans* models for cell migration and metastasis bear mentioning. As precursors of the vulval muscles, the hermaphrodite sex myoblasts (SMs) undergo anterior migration to the mid-body during larval development (Sulston and Horvitz, 1977). Multiple guidance signals in the form of attractants and repellents play a role in the migration of the SMs. Initially, a gonad-independent mechanism guides the SMs to move anteriorly into a broadly defined region. Next, a gonad-dependent mechanism guides the SMs into their precise locations at the center of the developing gonad (Sulston and Horvitz, 1977; Branda and Stern, 2000). EGL-17/FGF and EGL-15/FGFR, which have roles in the migration of other cells, are the predominant mediators of the gonad-dependent SM migration (Stern and Horvitz, 1991; Branda and Stern, 2000). In addition, Ras-MAPK pathway components also mediate SM migration through the gonad-dependent mechanism (Clark et al., 1992a; Sundaram et al., 1996; Chen et al., 1997). Conversely, the gonad-independent mechanism can be abolished by mutations in *unc-53*, *unc-71*, and *unc-73* (Chen et al., 1997). UNC-73, which contains a Cdc24p-like guanine nucleotide exchange factor domain, can induce cytoskeletal rearrangements that promote directed cell motility (Steven et al., 1998). UNC-71, an ADAM family protein with a catalytically inactive metalloprotease domain, promotes SM migration through its cell adhesion properties (Huang et al., 2003). A third mechanism, termed gonad-dependent repulsion, is revealed only in the absence of EGL-17 pathway activity and may serve to fine tune placement of the SMs (Stern and Horvitz, 1991). Several candidate genes have been implicated in the repulsion mechanism including an alternatively spliced form of EGL-15 that functions within the SMs (Branda and Stern, 2000; Lo et al., 2008). Notably, the propensity of certain tumor cells to reproducibly metastasize to specific locations and tissue types suggests that attractive and/or repulsive signals may influence the selection of colonization sites. One example is circulating melanoma cells that colonize the small intestine in response to an intestinally secreted chemokine (Amersi et al., 2008). Thus, greater knowledge of the signaling mechanisms used to guide cells during normal migrations may aid in the understanding of site selection by metastatic cancers.

In addition to individual cell movements, the complex processes of embryonic morphogenesis and organogenesis, which involve the coordinated movements of many cells, are also likely to share common genes and mechanistic features with metastatic cancers (e.g., Soto et al., 2002; Chisholm and Hardin, 2005; Patel et al., 2008). Examples include the human metastasis-associated (MTA) homologs EGL-27 and EGR-1, which regulate vulval morphogenesis, cell polarity, cell migration, and embryonic patterning in *C. elegans* (Herman et al., 1999; Solari et al., 1999; Chen and Han, 2001). MTAs are components of the NURD complex, and their elevated expression correlates with aggressive behavior in several human carcinomas (Nicolson et al., 2003). Likewise, increased expression of the FOXA family proteins is associated with several human cancers (Mirosevich et al., 2005; Nakshatri and Badve, 2007; Albergaria et al., 2009). In *C. elegans*, PHA-4, the only member of the FOXA family, functions as an organ identity factor during the development of the pharynx (Mango et al., 1994). Moreover, the tumor suppressor ortholog LIN-35/Rb contributes to the regulation of both vulval and pharyngeal morphogenesis through cell cycle-independent mechanisms (Fay et al., 2003, 2004; Bender et al., 2007; Mani and Fay, 2009).

miRNAs IN CANCER

A novel paradigm of eukaryotic gene regulation was heralded when the *lin-4* gene from *C. elegans* was cloned and discovered to encode not a protein but a regulatory RNA, termed a microRNA (miRNA; Lee et al., 1993; Wightman et al., 1993). miRNAs are ~22-nt transcripts that bind to the 3′UTR of their target mRNAs, resulting in translational inhibition through a mechanism that is still not well understood. Since the discovery of *lin-4*, the number of miRNAs has increased tremendously, with over 150 in *C. elegans* and more than 600 in humans (Griffiths-Jones, 2007). miRNAs have increasingly been demonstrated to play a role in multiple forms of cancer (Medina and Slack, 2008; Visone and Croce, 2009). Among these are members of the *let-7* family, which was first identified in *C. elegans*. Loss of *let-7* leads to excess cell divisions in both *C. elegans* (Reinhart et al., 2000) and *Drosophila* (Caygill and Johnston, 2008) and results in increased rates of proliferation in lung cancer cells (Johnson et al., 2007).

Indeed, *let-7* expression seems to increase as normal differentiation proceeds but is reduced in several cancers where its loss coincides with de-differentiation (Sempere et al., 2004; Thomson et al., 2004; Mineno et al., 2006; Thomson et al., 2006; Wulczyn et al., 2007; Peter, 2009).

Identification of *let-60*/RAS mRNA as a *let-7* target in both human and *C. elegans* suggested one potential mechanism for the role of *let-7* loss-of-function in malignancy (Johnson et al., 2005). Other *let-7* cell cycle-related targets include, but are not limited to, the myc (Koscianska et al., 2007; Kumar et al., 2007; Sampson et al., 2007; Shah et al., 2007) and HMGA2 oncogenes (Johnson et al., 2007; Lee and Dutta, 2007; Mayr et al., 2007; Park et al., 2007; Shell et al., 2007; Wang et al., 2007), the latter of which often exhibits truncation of its 3′UTR in cancerous tissues (Mayr et al., 2007). In addition, mammalian *let-7* is involved in cell cycle repression through the inhibition of CDC25A (Huang et al., 2007; Johnson et al., 2007), and cyclin D1 (Schultz et al., 2008). Other potential cancer-related targets of *let-7* include cyclins A2, B1, and E2; CDC2; CDC34; E2F family members 5 and 6; CDK6; CDK8; LIN28B; and SKP2 (Johnson et al., 2007). It is worth noting that whereas some miRNAs have been implicated as tumor suppressors (e.g., miR-15a, miR-16-1, and the miR-34 family, miR-99, miR-125a, and miR-126), others appear to have a positive role in tumor progression (e.g., miR-17-92 cluster, miR-21, miR-155, miR-224, miR-372, miR-373; Medina and Slack, 2008; Visone and Croce, 2009). Known targets of these regulatory RNAs are involved in multiple aspects of tumorigenesis including apoptosis, cell proliferation, and growth factor signaling (Medina and Slack, 2008; Visone and Croce, 2009).

Although the regulation of *let-7* is still being worked out, it involves homologs of the *C. elegans* LIN-28 protein, which binds to and prevents processing of the *let-7* precursor (Heo et al., 2008; Newman et al., 2008; Rybak et al., 2008; Viswanathan et al., 2008). Notably, mammalian LIN28 and LIN28B are overexpressed in several human tumors as well as in cancer cell lines, and their role as oncogenes is linked with their ability to derepress *let-7* targets, which leads to reacquisition of stem-cell traits and increased tumorigenic potential (Viswanathan et al., 2009). The oncogenic properties of mammalian LIN28 are also likely due in part to its ability to directly bind the 3′UTRs of at least two cyclin family members (A and B), as well as CDK4, thereby increasing their translation (Xu et al., 2009). In addition, *let-7* is also down-regulated by at least one of its own targets in both mammals (c-myc; Sampson et al., 2007; Chang et al., 2008) and *C. elegans* (LIN-41; Nimmo and Slack, 2009). Notably, a negative feedback loop involving *let-7* and Lin-28 has been demonstrated in mice, as *let-7* can repress the translation of Lin-28 mRNA (Rybak et al., 2008). Correspondingly in *C. elegans*, LIN-28 was previously shown to be negatively regulated by the *lin-4* miRNA (Moss et al., 1997). Of interest, mammalian *lin-4* homologs (the miR-125 family) are down-regulated in several types of cancers, including leukemia and ovarian, breast, and thyroid carcinomas (Iorio et al., 2005; Sonoki et al., 2005; Visone et al., 2007; Visone and Croce, 2009). Given the high degree of conservation between the *C. elegans* and mammalian miRNA processing pathways, as well as clear parallels in their biological functions and targets, further studies in *C. elegans* promise to provide potent insight into the roles of miRNAs in tumorigenesis.

SUMMARY

Studies in *C. elegans* have contributed broadly to our current understanding of basic mechanisms governing cancer progression. In several cases, these contributions have been seminal and unique, such as the discovery of apoptosis, RNAi, and miRNAs. In many other instances, *C. elegans* research has significantly informed ongoing active areas of cancer biology research. Although it is not possible to predict what future studies on the worm may divulge, the ultimate promise of better diagnostics and treatments for cancer patients are driving forces that will propel the field forward.

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