GEOLOGY

Taper or Channel?

Near the base of the Himalayas, a major fault system (the Main Central Thrust and related faults) is exposed that accommodated the collision and subduction of India into and beneath Asia around 50 million years ago. The metamorphic minerals there record the pressure and temperature conditions before and during the displacement along the thrust; dating of minerals and recognition of zoning or overgrowths provide a time sequence that in turn can be used to infer how the collision and thrusting occurred. Two major models have been proposed, one involving formation and maintenance of a taper extending back from the thrust fault, and the other extrusion through a lubricating channel formed from hot weak crust along the fault. Kohn has synthesized the metamorphic data in rocks near the Main Central Thrust to test these models. Just below the fault, rocks were heated to about 550°C at depths of about 25 km, whereas above it the rocks were heated to about 725°C at depths of ~35 km. The data support the first model over the second, suggesting that the active fault progressively deepened as erosion stripped material from the top of the Himalayan taper. — BH

Geol. Soc. Am. Bull. **120**, 259 (2008).

BIOMEDICINE

Depressing Ceramide

Cystic fibrosis, a genetic disease associated with frequent lung infections and a shortened life span, is caused by a defect in the *CFTR* gene, which encodes a membrane transporter. Although it is not clear exactly how defective *CFTR* links to the symptoms, the mutant protein is known to increase the pH in intracellular organelles. On the basis of results obtained from patients' cells and from mice carrying mutated *Cftr* (which produces a cystic fibrosis–like disease), Teichgräber *et al.* suggest that this rise in pH increases susceptibility to lung infection by altering levels of ceramide, a membrane constituent that can also trigger cell death. The higher pH inhibits the enzyme that breaks down ceramide, and the resulting excess of ceramide increases vulnerability to lung infection. Blocking the biosynthesis of ceramide via acid sphingomyelinase normalizes ceramide levels and, most tellingly, renders the *Cftr*-deficient mice resistant to lung infections. This block can be achieved with amitriptyline (Elavil), a drug approved for treatment of depression. Normalization of ceramide levels in the lungs of patients with cystic fibrosis may be a promising therapeutic approach. — KK

Nat. Med. **14**, 382 (2008).

CHEMISTRY

Gazing Down a Funnel

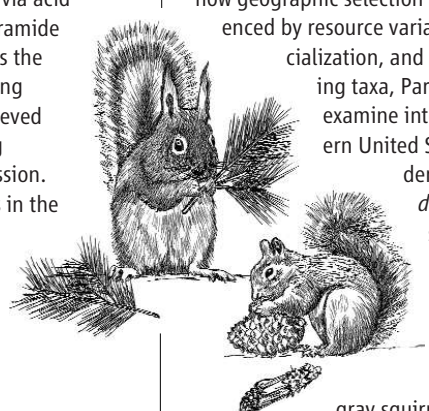
Because electrons generally move about much more rapidly than nuclei, most chemical reactions are modeled using a framework of potential energy surfaces in which effectively instantaneous electronic transitions between surfaces precede vibrational rearrangements confined to a single surface. However, this framework can break down in certain polyatomic reactions that couple vibrational and electronic motion through a feature linking two surfaces in a cone-shaped, or conical, intersection. Farrow *et al.* use ultrafast spectroscopy to extract the precise timing and details of vibrational coupling as electrons rush down through such a funnel in the energetic landscape after excitation of a square planar naphthalocyanine molecule coordinated to a central silicon moiety. Specifically, they monitor the polarization anisotropy decay of the electronic absorption signal, upon which periodic intensity fluctuations are superimposed that correspond to coherent vibrational motion. Modeling of the data supports a transition time of <200 fs for the relatively modest relaxation energy pertaining in this molecule; the electrons still outpace the nuclear vibrations, though only by a small margin. The data suggest that in chemical reactions with much higher driving forces, transitions through conical intersections could occur within several femtoseconds. — JSY

J. Chem. Phys. **128**, 144510 (2008).

EVOLUTION

Pine Cones, Squirrels, and Crossbills

Selection for coevolutionary adaptations is buffeted by geographical variation in community composition and species interactions. To explore how geographic selection mosaics are influenced by resource variability, feeding specialization, and vagility of interacting taxa, Parchman and Benkman examine interactions in the western United States among ponderosa pine (*Pinus ponderosa*), two allopatric species of tree squirrel (*Sciurus*), and one type of red crossbill (*Loxia curvirostra*). Feeding by western gray squirrels (*S. griseus*) selects for cone traits (such as size) that greatly reduce crossbill use of pine seeds, and crossbill specialization on ponderosa is limited to areas outside the gray squirrel's range. Preferentially foraging on inner bark, Abert's



CREDITS (TOP TO BOTTOM): PETER BARRITT/ALAMY; ELIZABETH RAHEL

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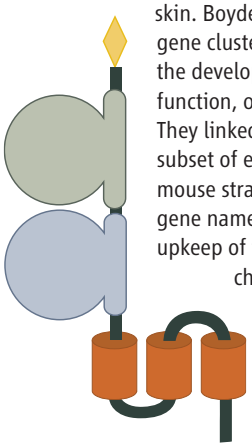
squirrels (*S. aberti*) cut twigs with developing cones, thereby depressing seed supply and lowering the selective impact of crossbills on the pine. Thus, crossbill-ponderosa coevolution is strongest in the absence of both squirrels. But high interannual variation in cone crop encourages the birds to be nomadic and move regularly among areas with and without Abert's squirrels. Such movements prevent strong selection mosaics and the local differentiation of crossbill populations found where they feed on more consistent seed supplies. — ShJS

Evolution **62**, 348 (2008).

IMMUNOLOGY

Skin-Deep Selection

T cells come in two flavors—gamma delta (γδ) and alpha beta (αβ)—that are distinct in function and dispersed differently through the body, with γδ cells defined by a regional distribution of subsets at sites such as mucosa and skin. Boyden *et al.* have identified a gene cluster in mice that influences the development, and likely the function, of γδ T cells in the skin. They linked deficiency of a specific subset of epidermal γδ T cells in a mouse strain to a mutation in a gene named *Skint1* (selection and upkeep of intraepithelial T cells) on chromosome 4. *Skint1* was characterized as a cell surface member of the immunoglobulin supergene family, with two extracellular domains, three transmembrane domains, and a short cytoplasmic tail. The presence of other members of the *Skint* family and the variation in expression between haplotypes point to the rapid evolution of the *Skint* family in mice, although functional orthologs appear to have been lost, possibly more than once, during mammalian evolution. Further work will be needed to establish the contribution of *Skint1* and other members of this family to the immune function of γδ T cells. — SJS



Predicted structure of Skint1.

CREDITS: BOYDEN *ET AL.*, *NAT. GENET.* **40**, 10.1038/NG.108 (2008)

Nat. Genet. **40**, 10.1038/ng.108 (2008).

MEDICINE

The ABC's of Herceptin

The breast cancer drug trastuzumab (Herceptin) has been heralded as a breakthrough in translational oncology because its development was based on the detailed characterization of a signaling pathway that promotes tumor cell growth. Trastuzumab is a humanized monoclonal antibody whose antigen-binding domain Fab recognizes a tyrosine kinase receptor (HER2/erbB2) that is overexpressed in some breast cancers, and its anticancer activity is thought to involve disruption of cell proliferation signaling through this receptor. Although some patients with HER2/erbB2-positive breast tumors improve when treated with trastuzumab, about 70% do not respond, and the reasons for this have been unclear.

Musolino *et al.* provide clinical evidence that trastuzumab's anticancer activity may be due, at least in part, to a completely distinct mode of action—antibody-dependent cell-mediated cytotoxicity (ADCC), a process by which immune effector cells such as natural killer cells lyse a target cell bound to an antibody. Studying 54 patients with HER2/erbB2-positive metastatic breast cancer, the authors discovered a correlation between the patients' response to trastuzumab and certain germline sequence variants in genes encoding Fcγ receptors, a class of proteins critically involved in ADCC. These results not only suggest how to predict which breast cancer patients would be most likely to respond to trastuzumab, but also raise the possibility that manipulations aimed at enhancing the drug's capacity to induce ADCC might improve or broaden its clinical efficacy. — PAK

J. Clin. Oncol. **26**, 1789 (2008).

OCEAN SCIENCE

North Versus South

The Atlantic meridional overturning circulation (AMOC) transports shallow, warm water to the north and deeper, cold water to the south. The strength of this circulation, and in particular the amount of heat it transports northward, is thought to have a major influence on climate. Presently, much of the northward surface flow of the AMOC originates as nutrient-rich water from intermediate depths in the South Atlantic, and it has been suggested that those southern waters penetrated less into the north during past cold intervals when the AMOC was weaker. Came *et al.* present a record of the nutrient content of the northward flow of the AMOC over the past 23,000 years, preserved by benthic foraminifera in a sediment core recovered from near Florida, in order to determine how the contribution of southern water varied since the beginning of the last deglaciation. Their data allow them to document in more detail the changes in ocean circulation during the transition from glacial to interglacial conditions, and to illustrate how North Atlantic deep water formation, Antarctic intermediate water production, and North Atlantic climate were linked over that time period. — HJS

Paleoceanography **23**, PA1217 (2008).

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