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In This Issue

GEOLOGY

Continental collision brought long-term cooling

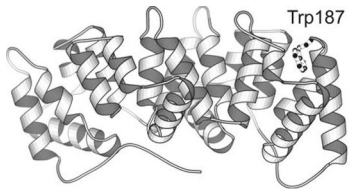
The collision of the Indian subcontinent with Eurasia may explain why temperatures in Earth's Cenozoic era peaked 50 million years ago (Ma) at the Early Eocene climatic optimum and have declined since. Dennis Kent and Giovanni Muttoni say the collision slowed the recycling of carbon deposits from below the Earth's surface, reducing CO_2 in the atmosphere and allowing Antarctic ice sheets to grow, starting a cooling trend that continues today. According to the authors, when the Indian and Eurasian continents met ≈50 Ma, subduction of Tethyan crust moved a highly productive ecosystem underground, where CO_2 could be released back into the atmosphere. Following the collision, India's Deccan Traps drifted into equatorial latitudes, where its silicates absorbed atmospheric CO_2, lowering the atmospheric CO_2 concentration and lessening the greenhouse effect. The rapid expansion of Antarctic ice sheets followed, beginning 35 Ma, when temperatures plunged and have been cooling ever since, the authors say. — P.D.

"Equatorial convergence of India and early Cenozoic climate trends" by Dennis V. Kent and Giovanni Muttoni (see pages 16065–16070)

APPLIED BIOLOGICAL SCIENCES

A familiar blue glow

An ideal fluorescent tag belies the presence of a particular protein without obscuring the protein's structure, producing a glow from within. Sandra Lepthien *et al.* report a method for making colorless proteins visible to the naked eye that uses only a slight modification of a protein building block to produce blue fluorescence. The technique relies on an analog of the amino acid tryptophan to induce a blue glow when illuminated with UV light. Tryptophan is important in protein stability and function, making its substitution a challenge. Lepthien *et al.* note that nitrogen-containing tryptophan analogs called azatryptophans produce a negligible structural change in the target protein but dramatically change its spectral properties. The authors added the precursor molecule for 4-azatryptophan to bacterial cells and found not only that the molecule had a high uptake rate into the target protein, but also that its fluorescence was much brighter than that of the existing molecule. Some of these structurally similar molecules were identified as valuable tools and may offer a more powerful and effective glow than those currently in use, according to the authors. — T.H.D.



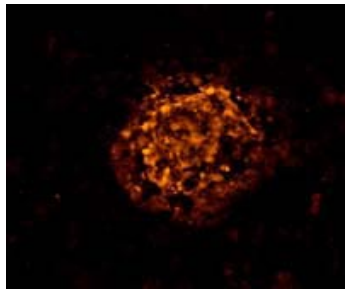
Human annexin A5 with tryptophan 187 in the hydrophobic pocket (at right).

"Azatryptophans endow proteins with intrinsic blue fluorescence" by Sandra Lepthien, Michael G. Hoesl, Lars Merkel, and Nediljko Budisa (see pages 16095–16100)

DEVELOPMENTAL BIOLOGY

Observing embryonic communication

For successful implantation, a human embryo and the uterine wall must engage in a "dialogue" during a short window of time. The failure of embryos to implant in the uterus is a major cause of infertility, but the exact nature of the breakdown in molecular conversation is unknown. Seema Grewal *et al.* report the use of an *in vitro* system for studying the molecules critical for implantation. To model the process, the authors cultured endometrial cells with human embryos and observed as the embryos invaded the cellular layer. Focusing on a group of enzymes called Rho GTPases, which are active in remodeling cellular struc-



Rac1 activation in human endometrial stromal cells during embryo implantation.

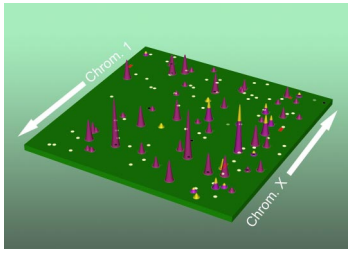
tures, the authors found that silencing the Rac1 enzyme in endometrial cells prevented the embryo from invading the cell layer, but that silencing RhoA increased the level of invasion. Their analysis suggests that Rac1 increases the motility of the maternal cells, enabling them to migrate so that the embryo can invade the cell layer. The authors note that because embryonic invasion must be tightly controlled, the interplay of stop-and-go signals like Rac1 and RhoA must be finely choreographed. Identifying the molecular characteristics of these signals may lead to infertility treatments or contraceptive targets, the authors say. — T.H.D.

"Implantation of the human embryo requires Rac1-dependent endometrial stromal cell migration" by Seema Grewal, Janet G. Carver, Anne J. Ridley, and Helen J. Mardon (see pages 16189–16194)

GENETICS

DNA disruptions in breast and colon cancers

Rebecca Leary *et al.* conducted a genome-wide analysis of 45 breast and 36 colorectal tumors and identified a group of common homozygous deletions and gene amplifications that occur in these cancers. The tumors harbored an average of 17 genes that had been either deleted or copied >12 times. Combining these data with findings from previous studies, the authors identified pathways and processes—including those regulating the cell cycle, cell adhesion, cell signaling, and DNA topology—that are frequently disrupted in cancers. In particular, Leary *et al.* noted that genetic disruption of FGFR, EGFR, ERBB2, and PI3K pathways occurred in >66% of the tumors studied. By contrast, breast cancers were plagued with mutations affecting DNA topology, according to the authors. — B.P.T.



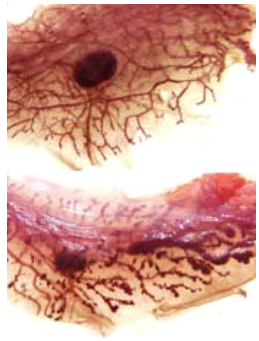
Genomic landscape of a copy number and nucleotide alterations in colorectal cancer sample.

"Integrated analysis of homozygous deletions, focal amplifications, and sequence alterations in breast and colorectal cancers" by Rebecca J. Leary, Jimmy C. Lin, Jordan Cummins, Simina Boca, Laura D. Wood, D. Williams Parsons, Siân Jones, Tobias Sjöblom, Ben-Ho Park, Ramon Parsons, Joseph Willis, Dawn Dawson, James K. V. Willson, Tatiana Nikolskaya, Yuri Nikolsky, Levy Kopelovich, Nick Papadopoulos, Len A. Pennacchio, Tian-Li Wang, Sanford D. Markowitz, Giovanni Parmigiani, Kenneth W. Kinzler, Bert Vogelstein, and Victor E. Velculescu (see pages 16224–16229)

IMMUNOLOGY

Two antibodies trigger antitumor response

High levels of human epidermal growth factor receptor-2 (ErbB-2/HER2) characterize 20–30% of breast tumors and are associated with a poor prognosis for controlling spread of the disease. A monoclonal antibody called trastuzumab blocks Erb-2 activity and recruits immune cells; previous research has shown that, when used in combination with chemotherapy, it can increase a patient's survival time. But broader strategies are needed because some patients develop resistance to the pharmaceutical drug that provides trastuzumab. John Stagg *et al.* report that a promising approach using proapoptotic receptor agonists (PARAs) triggers tumor necrosis factor-related apoptosis-inducing ligand-mediated apoptosis in cancer cells. The authors tested the combination of anti-DR5 monoclonal Ab (a PARA) and Erb-2 on breast cancers in mice and found that this treatment produced a synergistic effect that destroyed the tumors in a majority of the mice. The combination may not only kill existing tumors, but could also stimulate a systemic antitumor response within the body, the authors say. — B.P.T.


Mammary gland of wild-type (*Upper*) and experimental (*Lower*) mice.

"Antibodies targeted to TRAIL receptor-2 and ErbB-2 synergize in vivo and induce an antitumor immune response" by John Stagg, Janelle Sharkey, Sandra Pommey, Richard Young, Kazuyoshi Takeda, Hideo Yagita, Ricky W. Johnstone, and Mark J. Smyth (see pages 16254–16259)

MEDICAL SCIENCES

Noninvasive test for fetal aneuploidy

Tests for abnormal chromosome count, or fetal aneuploidy, are now carried out by chorionic villus sampling and amniocentesis, both of which are invasive procedures that carry risk to the fetus. Christina Fan *et al.* report a prototype noninvasive procedure for identifying fetal aneuploidy. According to the authors, ≈10% of the cell-free DNA in maternal blood comes from the fetus, so if a chromosome is overrepresented in the healthy mother's DNA, the fetus is likely the source. Examining maternal blood samples by using a method based on shotgun sequencing—attaching DNA fragments from plasma to universal adaptors, amplifying them by PCR, and then mapping the fragments to chromosomes—Fan *et al.* covered ≈4% of the genome and were able to pinpoint all cases of aneuploidy in a test cohort of 18 pregnant women. Of the most common aneuploidies, that on chromosome 21 (Down syndrome) was clearly identifiable in a statistically significant number of samples. The fetal DNA appeared to come from apoptotic cells. Because the cost of sequencing is declining, the authors suggest that this method could provide a cheaper and safer alternative to current invasive tests. — K.M.

"Noninvasive diagnosis of fetal aneuploidy by shotgun sequencing DNA from maternal blood" by H. Christina Fan, Yair J. Blumenfeld, Usha Chitkara, Louanne Hudgins, and Stephen R. Quake (see pages 16266–16271)