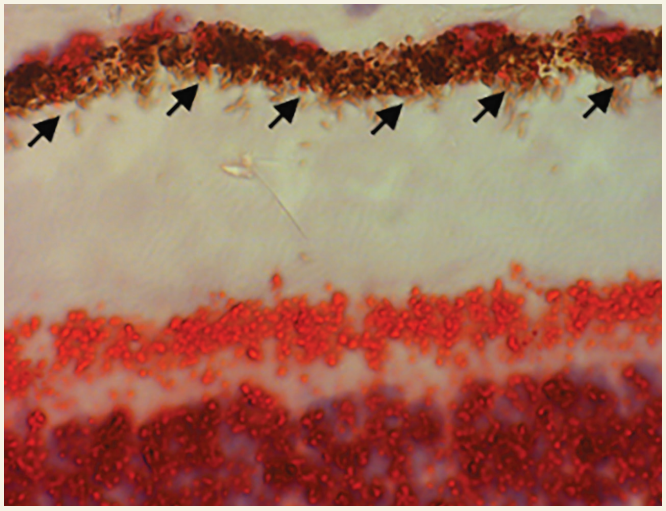
In this issue . . .

Role of retinal pigment epithelium in Stargardt macular degeneration

Recessive Stargardt disease (STGD1) is an inherited blinding disease with no effective treatment. The disease is caused by mutations in the *Abca4* gene, which encodes a transporter protein in photoreceptor cells that helps eliminate retinaldehyde, a toxic byproduct of vision, and prevent the buildup of lipofuscin pigments in the eye. Tamara Lenis et al. (pp. E11120–E11127) analyzed murine, bovine, and human retinal tissue and found that the ABCA4 protein is additionally expressed in cells of the retinal pigment epithelium (RPE) at around 1% of the level seen in photoreceptor cells. To uncover the role of ABCA4 in RPE cells, the authors generated transgenic mice that express ABCA4 in RPE cells but not photoreceptors. The transgenic mice exhibited less photoreceptor degeneration and lipofuscin accumulation, compared with mice lacking ABCA4. According to the authors, deficiency of ABCA4 in the RPE of patients may contribute to disease development, and RPE cells may represent therapeutic targets in STGD1. — M.S.



***Abca4* (red staining indicated by black arrows) in human RPE cells.**

Epigenetic factors and mammalian cloning

More than 90% of cloned mammalian embryos are lost during pregnancy, but the underlying mechanism has not been clear. Miscarriages related to nuclear transfer are thought to be caused by abnormal epigenetic patterns, which are heritable chemical modifications that can affect gene activity without altering the DNA sequence. Dawei Yu, Jing Wang, Huiying Zou, Tao Feng, et al. (pp. E11071–E11080) report that aberrant silencing of the *RTL1* gene is a principal epigenetic cause of pregnancy failure in mammalian cloning. The authors transplanted nuclei from pig stem cells into egg cells whose nuclei had been removed, and transferred the resulting zygotes into surrogate mothers. The fetuses showed widely distributed abnormalities in DNA methylation, an epigenetic modification. *RTL1* was completely silenced in the embryos due to hypermethylation, resulting in abortion of all fetuses. When the authors restored normal *RTL1* activity in the stem cells prior to nuclear transfer, six out of 10 surrogates carried to term and gave birth to a total of 16 live cloned piglets. Moreover, analysis of human fertility clinic data revealed that *RTL1* activity was lower in spontaneously aborted embryos compared with induced abortions. The results suggest that selecting donor cells with proper *RTL1* activity for nuclear transfer may increase cloning success. According to the authors, *RTL1* could serve as a biomarker for predicting and diagnosing pregnancy complications in humans and other mammals. — J.W.

Restoring normal *RTL1* activity in stem cells yielded cloned piglets.

Climate change and mountaintop extinctions

Climate change is driving many mountain-dwelling species to move upslope. Species living near mountain summits lack higher-elevation habitats to move into and are therefore predicted to decline or disappear. However, empirical evidence of such climate-driven, high-elevation species disappearances is scant. To determine whether mountaintop populations have been disappearing as predicted, Benjamin Freeman et al. (pp. 11982–11987) conducted a survey of birds in 2017 on a remote Peruvian mountain that had previously been surveyed in 1985, covering the same ground at the same time of year and using the same methods as the historic survey. The authors found that species' ranges shifted upslope on average between the two surveys. Species historically found up to the mountaintop occupied a narrower elevational range and a smaller total land area in 2017 than in 1985. Most species historically found at the highest elevations declined in abundance. Eight species found near the mountaintop in the historic survey were not observed in the modern survey. The results suggest that in the survey area, climate warming is driving extinction, with species moving to progressively higher elevations until they run out of habitat. According to the authors, tropical, high-elevation species may be especially vulnerable to climate change. — B.D.

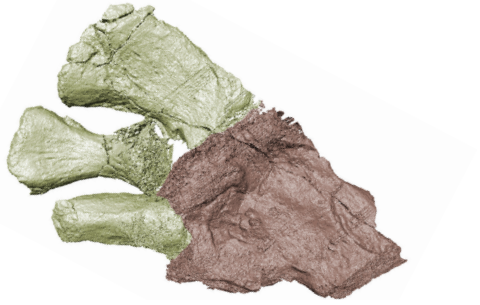
The Cerro de Pantiacolla Ridge, viewed from the Palatoa River. Image courtesy of Graham Montgomery (University of Connecticut, Storrs, CT).

Structure-guided drug design and side effects

Drugs that target muscarinic acetylcholine receptors show potential for the treatment of a variety of disorders, but their clinical development has been hindered by side effects caused by limited selectivity for receptor subtypes. Using molecular modeling and structure-based drug design, Hongtao Liu, Josefa Hofmann, Inbar Fish, et al. (pp. 12046–12050) developed a selective inhibitor, or antagonist, of the M3 muscarinic acetylcholine receptor. The authors first compared recently determined crystal structures of the M2 and M3 muscarinic acetylcholine receptors. Exploiting a single amino acid difference in the binding sites of the two receptors, the authors designed highly specific antagonists. One of the resulting antagonists binds roughly 100 times more selectively to the M3 muscarinic acetylcholine receptor than the M2 muscarinic acetylcholine receptor in vitro and 4,000 times more selectively in mice. To provide a template for future design, the authors used X-ray crystallography to determine the structure of the antagonist bound to the M3 muscarinic acetylcholine receptor. According to the authors, compounds similar to the antagonist could improve the treatment of asthma and chronic obstructive pulmonary disease by reducing off-target effects in the heart. More broadly, the study highlights the potential of structure-based drug design to develop selective drugs with reduced side effects, according to the authors. — J.W.

Evolution of limb patterning in tetrapods

Living four-limbed vertebrates, or tetrapods, exhibit a common skeletal pattern in the proximal part of their limbs, with a single bone at the base of the limb joining to two parallel radials at the distal end. The same pattern has been observed in tetrapod-like fossil fishes, but the origins of this pattern are unclear. Jonathan Jeffery et al. (pp. 12005–12010) describe a near-complete skeleton of *Rhizodus hibberti*, a fossil lobe-finned fish and member of the stem tetrapod group. The bones at the base of the pelvic fins, the femurs, from both pelvic fins were well-preserved. The distal end of each femur formed joints with three parallel radial bones, in contrast to the two radials observed in other tetrapods, both living and fossilized. Each of the three radials had a distinct morphology, with the morphologies on the left fin matching those on the right. *Rhizodus* may therefore represent an early stage in the evolution of hind-limb development, before development became constrained to the familiar one-to-two pattern. The latter finding suggests that developmental mechanisms were once flexible enough to allow for more varied skeletal patterns than those currently observed, according to the authors. — B.D.



Computed tomography scan of the fin skeleton of *Rhizodus hibberti*, showing the femur (red) and three radials (green).