Genetic variant tied to risk of typhoid fever

Worldwide, *Salmonella enterica* serovar Typhi (S. Typhi) causes around 20 million typhoid infections every year, and 1–5% of infected individuals chronically carry the pathogen, notable among which is the storied case of Typhoid Mary. Yet the genetic determinants of typhoid risk remain unclear. Monica Alvarez et al. (pp. E7746–E7755) performed a genome-wide association study to uncover host factors that influence the ability of *S. Typhi* to invade human cells—a property associated with bacterial virulence. A single-nucleotide variant dubbed rs8060947 in the lipid metabolism-related VAC14 gene that reduced expression of the encoded protein increased the ability of *S. Typhi* to invade human cells; the finding was corroborated through RNA interference and CRISPR-Cas9-mediated knockout of VAC14. By reducing the cholesterol content in the membrane surrounding host cells, VAC14, the authors found, blocks the bacterium from docking with cells. As predicted, a cholesterol-depleting compound mimicked the action of VAC14, reducing bacterial invasion in a dose-dependent fashion. Similarly, zebrafish treated with ezetimibe, an FDA-approved cholesterol-lowering drug, exhibited increased bacterial clearance and improved survival upon exposure to *S. Typhi*, compared with mock-treated fish. Genotyping of rs8060947 in 496 people with typhoid and 500 healthy people from a Vietnamese cohort revealed that individuals with the allele that increased *S. Typhi* invasion exhibited increased susceptibility to typhoid fever. The findings raise the intriguing possibility that cholesterol-lowering drugs, combined with vaccines, might help protect against typhoid, according to the authors. — P.N.

Evolutionary histories of Neanderthals and Denisovans

The evolutionary relationship between modern humans, Neanderthals, and Denisovans remains controversial. In an effort to resolve the controversy, Alan Rogers et al. (pp. 9859–9863) developed an improved statistical method for reconstructing evolutionary histories based on the frequencies of shared alleles between various populations. The authors used the method to analyze the relationship between African and Eurasian modern humans, Neanderthals, and Denisovans. The analysis yielded estimates of the sizes of various ancestral populations, the age at which Neanderthals and Denisovans diverged, and the degree of admixture between Neanderthals and Eurasian modern humans. The results suggest that Neanderthals and Denisovans diverged more than 700,000 years ago, or about 300 generations after the Neanderthal–Denisovan lineage diverged from modern humans. The results also suggest that during...
the period between these two divergence events, the Neanderthal–Denisovan ancestral population was small, numbering in the hundreds. Following the split with Denisovans, the Neanderthal population grew to tens of thousands, but also fragmented into largely isolated groups, explaining the abundance of deleterious mutations previously observed among Neanderthals, according to the authors.—B.D.

Skeleton formation in corals

Like many marine organisms, corals form hard body structures through calcium carbonate (CaCO₃) biomineralization. Classic theories hold that corals precipitate ions from seawater to form skeletal components. However, an alternative hypothesis suggests that amorphous calcium carbonate (ACC) precursor particles that form in the animal’s tissue might contribute to skeleton growth in corals. Tali Mass et al. (pp. E7670–E7678) used X-ray spectromicroscopy to study ACC formation in Stylophora pistillata corals. Contrary to conventional assumptions about the growth of coral skeletons, the authors report two ACC types that formed in the coral tissue. The ACCs, which included hydrated and dehydrated forms, formed as approximately 400-nm particles that were present near the growth surface of the coral skeleton and later crystallized into the hard skeletal CaCO₃ component, aragonite. In further laboratory analyses examining growth rates in synthetic aragonite and S. pistillata, the authors found that skeleton growth by the attachment of ACC particles was more than 100 times faster than growth by ion attachment from solution. The authors suggest that the increased growth rate might give corals distinct physiological advantages in competitive reef systems. According to the authors, the findings might have implications for understanding coral resilience to ocean acidification and for improving coral-based paleoclimate reconstructions.—C.S.

Single-cell transcriptomics, plasma RNA profiles, and placental dysfunction

During pregnancy, the placenta provides a crucial, ephemeral interface between the mother and developing fetus that helps maintain fetal homeostasis. Dysfunction of the placenta, a complex, multilobulated organ comprised of cells of both maternal and fetal origin, has been implicated in several prenatal complications including preeclampsia, a potentially lethal hypertensive disorder. Citing previous studies showing that preeclamptic placentas exhibit altered gene expression profiles, Jason Tsang et al. (pp. E7786–E7795) examined circulating, cell-free, fetal RNA in maternal plasma using large-scale, single-cell transcriptomic profiles as references. With a dataset of more than 24,000 nonmarker-selected cells from both term-and early preeclamptic placentas, the authors cataloged cellular heterogeneity in the human placenta and identified placental cell-type–specific gene signatures. Based on the analysis, the authors mapped trophoblast differentiation trajectories, reconstructed fetal and maternal cellular dynamics during normal pregnancy, and differentiated the dynamics from the cellular pathology in early preeclamptic placentas. In addition to establishing a cellular transcriptomic atlas of the human placenta, the findings demonstrate that circulating, cell-free mRNA released by placenta into maternal plasma offers diagnostic insights.

mRNA released by placenta into maternal plasma offers diagnostic insights.

ACC helps form coral skeletons. Image courtesy of Wikipedia Commons/Jim E. Maragos.

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RNA in maternal plasma can be used to develop a potential noninvasive test for conditions such as pre-eclampsia, according to the authors. — T.J.

**Origin of photosynthesis in eukaryotes**

Eukaryotes are thought to have evolved the capacity for photosynthesis through a process called endosymbiosis, in which a protist host encapsulated a photosynthetic cyanobacterium. The first such endosymbiotic event gave rise to the group called archaeplastida, which includes glaucophytes, red algae, green algae, and land plants. The timing and circumstances of the first endosymbiotic event and the dates of divergence of the major subgroups within archaeplasts remain unestablished, partly due to incomplete phylogenies and gaps in the fossil record. Patricia Sánchez-Baracaldo et al. (pp. E7737–E7745) performed molecular clock and phylogenomic analyses on two datasets, comprising 49 cyanobacterial genomes and 119 taxa including cyanobacteria and photosynthetic eukaryotes, to estimate the age of the primary endosymbiotic event as well as subgroup divergence times. Analysis revealed that the cyanobacterium Gloeomargarita, the closest relative of archaeplastids, likely diverged from its sister group, the chloroplast lineage, around 2.1 billion years ago in freshwater. Further, the common ancestor of archaeplasts likely became established around 1.9 billion years ago, marking the plausible origin of the first photosynthetic eukaryote. Over the next 1 billion years, major groups of modern photosynthetic eukaryotes diversified in freshwater habitats, but likely did not gain an ecological foothold in marine habitats until around 800 million years ago. The findings bolster fossil evidence and help unravel the origins of photosynthetic eukaryotes, according to the authors. — P.N.

**How ovipositors penetrate solid substrates**

Parasitoid wasps use a long, thin tube called an ovipositor to probe solid substrates, locate hidden insects, and deposit eggs into hosts. As a mechanical device, the ovipositor routinely performs challenging tasks, such as steering, drilling, and penetrating fruit and wood without buckling or breaking. Uroš Cerkvenik et al. (pp. E7822–E7831) present in vivo 2D and 3D motion analyses that illuminate ovipositor probing behavior in Diachasmimorpha longicaudata, a braconid wasp that parasitizes a species of Caribbean fruit fly. In general, ovipositors comprise four elements called valves, which slide along one another through a tongue-and-groove mechanism. The authors demonstrate that this morphology allows wasps to employ two distinct methods of insertion: one that pushes the entire ovipositor through soft media and another that uses alternating valve movements to move the organ through substrates with higher resistance. Furthermore, the analyses revealed that wasps can steer and curve the ovipositor in any direction relative to their bodies, allowing them to probe widely through large spaces from a single entry point. The findings could help improve the design of human-made, steerable probes, according to the authors. — T.J.