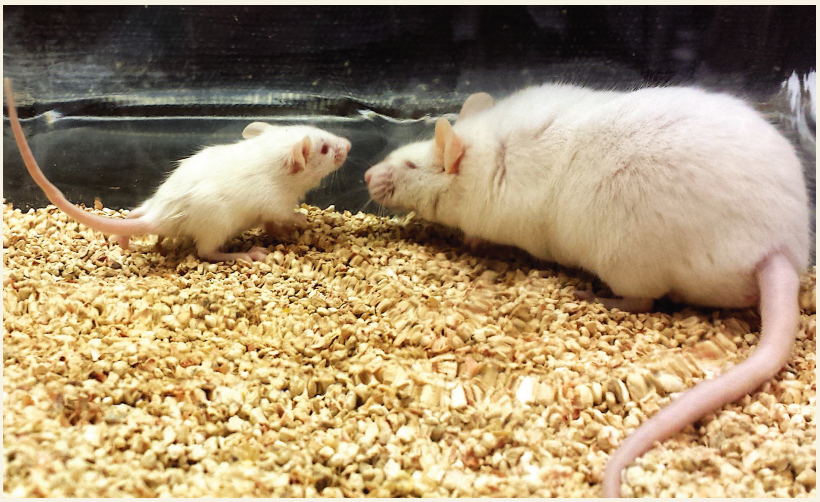
In this issue . . .

Synapse-boosting factors in young blood



Young (15-day-old; *Left*) and aged (15-month-old; *Right*) mice used in the experiments.

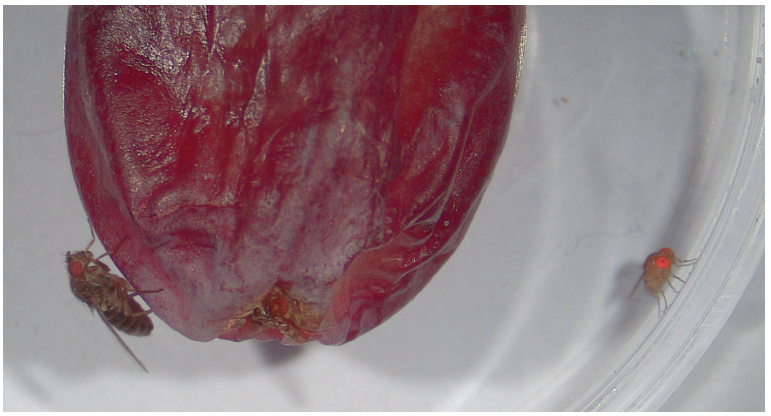
Cognitive aging is driven by changes in systemic factors circulating in blood, according to one hypothesis. Studies supporting this hypothesis have found that transfusing the blood of young mice into old mice—a process called parabiosis—increases brain synaptic connectivity and reverses learning and memory deficits. Putative factors in the blood of young mice have been reported, but whether these factors act directly on the brain or through indirect mechanisms remains unclear. Kathlyn Gan and Thomas Südhof (pp. 12524–12533) report that unlike blood serum from 12- to 15-month-old mice, serum from 15-day-old mice enhanced neuronal dendrite branching, synapse numbers, neurotransmitter release, and N-methyl-D-aspartate receptor (NMDAR)-mediated synaptic function in cultured neurons differentiated from human embryonic stem cells. Electrophysiological experiments revealed that serum from young mice directly acted on human neurons and boosted their synaptic connectivity, unlike serum from old mice. Adding young serum to neurons that had been cultured in old serum increased synaptic function, whereas adding old serum to neurons cultured in young serum slightly reduced synaptic function, suggesting a causal role for synapse-promoting factors in young serum rather than a role for synapse-inhibiting factors in old serum. Using tandem mass spectrometry, the authors identified 2 proteins—thrombospondin 4 (THBS4) and SPARC-like protein 1 (SPARCL1)—that were enriched in young serum and whose recombinant versions recapitulated many of the synapse-promoting effects of young serum. Both proteins increased synaptic connectivity, whereas SPARCL1, but not THBS4, enhanced NMDAR synaptic responses. According to the authors, young blood may contain multiple synapse-promoting factors, whose gradual loss might lead to cognitive aging and decline. — P.N.

Increasing global fishing fleets

Managing fishing capacity is vital to preserving the health of the world's oceans. However, previous research has reconstructed fishing fleets without including artisanal and industrial sectors. Yannick Rousseau et al. (pp. 12238–12243) reconstructed the artisanal and industrial fishing sectors of the global marine fleet by examining engine power, fishing effort, and the number of vessels between 1950 and 2015. By 2015, 68% of the global fishing fleet became motorized as the number of unpowered artisanal vessels decreased. However, the overall number of fleet vessels increased from 1.7 million to 3.7 million. The increase was most notable in Asia, where the global fleet contribution increased by 400%, but was slightly compensated by a minor fleet reduction in North America and Western Europe. Amid the global fleet expansion was a consistent decrease in the catch per unit of effort (CPUE). While the CPUE of Asian fleets decreased over time, Oceania's CPUE increased. By 2015, the average CPUE of most countries decreased by 80% since the 1950s. The combined global engine power of the motorized artisanal and industrial fleet increased from 25GW to 145GW by 2015. The findings suggest that despite decreasing CPUE and catches, the global fishing fleet continues to increase, which may also decrease seafood abundance and increase fuel emissions, according to the authors. — M.S.

Regulatory mutations shape protein quantitative evolution

Differences in traits between species can arise from both qualitative differences in the primary sequences of functional proteins and quantitative differences in protein activity. Quantitative differences depend on protein level as well as specific activity. David Loehlin et al. (pp. 12383–12389) used the fruit fly alcohol dehydrogenase (ADH) enzyme, which metabolizes ethanol, as a model to explore factors influencing the quantitative evolution of protein activity. Some species of fruit flies inhabit low-alcohol habitats, such as fresh fruits and fungi, whereas others are adapted to alcohol-rich environments, such as breweries and wine cellars. The authors mapped parts of the *Adh* gene that contribute to differing levels of ADH activity in 4 pairs of *Drosophila* lineages from different habitats. Changes in the gene's protein-coding sequence contributed to no more than 25% of the observed differences in enzyme activity within and between species. By contrast, changes in multiple noncoding regulatory regions, including enhancers, promoters, and 5′ and 3′ untranslated regions, accounted for most of the variation in enzyme activity, with 6 mutations playing causal roles in *Drosophila melanogaster*. Importantly, the flies' resistance to ethanol toxicity was directly correlated with ADH activity, with both coding and noncoding mutations contributing to resistance. Coding sequence mutations that increase enzyme reaction rates may inadvertently compromise enzyme stability, solubility, or substrate specificity. Hence, the authors suggest, natural selection largely relies on regulatory mutations to shape the quantitative evolution of proteins. — P.N.



Fermenting grape with alcohol-resistant *Drosophila virilis* (*Left*) and alcohol-sensitive *Drosophila santomea* (*Right*).

Ameliorating Alzheimer's disease in mice

Alzheimer's disease (AD) is the most common type of dementia and is characterized by the accumulation of plaque deposits of the amyloid-β peptide in the brain. Levels of the enzyme BACE1, which produces amyloid-β plaques, are elevated in the brains of patients with AD, but the underlying molecular mechanisms are unclear. Gahee Bahn, Jong-Sung Park, Ui Jeong Yun, et al. (pp. 12516–12523) report that the protein NRF2 decreases *Bace1* mRNA and BACE1 protein levels, reduces amyloid-β plaques, and improves cognitive performance. In a mouse model of AD, ablation of the *Nrf2* gene resulted in increased levels of *Bace1* mRNA and BACE1 protein in brain tissues, increased amyloid-β plaque loads in the hippocampus and cortex of the brain, and increased cognitive impairment in a learning and memory test. In 2 different mouse models of AD, treatment with the NRF2 activator sulforaphane, present in high amounts in vegetables such as broccoli and leafy greens, decreased *Bace1* mRNA and BACE1 protein levels in brain tissues, reduced amyloid-β plaque loads in the hippocampus and cortex, and improved learning and memory performance in 2 behavioral tests. According to the authors, the findings suggest that treatment with NRF2-activating plant compounds or synthetic small molecules could represent a potential therapeutic strategy for AD. — J.W.

Sex ratios in Darwin's finches

The adult sex ratio of populations is influenced by social and environmental forces. However, whether the adult sex ratio changes over time, and if so, how such changes affect mating patterns and fitness remain unclear. Peter Grant and B. Rosemary Grant (pp. 12373–12382) analyzed 21 years of data on 2 species of Darwin's finches—the medium ground finch (*Geospiza fortis*) and the cactus finch (*Geospiza scandens*)—in the Galápagos archipelago. Environmental perturbations caused starvation, especially among females, resulting in strongly male-biased sex ratios. The 1983 El Niño event, which primarily affected *G. scandens* due to the destruction of cactus bushes, resulted in males of this species outnumbering females 3 to 1 in 1987, but no bias in the sex

***G. scandens*. Image courtesy of Ruben Heleno (University of Coimbra, Coimbra, Portugal).**

ratio was observed for *G. fortis* during that year. Due to the increased opportunity for females to choose high-quality males, the frequency of mate changes in 1987 was 3 times higher in *G. scandens* than in *G. fortis*. Females that changed mates gained a clear fitness advantage in terms of numbers of offspring that survived to the following year. According to the authors, the findings demonstrate that environmental fluctuations can strongly bias the adult sex ratio of populations, altering mating patterns and reproductive success. — J.W.

Elephants' quantitative ability may be rooted in olfaction

Several nonhuman species, including some primates, cetaceans, birds, and elephants, can visually identify the greater of two quantities. Wild elephants, however, likely rely on their sense of smell, hearing, and touch to find water and food, using vision as a complementary sense. Joshua Plotnik et al. (pp. 12566–12571) tested whether six 12- to 45-year-old Asian elephants (*Elephas maximus*) living on the grounds of a hotel in northern Thailand could distinguish between two quantities of food using only their sense of smell. The authors used a sliding table to present pairs of locked buckets containing 11 different ratios of sunflower seeds that the elephants could smell but not see. Subsequently, the buckets were unlocked, and the elephants chose one of the two buckets, slid open its lid, and consumed the seeds inside. Overall, the elephants chose the greater quantity of seeds in each pair, regardless of the actual quantity of seeds presented. As expected, the elephants' performance improved as the difference between the quantities of seeds in each pair increased and worsened as the ratio between the pair of presented quantities increased, reinforcing the notion that elephants have a nose for quantity. Additionally, the authors ruled out the possibility that the elephants were using a sense other than smell, acting on inadvertent cues from the experimenters, or responding to unrelated olfactory cues during trials. According to the authors, understanding how elephants use their sense of smell while foraging might help mitigate conflict in regions where elephant habitats and human settlements overlap, aiding conservation efforts. — P.N.

Elephants at the Golden Triangle Asian Elephant Foundation in Chiang Rai, Thailand. Image courtesy of Hoi-Lam Jim (Vetmeduni Vienna, Vienna, Austria).