Variable Number Tandem Repeats Contribute to Complex Traits

Despite the advances in genetic sequencing and analysis methods, the contribution of variable number tandem repeats (VNTRs) to the inheritance of complex traits has remained challenging. Mukamel et al. (2021) developed methods for analyzing these repeats, which contain sequences of at least seven base pairs that are repeated in tandem from a few copies to hundreds of copies, and conducted an analysis of 118 protein-coding VNTRs from 415,000 UK Biobank participants in association with 786 phenotypes. These investigations uncovered 19 phenotype associations linked to five unique VNTRs. Fine mapping supported a causal role for these variants in lipoprotein(a) concentration, height, kidney function, and hair morphology, revealing the strength of effects of protein-coding VNTRs on human phenotypes. Sequencing methodology will continue to evolve, powering studies of the contribution of repetitive variants, including those in noncoding sequences and those that are too short or too mutable for current methods of analysis, to complex traits. These findings will provide insight into the biological mechanisms that underlie these complex traits, especially continuous phenotypes, in health and disease. (Science. 373:1499–1505, 2021; https://doi.org/10.1126/science.abg8289; see also Science. 373:1440–1441, 2021; https://doi.org/10.1126/science.abb7794) Selected by M. Udey

Cross-Reactive Immunity Enhances Protection in COVID-19

Most individuals who are infected with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have asymptomatic or mild disease, whereas as many as 5% exhibit severe disease. Although it was believed that the population at large was immunologically naïve to SARS-CoV-2, this coronavirus exhibits homology with endemic seasonal cold coronaviruses, and recent infection with these homologous viruses often results in a less severe COVID-19 disease presentation. Loyal et al. (2021) recently showed that CD4⁺ T cells that are cross-reactive to an immunodominant spike protein from both endemic coronavirus and SARS-CoV-2 are ubiquitous but decrease with age, supporting the observation that the elderly are more susceptible to severe COVID-19 disease. These T cells were recruited in immune responses to both SARS-CoV-2 infection and BNT162b2 mRNA vaccination at frequencies correlated with anti-spike protein IgG antibodies. Pre-existing cross-reactive CD4⁺ T cells enhance the immune response to infection and vaccination and may underlie not only the rapid induction of protective immunity after primary vaccination but also the high rate of asymptomatic and mild cases of COVID-19 in the general population. (Science. 374:eabh1823, 2021; https://doi.org/10.1126/science.abh1823) Selected by M. Udey

Mutant Clones in Normal Epithelial Tissue Play a Protective Role Against Cancer

Somatic mutations in cancer driver genes are sometimes more prevalent in normal epithelial tissue than in neoplastic lesions. Colom et al. (2021) investigated whether the development of new neoplasms is altered through competition with selected clones in the surrounding epithelium in a murine esophageal carcinogenesis model. In this model, neoplasms that persist over time acquired transformation features, although most of the microscopic tumors resolved soon after formation. However, these tumors were not lost by apoptosis, loss of proliferative cells, or elimination by the immune system but rather as the result of competition with highly fit clones in the adjacent normal epithelium. Strong competition and selection of highly fit mutant clones in normal esophageal epithelium acted as a selective pressure on the mutated tumor cells, ultimately eliminating most of them and playing a protective role against carcinogenesis. These findings suggest that survival of early tumors in the epithelium depends on both the mutations they carry and the mutational landscape of the neighboring clones in normal tissue. (Nature. 598:510–514, 2021; https://doi.org/10.1038/s41586-021-03965-7) Selected by D. Kelsell

Hygromycin A Selectively Targets Spirochetes

The use of traditional broad-spectrum antibiotics is thwarted by the rise in antibiotic resistance and the detrimental effects of these compounds on the healthy microbiome, supporting the need to transition to more selective antibiotics to combat important bacterial infections. In a differential screen of soil actinomycetes against the spirochete Borrelia burgdorferi, the causative agent of Lyme disease, versus against Staphylococcus aureus, Leimer et al. (2021) identified hygromycin A as an antibiotic with selective activity against spirochete bacteria and poor activity against Gram-positive and Gram-negative bacteria. Hygromycin A, which targets the ribosome common in bacterial species, is selectively transported into spirochetes by the BmpDEFG transporter. This antibiotic cleared a B. burgdorferi infection in mice after oral administration. These studies show that hygromycin A selectively kills B. burgdorferi, has limited effects on the microbiome, is not cytotoxic to human cells, and rarely induces resistance, supporting further development of this antibiotic for the treatment, prophylaxis, and even environmental eradication of Lyme disease. (Cell. 184:5405–5418, 2021; https://doi.org/10.1016/j.cell.2021.09.011) Selected by I. Brownell

Dysregulation of Host–Microbial Symbiosis Promotes Alopecia

Hair follicles (HFs), which harbor commensal microbes, are known regulators of skin immunity, and dysregulation of inflammation can lead to hair loss. Sakamoto et al. (2021) showed that ablation of a disintegrin and metalloproteinase 10 (ADAM10), which has previously been implicated in HF morphogenesis, in mice led to inflammation and alopecia. Inflammatory destruction of HFs and stem cell niches in these mice was caused by inflammatory type 2 innate lymphoid cells. Furthermore, type 1 IFN–responsive HF cells were found to regulate the microbiome in follicles through ADAM10–Notch signaling and depletion of ADAM10 in mice led to alteration of Delb6 expression at follicular openings and expansion of Corynebacterium mastitidis, ultimately driving inflammatory alopecia. These studies identify a prominent role for ADAM10–Notch signaling in the control of the local microbiome and inflammation to maintain homeostasis in HFs. (Immunity. 54:2321–2337, 2021; https://doi.org/10.1016/j.immuni.2021.09.001) Selected by I. Brownell