Clues to human ichthyosis from GWAS of golden retrievers

Individuals with autosomal recessive congenital ichthyoses (ARCIs) have scaling and flaky skin due to skin barrier defects. Identifying genetic causes of ARCI is difficult owing to the rarity and heterogeneity of these diseases. Based on the observation that a skin condition with similar features occurs spontaneously in golden retrievers, Grall et al. carried out a genome-wide association study (GWAS) of 40 dogs and identified a causative mutation in PNPLA1, a previously uncharacterised protein. They subsequently identified PNPLA1 mutations in two unrelated families with ARCI not yet linked with other mutations, and found similar abnormalities in skin biopsies from patients and affected dogs. Further studies of PNPLA1 showed that it is present in the upper epidermis and suggest that it functions in epidermal glycerophospholipid metabolism; disease-associated mutations seem to alter the levels of lipids that are important for cell membrane integrity. These data provide new information about the pathological mechanisms underlying at least one form of ARCI and, more broadly, about skin barrier formation. Furthermore, they suggest that studies of ichthyoses common to different dog breeds might shed light on other genes involved in human ARCI.

iPSC-based model of viral infection

Models that allow dissection of the interplay between viral infection and host genetics are limited. Such models are becoming increasingly important to follow up the results of genome-wide association studies (GWAS) that implicate specific genes in conferring increased susceptibility or resistance to infections. Schwartz, Trehan et al. now report a system using human induced pluripotent stem cells (iPSCs) that will help to address this issue. iPSCs, which have the potential to differentiate into any cell type, have been used to investigate the aetiology of several other diseases, but they have not yet been applied to study infections. Here, the authors differentiated human iPSCs into hepatocyte-like cells (hHLCs) and infected them with hepatitis C virus (HCV). They show that, similar to primary human hepatocytes, iHLCs support the entire HCV life cycle. They express the host factors necessary for HCV entry, produce live virus capable of infecting other cells and mount an antiviral response. These data introduce iHLCs as a new tool for studying virus-host interactions, expanding the currently limited systems that are available for studying HCV infection. M.R.


p53-induced inflammation links heart failure with insulin resistance

Heart failure is known to be associated with insulin resistance, but the underlying mechanisms have been unclear. Shimizu et al. used mouse models to investigate this link and uncovered an important role for p53-induced adipose tissue inflammation in the co-development of these conditions. Surgically induced heart failure in mice caused insulin resistance, which was accompanied by increased adipose tissue lipolysis and inflammation. When subjected to the same procedure, mice lacking p53 specifically in adipose tissue did not become insulin resistant, showed less adipose tissue inflammation and had better cardiac function. Subsequent studies suggest an underlying mechanism whereby heart failure triggers adrenergic activation, which increases lipolysis in adipose tissue; in turn, this results in the production of DNA-damaging reactive oxygen species that initiate a p53-mediated cascade producing proinflammatory cytokines that contribute to insulin resistance. S.A.

Regulating responses to alcohol: role for CLIC genes

Alcohol abuse is known to have a hereditary component, but little is known about the specific genes that underlie this tendency. Bhandari et al. now uncover a cross-species role for chloride intracellular channels (CLICs) in modulating behavioural responses to alcohol. After applying bioinformatics to identify alcohol-responsive loci in humans and mice, they followed up the most highly ranked gene — CLICA4 — in functional studies with model organisms. They found that behavioural and/or physiological responses to alcohol were modulated by the sole Clc gene in flies, by the two clc genes in worms (exc-4 and exl-1) and by Clc4 in mice. Although further studies are required to determine the exact mechanism of CLIC genes in modulating alcohol responses, the authors’ bioinformatic analyses suggest that CLIC proteins might affect RNA processing and trafficking, whereas other proposed roles include the regulation of ryanodine receptors or the TGFβ signalling pathway. S.A.


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