Insights into cancer risk from a tuberous sclerosis complex zebrafish model

Tuberous sclerosis complex (TSC) is a rare genetic disorder associated with benign tumour formation. The disease is caused by loss-of-function mutations in either of the tumour suppressor genes *TSC1* or *TSC2*. In normal cells, the proteins encoded by these genes collectively inhibit mTORC1 (mechanistic target of rapamycin complex I) signalling; when absent, mTORC1 signalling is increased. Paradoxically, in other disorders characterised by augmented mTORC1 signalling, overt malignancies are observed. Ess and colleagues exploited this difference to gain mechanistic insights into tumorigenesis. They established a zebrafish model of TSC that develops cancer, by generating *tsc2;p53* compound mutants. Compared with *p53* single mutants, tumorigenesis and angiogenesis were enhanced in *tsc2;p53* zebrafish. Treatment with an mTORC1 inhibitor, rapamycin, inhibited tumour formation. This work provides *in vivo* evidence that cancer risk in p53-deficient individuals might be modulated by TSC1 or TSC2 mutations. **Page 925**

Inhibition of sepsis-induced organ injury

Sepsis is a complex condition in which a systematic inflammatory response is activated by infection, setting off a cascade of events that can culminate in multiple organ failure and death. New therapeutic strategies are urgently needed, with a key goal being the development of drugs that can be administered when sepsis is already underway. Inhibition of the transcription factor NF-κB has been shown to have a protective role in sepsis. Here, Christoph Thiemermann and colleagues tested the effect of inhibiting the IKK complex, which is involved in the early stages of NF-κB activation, on organ dysfunction and injury in mouse models of sepsis. They report that sepsis-induced organ injury is attenuated upon delayed administration of an IKK inhibitor, suggesting that this inhibitor could be given to sepsis patients during the devastating late stages in disease progression. **Page 1031**

A role for hypoxia in craniofacial abnormalities

Holoprosencephaly is a form of craniofacial abnormality that can result in miscarriage or stillbirth. Genetic and environmental factors are thought to play a role in the pathogenesis of holoprosencephaly and related birth defects, and recent studies have suggested that hypoxia (low oxygen conditions) might be associated with increased risk. In this study, Marcucio and colleagues explored the effects of a low-oxygen environment on craniofacial development in a chicken embryo model. Embryos exposed to hypoxia demonstrated a variety of craniofacial anomalies, including holoprosencephaly, and were less likely to survive. On a cellular level, hypoxia reduced cell proliferation and increased cell death (apoptosis). These data lend weight to the hypothesis that reduced oxygen conditions are detrimental during early development, and indicate that avoidance of factors that deplete oxygen levels during pregnancy, such as smoking, could reduce the occurrence of birth defects. **Page 915**

A new *Drosophila* model of cardiac hypertrophy

Abnormalities in receptor tyrosine kinase and serine/threonine kinase signalling pathways have been implicated in the development of cardiac hypertrophy, a condition characterised by enlargement of heart muscle cells, which can lead to heart failure and sudden cardiac death. The mechanisms underlying progression to cardiac hypertrophy remain poorly understood. In this study, a group led by Matthew J. Wolf described the first *Drosophila* model of the disorder. The authors report that the affected flies recapitulate the canonical features of human cardiac hypertrophy, including enlargement of cardiomyocytes and a decrease in the volume of the cardiac lumen in response to Raf-mediated molecular signals. This new model, which is free from the complexities associated with mammalian cardiac systems, could provide a platform for the discovery of downstream signalling molecules that contribute to cardiac hypertrophy in humans. **Page 964**

Targeting blood-derived IL-1 to treat brain injury

The inflammatory mediator interleukin-1 (IL-1), which is known to be a driver of chronic diseases such as diabetes and hypertension, has recently been identified as a major contributor to ischaemic brain injury. IL-1 is made by the haematopoietic (blood) system and also by cells in the brain. The relative contributions of central versus peripheral sources of IL-1 to brain injury have not been previously investigated. Here, Stuart Allan and colleagues selectively eliminated haematopoietic-derived IL-1 in a chimeric mouse model of ischaemic brain injury. They demonstrate that both sources of IL-1 are important for disease development, but removal of the peripheral source alone is sufficient to improve neurological outcome in the mice. This suggests that therapies that target peripheral IL-1 could be beneficial in brain injury, potentially overriding the need to deliver drugs across the blood-brain barrier. **Page 1043**

Long-term changes in gene expression in fetal alcohol spectrum disorders

Consumption of alcohol during pregnancy is associated with a variety of birth defects. Alcohol-related birth defects are collectively known as fetal alcohol spectrum disorders (FASDs), which are a leading cause of cognitive defects in North America. Studies using animal models have shown that alcohol induces global changes in gene expression in the developing brain. Using an FASD mouse model that they previously established, Shiva Singh and colleagues tested the hypothesis that long-term alterations in gene expression, mediated by epigenetic mechanisms, are a feature of FASDs. Developing mice were exposed to alcohol and, as adults, their epigenomes were assessed for changes in DNA methylation patterns and non-coding RNA (ncRNA) expression. The analysis unveiled long-lasting alterations in DNA methylation in response to fetal alcohol exposure. These changes mapped to the promoters of certain ncRNAs, implicating ncRNA deregulation in FASDs. **Page 977**

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