From pigs to men

The hormone insulin, produced by the beta cells in the pancreatic islets, is essential for glucose homeostasis. Destruction of the beta cells triggered by autoimmune responses results in type 1 diabetes, for which the standard treatment is a daily regimen of insulin injections. A potential long-term alternative approach is islet transplantation, but there has been limited success with human islet transplants, presumably due to immune rejection of the graft. Now Raleigh, Verchere and colleagues propose that another factor might contribute to graft failure: formation of cytotoxic amyloid fibrils. Previous work showed that, when transplanted into immunodeficient diabetic mice, human islets or transgenic murine islets expressing the human hormone islet amyloid polypeptide (IAPP) accumulate amyloid fibrils, leading to loss of beta cells over time. Notably, the murine IAPP does not form fibrils, as it contains proline residues that disrupt the typical amyloid β-sheet structure. In contrast to the failure of human islet grafts, porcine islets seem to maintain long-term function when transplanted into nonhuman primates and even a few reported human diabetic patients. The authors show that porcine islets work better than human islets when transplanted into diabetic mice. Whereas the human islets showed extensive amyloid deposits eight weeks after transplant (with associated loss of beta cells), the porcine transplants showed no amyloid deposition and were viable and functional for up to six months. The authors sequenced the porcine IAPP cDNA and found that the derived residue sequence contains substitutions in 10 positions compared to human IAPP and should be less prone to form amyloid fibrils; this prediction is confirmed by *in vitro* assays with synthetic peptides corresponding to human and porcine IAPPs. It is unclear why human IAPP fibrils form so rapidly in the grafts, but the results point to the potential role of IAPP amyloids in human islet graft failure, and to the possibility of inhibiting IAPP fibril formation to improve the outcome of human islet transplants. Although there are inherent limitations to xenotransplantation, including the possibility of infection with pig endogenous retroviruses, the work here provides support for the use of porcine islets therapeutically, which, as the authors note, would also help overcome the problems of low availability of donor tissue. (*Proc. Natl. Acad. Sci. USA* doi:10.1073/pnas.0909024107, published online 16 February 2010) *IC*

Switching splice site with histone marks

Many human genes are alternatively spliced in a cell-type- and tissue-specific manner, but how alternative splicing is regulated is only poorly understood. In the human fibroblast growth factor receptor 2 gene (*FGFR2*), exon IIB is predominantly used in epithelial PNT2 prostate cells, whereas exon IIIc is used in mesenchymal stem cells (MSCs). Differential inclusion of these exons is regulated by the polypyrimidine tract–binding protein (PTB), which binds a silencing element in exon IIIb, resulting in its repression. Misteli and colleagues asked whether histone modifications might play a role in the alternative splicing of *FGFR2*. They mapped histone modifications across the alternatively spliced region in both cell types and identified some histone modifications, including H3K36me3, that were enriched in MSCs, and others, including H3K4me3, that were enriched in PNT2 cells. The causal roles of H3K36me3 and H3K4me3 in alternative splicing were confirmed by modulating the levels of these histone modifications and assessing the effects on *FGFR2* mRNA splicing. Moreover, the distribution of the histone tail–binding protein MRG15 along *FGFR2* and other PTB-dependent alternatively spliced genes mimics that of H3K36me3, and PTB and MRG15 physically interact and associate simultaneously with *FGFR2* pre-mRNA, suggesting that MRG15 recruits PTB to its target exons. In fact, overexpression of MRG15 causes the exclusion of PTB-dependent exons and the recruitment of PTB to exon IIIb. By contrast, knockdown of MRG15 increases the use of PTB-dependent exons and blocks the splice-site switch. The authors propose a direct role for histone modifications in alternative splicing through a mechanism involving a chromatin-binding protein that reads histone marks and an interacting splicing regulator. (*Science* doi:10.1126/science.1184208, published online 4 February 2010) *AH*

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A new sensation

It is known that obese individuals experience chronic, low-grade inflammation and cellular stress—called 'metaflammation'—in metabolic tissues. However, the underlying mechanism by which the inflammatory, cellular-stress and metabolic pathways are linked and regulated is not known. Hotamisligil and colleagues recently determined that the double-stranded RNA–dependent protein kinase (PKR), involved in pathogen sensing in higher eukaryotes, is also a key link between these distinct biological processes. The authors found a large increase in PKR activity in a leptin-deficient mouse model of obesity and in non-obese mice experiencing nutrient excess (they were fed a high-fat diet or exposed to lipids via intravenous infusion). PKR was known to modulate the activity of *c*-Jun N-terminal kinase (JNK), an inflammatory kinase activated by fatty acid and endoplasmic reticulum (ER) stress; earlier work from the same group had shown that JNK is also a critical mediator of insulin resistance in obese animals. The authors now showed that JNK activation occurs via PKR, as fatty acids or thapsigarin (a drug that induces ER stress) were unable to activate JNK when the kinase domain of PKR was absent. Moreover, the RNA-binding properties of PKR are required for the fatty acid– or ER stress–induced activation of PKR. The authors propose that PKR directly detects metabolic stress via an endogenous signal whose nature remains to be determined and assembles a complex (the 'metaflammasome') to integrate multiple inflammatory pathways with metabolic control. Interestingly, mice expressing a kinase-deficient version of PKR gained significantly less weight than wild-type mice when put on a high-fat diet, and PKR-deficient mice required higher levels of glucose to maintain their blood glucose levels, indicating an increased sensitivity to insulin. Thus, in addition to revealing how these different pathways are linked in mammalian cells, the work suggests that small molecules selectively targeting PKR could be used to treat metabolic diseases. (*Cell* **140**, 338–348, 2010) *JMF*