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In This Issue

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New role for mast cells in afib Atrial fibrosis is a hallmark of atrial fibrillation (AF), the most common cardiac arrhythmia. It is thought to perpetuate AF. The mechanisms underlying the development of atrial fibrosis in AF remain unclear, although a role for inflammation has been suggested. Consistent with this, Liao and colleagues have identified a role for immune cells known as mast cells in inducing atrial fibrosis and AF in pressure-overloaded mouse hearts (242–253). Initial analysis indicated that mast cells accumulate and become activated in the atrium of pressure-overloaded mouse hearts, which are characterized by atrial fibrosis and enhanced susceptibility to induction of AF. Stabilizing mast cells with cromolyn and generating mast cell–deficient mice through bone marrow transplantation reduced fibrotic atrial remodeling and susceptibility to AF induction after pressure overload. Mechanistic studies determined that atrium-infiltrating mast cells increased PDGF-A synthesis, which subsequently promoted atrial fibrosis and susceptibility to AF induction in pressure-overloaded mouse hearts. These data led the authors to suggest that targeting the mast cell/PDGF-A axis might provide a way to prevent AF in stressed hearts, although they caution that further studies are needed to determine whether the same mechanism operates upstream of AF in large animals.Epigenetic silencing of an HCC suppressor It has long been known that genetic inactivation of tumor suppressor genes can contribute to tumor […]

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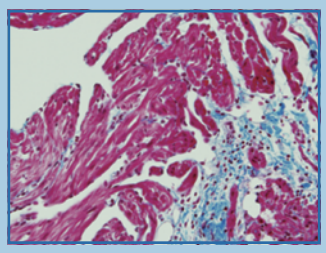
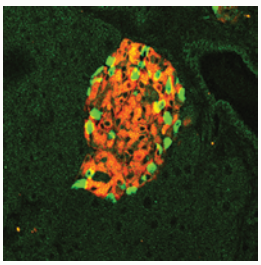


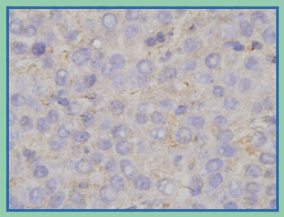
C/EBPβ stresses out pancreatic β cells



A key event in the development of type 2 diabetes is pancreatic β cell failure, one component of which is reduction in β cell mass. ER stress is thought to contribute to β cell failure, largely through loss of β cell mass. In this issue, Matsuda and colleagues report several lines of evidence from mice to indicate that the transcription factor CCAAT/enhancer-binding protein β (C/EBPβ) enhances susceptibility to ER stress and thereby contributes to β cell failure (115–126). First, C/EBPβ accumulated both in the islets of diabetic mice and in islets from normal mice exposed in vitro to an inducer of ER stress. Second, in 2 mouse models of diabetes, β cell–specific deletion of the gene encoding C/EBPβ increased β cell mass and markedly reduced the extent of hyperglycemia. Third, in transgenic mice overexpressing C/EBPβ in β cells only, β cell mass declined, leading to diabetes onset. Mechanistically, C/EBPβ enhanced β cell susceptibility to ER stress by reducing the abundance of the molecular chaperone glucose-regulated protein of 78 kDa (GRP78), providing insight into how C/EBPβ plays such a key role in β cell failure.

Epigenetic silencing of an HCC suppressor

It has long been known that genetic inactivation of tumor suppressor genes can contribute to tumor development and progression; only recently has epigenetic silencing of such genes also been implicated in these processes. Using a genome-wide approach to study the epigenomic patterns of 15 human hepatocellular carcinoma (HCC) cell lines, Huang, Zheng, and colleagues identified scavenger receptor class A, member 5 (*SCARA5*) as a candidate tumor suppressor gene (223–241). Further analysis of HCC tissue samples indicated that *SCARA5* was frequently subjected to allelic loss and epigenetic silencing by promoter hypermethylation in HCC and that SCARA5 protein downregulation was most marked in HCC tissue samples characterized by vascular invasion. Consistent with *SCARA5* being a tumor suppressor gene, *SCARA5* knockdown in HCC cell lines promoted malignant phenotypes, including tumorigenicity and metastatic potential after xenotransplantation, whereas SCARA5 overexpression suppressed these characteristics. Mechanistic studies determined that SCARA5 physically associated with focal adhesion kinase (FAK) and inhibited the FAK signaling pathway, leading the authors to suggest that SCARA5 downregulation can contribute to HCC tumorigenesis and metastasis via activation of the FAK signaling pathway.



Molecular insights into thymic GVHD

Treatment for a number of malignant and nonmalignant medical conditions is allogeneic BM transplantation (allo-BMT). The treatment often causes an extended period of immune deficiency, resulting in susceptibility to infections and recurrence of malignancies. Damage to the thymus elicited by T cells derived from the donor BM (thymic graft-versus-host disease; tGVHD) contributes to the deficit in T cell immunity. Using mouse models of allo-BMT, Na, Lu and colleagues have now identified several of the molecules required by donor-derived alloreactive T cells to mediate tGVHD (343–356). Many of these molecules were involved in T cell trafficking or costimulation/coinhibition. Of critical importance, donor-derived alloreactive T cells required the death receptor ligands FasL and TNF-related apoptosis-inducing ligand (TRAIL) to damage the thymus and mediate tGVHD. These molecules bound to their cognate death receptors Fas and death receptor 5 (DR5), respectively. Expression of these death receptors was upregulated on thymic stromal cells, in particular thymic epithelial cells, by radiation, a key step in BMT conditioning regimens. The results identifying Fas/FasL and TRAIL/DR5 interactions as critical to tGVHD induction led the authors to suggest that targeting these pathways may provide a way to attenuate tGVHD and improve T cell reconstitution in allo-BMT recipients.