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In This Issue

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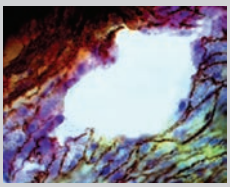
In this issue

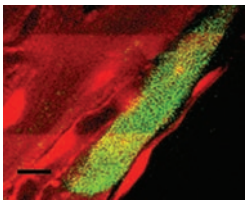
Picking protective prostanoids Atheroscle-rosis is an inflammation in the intima of arteries. Two prostanoids, PG I2/prostacyclin (PGI2) and thromboxane A2 (TXA2), are elevated in individuals with atherosclerosis, but their roles in the initiation and development of atherosclerosis remain ill-defined. Shuh Narumiya and colleagues have crossbred an atherosclerotic mouse model (apoE–/–) with mice that were deficient in either the PGI receptor (IP) or the TXA receptor (TP) to examine the effect of loss of PGI or TXA action on atherosclerosis development (pages 784–794). Relative to apoE–/– mice, the apoE–/–IP–/– mice had accelerated initiation and development of atherosclerosis, while the apoE–/–TP–/– mice had delayed development. apoE–/–IP–/– mice also demonstrated other markers of more severe disease, compared with apoE–/– mice. apoE–/–TP–/– mice presented with fewer markers of disease. These data indicate that PGI2 protects against and TXA2 promotes atherosclerosis development. The use of TP antagonists and molecules with PG-like activity may therefore aid in atherosclerosis prevention. See figure Become one: beat as one Skeletal myoblast transplantation into injured hearts can limit adverse remodeling. Understanding of donor-host interaction at a cellular level, however, is currently limited. To gain insight into this system, Loren J. Field and colleagues transplanted enhanced GFP–expressing (EGFP-expressing) myoblasts into nontransgenic mouse recipient hearts and examined intracellular calcium transients using two-photon molecular excitation laser scanning microscopy (pages 775–783). Synchronous intracellular calcium […]

Picking protective prostanoids

Atherosclerosis is an inflammation in the intima of arteries. Two prostanoids, PG I_2/prostacyclin (PGI_2) and thromboxane A_2 (TXA_2), are elevated in individuals with atherosclerosis, but their roles in the initiation and development of atherosclerosis remain ill-defined. Shuh Narumiya and colleagues have crossbred an atherosclerotic mouse model (*apoE*$^{-/-}$) with mice that were deficient in either the PGI receptor (IP) or the TXA receptor (TP) to examine the effect of loss of PGI or TXA action on atherosclerosis development (pages 784–794). Relative to *apoE*$^{-/-}$ mice, the *apoE*$^{-/-}$*IP*$^{-/-}$ mice had accelerated initiation and development of atherosclerosis, while the *apoE*$^{-/-}$*TP*$^{-/-}$ mice had delayed development. *apoE*$^{-/-}$*IP*$^{-/-}$ mice also demonstrated other markers of more severe disease, compared with *apoE*$^{-/-}$ mice. *apoE*$^{-/-}$*TP*$^{-/-}$ mice presented with fewer markers of disease. These data indicate that PGI_2 protects against and TXA_2 promotes atherosclerosis development. The use of TP antagonists and molecules with PG-like activity may therefore aid in atherosclerosis prevention.

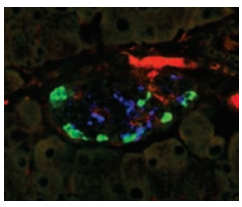


Become one: beat as one



Skeletal myoblast transplantation into injured hearts can limit adverse remodeling. Understanding of donor-host interaction at a cellular level, however, is currently limited. To gain insight into this system, Loren J. Field and colleagues transplanted enhanced GFP–expressing (EGFP-expressing) myoblasts into nontransgenic mouse recipient hearts and examined intracellular calcium transients using two-photon molecular excitation laser scanning microscopy (pages 775–783). Synchronous intracellular calcium transients occurred primarily only in host cardiomyocytes, but did also occur in a small fraction of donor-derived myocytes at the graft-host border. EGFP-marked donor myoblasts were transplanted into hearts of transgenic mice expressing a cardiomyocyte-restricted β-gal reporter gene, where histology demonstrated a small portion of myocytes expressed both donor- and host-derived transgenes, indicating fusion of these cells. These double-expressing cells had incidence and location similar to that of the functionally coupled EGFP-positive myocytes. This study indicates that while most engrafted donor-derived myocytes remain functionally separate from host myocardium cells, a small subset of skeletal myoblasts at the myocardial/skeletal muscle interface can become functionally coupled with host cardiomyoblasts, likely through fusion events between donor and host cells.

No compensation without PDX-1



Hyperplasia of β cells can abrogate insulin resistance effects. Loss of this compensatory hyperplasia, however, often results in diabetes development. Rohit Kulkarni and colleagues examined this islet-growth response in two different insulin-resistance mouse models (pages 828–836). The researchers found that when they brought pancreatic homeodomain protein (PDX-1) haploinsufficiency into the background of either insulin receptor/insulin receptor substrate–1 double-heterozygous mice or liver-specific insulin receptor knockouts, β cell hyperplasia was severely limited. Further analyses provided evidence that the hyperplasia loss was due to a reduction in β cell growth and to an extensive increase in apoptosis. While PDX-1 is known to be important for pancreatic progenitor cell growth, these studies indicate that it also has a vital role in regulating adult β cell proliferation and is a key component of the mechanisms underlying compensatory β cell hyperplasia in response to insulin resistance.

Pathways to immunity

The presence of bacterial components triggers Toll-like receptors (TLRs) to activate macrophages and DCs through various signal transduction pathways. In response to LPS, a TLR turns on the serine/threonine kinase Cot/Tpl2, which then activates ERK1/2 in macrophages. It remains unknown whether Cot/Tpl2 is involved in responses to other bacterial components or in the activation of other immune cell types. Tetsuya Matsuguchi and colleagues examine the importance of Cot/Tpl2 in response to LPS, synthetic lipopeptide, and bacterial DNA (CpG-DNA) (pages 857–866). Using RAW 264.7 cells, the authors showed that all 3 ligands activated Cot/Tpl2. In peritoneal macrophages from *Cot/Tpl2*$^{-/-}$ mice, however, only CpG-DNA could activate ERK, thus it could function through a Cot/Tpl2-independent pathway. Both peritoneal macrophages and immature DCs from the bone marrow of *Cot/Tpl2*$^{-/-}$ mice showed increased IL-12 expression in response to CpG-DNA. Northern blot analysis and gel shift assays demonstrated that enhanced IL-12 levels occurred at least partially through loss of transcriptional repression. In vivo, OVA immunization and *Leishmania major* infection in *Cot/Tpl2*-deficient mice showed Th1-skewed antigen-specific immune responses. This study indicates that Cot/Tpl2 may be a significant regulator of the Th1/Th2 balance through negative regulation of IL-12 and may therefore be a useful target molecule for improving CpG-DNA–guided vaccination.