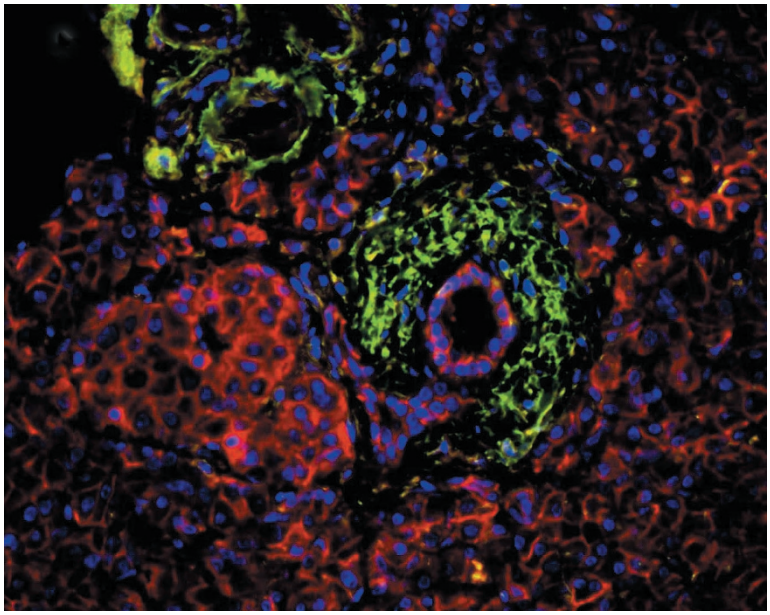
Laboratory Investigation (2009) 89, 108-109

INSIDE LI

doi:10.1038/labinvest.2008.166



Origin of pancreatic mesenchymal stem cells explored

See page 110

Diabetes is one of the most common and debilitating illnesses known to humans. Although there has been great progress in treating patients with exogenous insulin, a major treatment goal has been the implantation of functional insulin-producing cells. There has been some success with islet cell transplants, although only 10% of recipients remain insulin-independent 5 years after transplant and all recipients need to remain on immunosuppressive therapy. Furthermore, the limited supply of available pancreas tissue further restricts the applicability of islet cell transplants. Thus, it has become desirable to develop an unlimited source of β-cells for use in diabetes therapy.

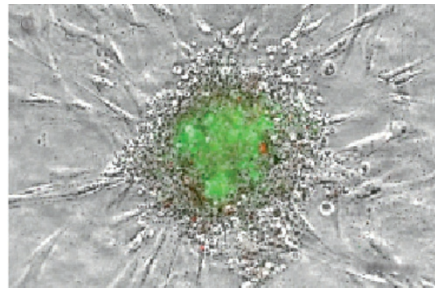
Mesenchymal stem cells (MSCs) hold great promise as candidates that might be able to differentiate into functional β-cells for transplantation. Seeberger and colleagues wondered whether MSCs derived from the pancreas itself might be able to differentiate into functional insulin-secreting β-cells. They asked whether MSCs could be derived from pancreatic epithelial cells, and, if so, whether they could differentiate into functional β-cells. Via examination of human pancreatic tissue biopsies and analysis of cultures derived from the non-exocrine portions of the pancreas, they found that MSCs were unlikely to be derived from epithelial cells and were more likely to be derived from expanded populations of MSCs that live within the pancreas. Unfortunately, they were unable to differentiate MSCs into functional insulin-secreting β-cells. Although this work highlights the difficulties inherent in this type of research, the benefits of success are obvious. It is easy to envision a day when a diabetic individual's pancreatic biopsy can be used to create an unlimited source of functional insulin-secreting β-cells for implantation without the need for immunosuppressive therapy.

Sophisticated three-dimensional model of placental vasculogenesis

See page 152

One can hardly imagine a more complex tissue than placenta, which is composed of several fetal-derived cell types that organize and invade the maternal tissues to establish a fetal blood supply. Establishment of the fetal blood supply is a crucial and early step in fetal development, and its success is predictive of fetal success. Because failure results in serious pregnancy-related complications such as intrauterine growth restriction, preeclampsia, and early pregnancy loss, it is important to understand this process. The development of models that recapitulate the complexity of placental tissue is critical to studying placental vasculogenesis.

To this end, Baal *et al* have developed a co-culture spheroid model of placental vasculogenesis that successfully reproduces many of the salient features. This is achieved by co-culturing cytotrophoblasts, villous stromal cells, and endothelial precursor cells. The cells form spheroids that show remarkable similarity to early placental

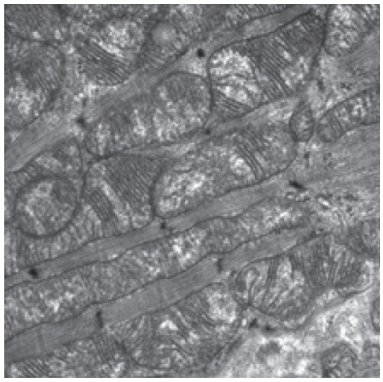


chorionic villous tissue. Furthermore, by varying the oxygen levels, trophoblasts invade collagen at appropriately low levels, further supporting the relevance of this system. Although it is not perfect—e.g., synciotrophoblasts do not form—it appears to be an excellent foundation on which to build an even better model, which should have advantages of both *in vitro* and *in vivo* model systems.

Molecular basis of cardiac toxicity to AIDS therapies

See page 122

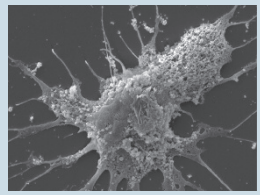
Due to the extraordinary energy demands of the heart, cardiac muscle is loaded with mitochondria, which



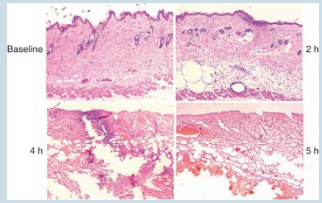
comprise approximately 40% of the total cardiomyocyte volume. This places the heart at great risk to drugs that affect mitochondria. Although pyrimidine nucleoside reverse transcriptase inhibitors (NRTIs) have been effective in the treatment of patients with HIV/AIDS, owing to their antiretroviral effects, they are not without complications. Severe cardiomyopathy is a serious side effect of NRTIs and is mediated by altered mitochondrial DNA (mtDNA) replication.

To investigate the factors that influence susceptibility to cardiac toxicity from NRTIs, Kohler *et al* have employed four transgenic mouse models that selectively express enzymes known to play an important role in mtDNA replication, including wild-type and two thymidine kinase 2 (TK2) mutants and a mutant of DNA polymerase-γ. All of the mutants were selected on the basis of their occurrence in known inherited mitochondrial disease syndromes. Mice harboring the transgenic alleles were subjected to HIV/AIDS treatment regimens containing NRTIs. Interestingly, the different strains were affected differentially, as reflected by measurements of mtDNA quantity, ultrastructural mitochondrial abnormalities, and echocardiographic measurements. These results suggest that mutations/polymorphisms of enzymes that are important in mtDNA replication may explain differences in susceptibility to cardiac side effects and lay the groundwork for further studies in this interesting area.

nature.com/pathology



Neoplasms communicate with the microenvironment through microvesicle stealth bombs Many cell types, including neoplastic cells, can package intracellular proteins and RNAs into microvesicles that are released into the surrounding tissues and bloodstream. In a recent letter in *Nature Cell Biology*, Skog and colleagues analyze the contents of microvesicles from glioblastoma multiforme tumor samples and cell lines. They found that they contained mRNA, miRNA, and proteins relating to virtually all cellular processes, including angiogenesis and cellular proliferation. Some microvesicles are taken up by the surrounding cells, from which the contents are delivered to the non-neoplastic cell. Thus, microvesicles have the potential to reprogram the cellular microenvironment. Furthermore, microvesicles can find their way into the bloodstream, suggesting that novel tumor nucleic acids and proteins derived from microvesicles can be monitored for diagnostic and therapeutic purposes.
Nature Cell Biology 2008;10:1470–1476; doi:10.1038/ncb1800



Pathogenesis of Stevens-Johnson syndrome and toxic epidermal necrolysis revealed Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are dramatic and life-threatening cutaneous reactions to drugs. In a recent letter in *Nature Medicine*, Chung and colleagues elucidate the pathogenesis. In a set of elegant experiments, they found that blister cells in both disorders were composed predominantly of $CD8^+$ cytotoxic T lymphocytes (CTLs) and $CD56^+$ natural killer (NK) and NK T cells. In contrast to previous theories about the pathogenesis, they found that the blister fluid contained massive amounts of granulysin, a cationic cytolytic protein released primarily by CTLs and NK cells. Injection of purified granulysin recapitulated the salient features of the disease in a mouse model system. They went on to suggest that granulysin may be responsible for the pathology seen in other disorders, such as graft-vs.-host disease. Finally, this work suggests that granulysin provides a potential target for therapeutic intervention in these devastating diseases.
Nature Medicine 2008;14:1343–1350; doi:10.1038/nm.1884

IL-6 pathway activation in inflammatory hepatocellular adenomas Inflammatory hepatocellular adenomas (IHCAs) are benign hepatocellular tumors characterized by prominent inflammatory infiltrates. In a recent letter in *Nature*, Rebouissou and colleagues identify activating mutations in the *IL6ST* gene, which encodes gp130, a component of the interleukin (IL)-6 receptor complex, in 60% of IHCAs. These mutations result in ligand-independent activation of signal transducer and activator of transcription 3 (STAT3). The authors go on to show that a subset of IHCAs also harbored activating mutations in *CTNNB1*-encoding β-catenin. Finally, they found both *IL6ST* and *CTNNB1* mutations in hepatocellular carcinomas (HCCs) that were associated with two IHCAs, suggesting that *IL6ST* and *CTNNB1* mutations might collaborate in HCC formation in this setting. Beyond the relevance in IHCAs, this work suggests that *IL6ST* mutations may play a role in other neoplasms displaying STAT3 activation and associated inflammation.
Nature, published online 19 November 2008; doi:10.1038/nature07475

Mechanism of estrogen receptor resistance in breast cancer explained Tamoxifen, an anti-estrogenic therapy, is a mainstay of breast cancer therapy. However, some estrogen-receptor (ER)-positive breast cancers are resistant. In a recent letter in *Nature*, Hurtado and colleagues attempt to explain this apparent paradox. Through careful mapping of ER-binding sites via chromatin immunoprecipitation (CHIP) experiments, they found that ER forms a complex with PAX2 that binds to a *cis*-regulatory element within the *ERBB2* gene and represses transcription of *ERBB2*. In addition, they found that AIB-1, which is known to promote ERBB2-mediated breast cancer, competes with PAX2 for this binding site and promotes *ERBB2* transcription. Thus, the balance of PAX2 and AIB-1 plays an important role in determining response to tamoxifen.
Nature 2008;456:663–666; doi:10.1038/nature07483