FEATURES

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IGF-1 Regulates Skeletal and Energy Homeostasis

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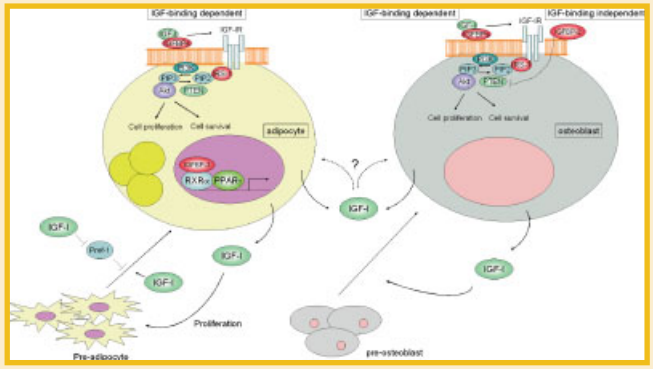

Recent advances in our understanding of adipose and skeletal tissue biology have highlighted the emerging roles of these tissues as endocrine organs that work in concert through hormonal, autocrine and paracrine signaling pathways to fine tune metabolic status. Accumulating evidence demonstrates that regulatory systems governed by the IGFs(IGF-I,II) and insulin-like growth factor binding proteins (IGFBPs) play an important role in these networks. The IGFs are bimodal modulators of metabolic function. In particular, these peptides regulate gene expression of downstream targets that affect the differentiative functions of osteoblasts and adipocytes. In addition, these growth factors are potent mitogens controlling the proliferation of mesenchymal stromal cells and preadipocytes during the earliest stages of differentiation. IGFBPs were long considered as inert carriers for IGFs modulating their access to the IGF receptor and their half life in the extracellular space. However, emerging evidence from human and animal studies suggest that IGFBPs are important in the regulation of body composition and glucose metabolism. These pro-proliferative properties are in part exerted by modulating IGF action at the IGF receptor level, but also through IGF-binding independent actions. The latter include heparin-binding domains and RGD sequence sites which signal through non-IGF1R pathways. It is also possible that the ligand IGF-I in this case, can potentiate the non-IGF dependent actions of the IGFBPs. This review discusses these novel concepts and the interaction of skeletal and adipose tissue through the IGF-I /IGFBP regulatory system.

Endothelial Cells Induce Cardiomyocytes From ES Cells

Kang Chen, Hao Bai, Melanie Arzigian, Yong-Xing Gao, Jing Bao, Wen-Shu Wu, Wei-Feng Shen, Liqun Wu, and Zack Z. Wang

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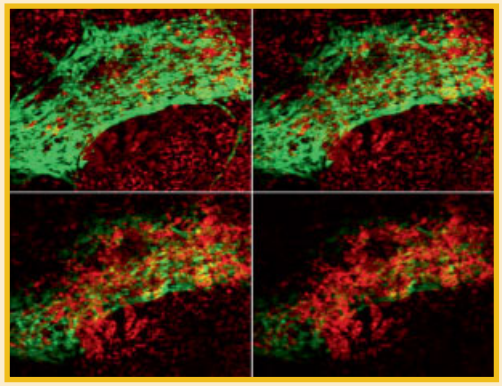

Cardiovascular disease, including hypertension, coronary heart disease, stroke, and congestive heart failure, remains the number one killer in the developed world. The damage to cardiomyocytes resulting from ischemic injury is irreversible and leads to progressive heart failure. Restoring damaged heart function may result from implantation of cardiomyocytes to the damaged myocardial tissue. The signals that direct ES cell differentiation into cardiomyocytes are largely unknown. Chen et al. explore the mechanisms by which endothelial cells provide signals to induce cardiomyocyte generation from ES cells. A strong contender involved in the mechanism is EphB4, a receptor tyrosine kinase that is expressed in endothelial cells underneath the cardiomyocytes in beating EBs. Inactivation of EphB4 results in decrease of beating EBs and decrease of cardiac gene expression. The cardiac defect in EphB4-deficient ES cells is rescued by coculture of endothelial cells with EphB4-deficient ES cells, suggesting that EphB4 is a critical component of endothelial niche to induce cardiomyocyte generation from ES cells.

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MsrA Protects Oxidative Damage in Stem Cells

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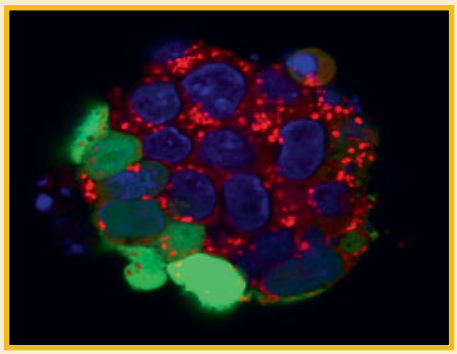

The methionine sulfoxide reductase system (Msr) has been shown to play an important role in protecting cells against oxidative damage. MsrA is major member of this family. Previous work has shown that over-expression of MsrA in Drosophila significantly increases life span, whereas MsrA knockout makes cells and organisms more sensitive to oxidative stress. In this issue Zhang et al. investigated the role of MsrA in cultured mouse embryonic stem cells (MESC). When MESCs were transfected with an MsrA-eGFP fusion protein and co-stained with the mitochondrial-selective dye Mitotracker Red, confocal microscopy revealed significant co-localization of MsrA inside the mitochondria, a primary intracellular source of oxidative stress. Knock down of endogenous MsrA in MESCs, using a specific siRNA, sensitized cells to H_2O_2-induced death whereas over-expression by gene transfection significantly reduced H_2O_2 mediated death. Because MsrA can combat oxidative stress without interfering with essential "signaling" ROS, these studies have important implications for stem cell therapy, especially for diseases like myocardial infarction that involve high levels of oxidative stress. For these diseases cell survival is a major limitation for stem cell treatment. It seems likely that enhanced expression of MsrA before cell transfer will optimize survival and improve therapy without deleterious side effects.

Prion Proteins in Infection

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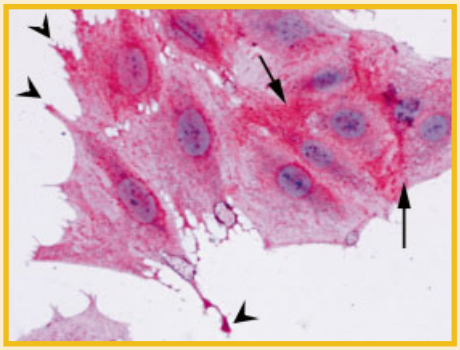

Host prion protein (PrP) is most abundant in neurons where its functions are unclear. The authors used rat neuronal precursor cells, transduced with the temperature sensitive SV-40 T antigen just before terminal differentiation, to explore whether proliferative arrest was sufficient to cause an increase in PrP. Proliferative arrest at 37.5°C induced a 7-fold increase in PrP by 2 days. Very few cells incorporated BrdU, and T antigen was markedly reduced, indicating effective arrest. Moreover, additional neuritic processes with abundant plasma membrane PrP connected many cells. PrP also concentrated between apposed stationary cells, as well as on extending growth cones and their filopodia. Stationary cells with high PrP could be maintained for 30 days in their original plate, and they reverted to a proliferating low PrP state at 33°C. Electron microscopy confirmed an increase in nanotubes, adherent junctions, and apparently open synctial regions between high PrP cells. Notably, nanotubes are conduits for the exchange of viruses between cells. The association of PrP with dynamic recognition and contact structures that have known viral functions indicates its specific role in transmissible encephalopathies (TSEs): host PrP is the essential receptor that binds infectious ~25nm particles to facilitate their transfer between cells.