FEATURES

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β-Catenin and Skeletal Support

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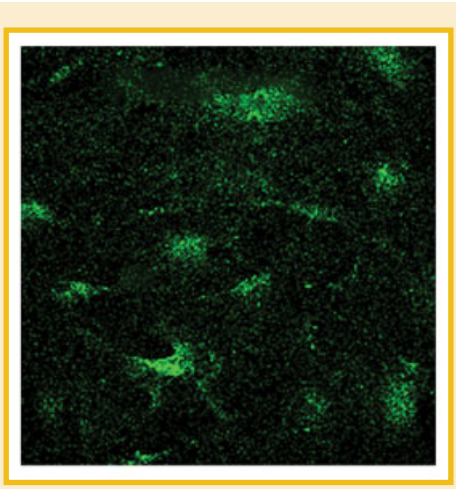

Interest in the role of β-catenin in bone biology emerged quickly once it was discovered that a human Lrp5 mutation which caused β-catenin activation was associated with high skeletal mass. Indeed, β-catenin is required for normal bone development. A primary effect of β-catenin is at the level of the mesenchymal stem cell (MSC), where sustained intracellular β-catenin prevents distribution of MSC into alternate cell lineages, such as adipocytes or chondrocytes, retaining precursors in a state where they can respond to osteogenic input. In postnatal bone remodeling, β-catenin influences bone resorption via alteration of the osteoprotegerin/RANKL ratio, but its contribution to bone formation through effects on osteoblast maturation remains unclear. The "Prospect" by Case and Rubin reviews the mounting evidence for a critical role of β-catenin in the skeleton, where β-catenin supports the downstream effects of multiple osteogenic factors, including skeletal loading. Importantly, biophysical factors, such as strain and shear generated in the skeleton during exercise, prevent β-catenin degradation and induce nuclear translocation through Lrp-independent mechanisms. As such, the authors conclude that biophysical induction of β-catenin in marrow-derived MSC influences bone formation through control of lineage allocation, preventing precursor distribution into the adipocyte pool.

Models for Adipogenesis, Adipose Dysfunction and Obesity

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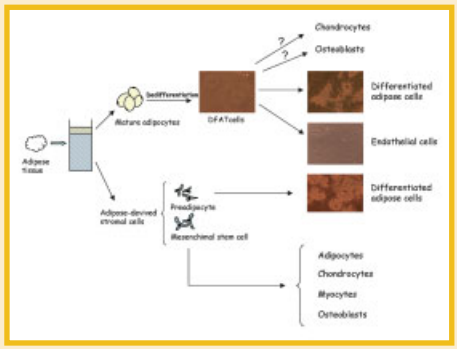

Adipose tissue does not work just as a depot for energy storage but also produces and releases factors capable of regulating several physiological processes. Alterations in its function play a key role in the pathogenesis of obesity and its related metabolic diseases. The complexity of studies focusing on adipocyte biology derives from the peculiarity of adipose tissue as an endocrine organ, with a marked cellular heterogeneity and anatomical discontinuity. A large amount of experimental work employing preadipocyte cell lines and primary adipocytes has led to the characterization of several factors and pathways involved in the main processes of adipocyte physiology. However, the complex network of hormonal signals linking the adipocyte to other organs and tissues requires additional models: co-culture techniques of adipocytes with different cell types allows the analysis of the delicate cross-talk occurring between fat and other tissues. Our review describes cell culture models currently available for the study of adipocyte biology, providing novel insights into co-culture and three-dimensional culture systems. These models allow a deeper analysis of cell-cell interactions within and outside adipose tissue, allowing new strategic approaches which could lead to a deeper understanding of metabolic disorders such as diabetes and obesity.

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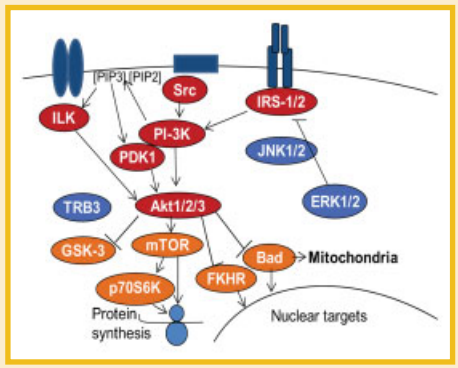
Chondrocytes provide the framework for the developing skeleton and regulate long-bone growth through the activity of the growth plate. Chondrocytes in the articular cartilage, found at the ends of bones in diarthroidial joints, are responsible for maintenance of the tissue through synthesis and degradation of the extracellular matrix. The processes of growth, differentiation, cell death and matrix remodeling are regulated by a network of cell signaling pathways in response to a variety of extracellular stimuli. These stimuli consist of soluble ligands, including growth factors and cytokines, extracellular matrix proteins, and mechanical factors that act in concert to regulate chondrocyte function through a variety of canonical and non-canonical signaling pathways. Key chondrocyte signaling pathways include, but are not limited to, the p38, JNK and ERK MAP kinases, the PI-3 kinase-Akt pathway, the Jak-STAT pathway, Rho GTPases and Wnt-β-catenin and Smad pathways. Modulation of the activity of any of these pathways has been associated with various pathological states in cartilage. This review focuses on the Rho GTPases, the PI-3 kinase-Akt pathway, and some selected aspects of MAP kinase signaling. Most studies to date have examined these pathways in isolation but it is becoming clear that there is significant cross-talk among the pathways and that the overall effects on chondrocyte function depend on the balance in activity of multiple signaling proteins.



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Nuclear receptor corepressors play important roles in differentiation and development by mediating chromatin reorganization to suppress transcription of target genes. Hairless (Hr) is a corepressor expressed predominantly in skin and brain, which interacts with the vitamin D receptor (VDR) and thyroid hormone receptor (TR). Little is known about the molecular mechanism(s) through which Hr collaborates with VDR and TR to maintain normal skin and hair cycling. Hsieh et al. comprehensively analyzed Hr mutants, many of which confer alopecia and skin hyperproliferation, for their physical and functional interaction with VDR and TR in human keratinocytes. All four LXXLL-like, hydrophobic nuclear receptor interaction motifs in Hr were required for repression of VDR-mediated transcription, unlike Hr-TR cooperation wherein only the two C-terminal hydrophobic motifs are essential. Naturally occurring Hr mutants that produce the alopecic phenotype were observed to bind VDR normally but display deficient VDR transrepression activity, sorting into those affecting histone deacetylase (HDAC) association and those residing in the C-terminal Jumonji C-domain. Because the Jumonji C-cassette catalyzes histone demethylation in related protein family members, Hsieh et al. postulate that Hr functions to repress VDR- and TR-targeted gene expression in chromatin via intrinsic histone demethylase activity, and through HDAC recruitment.