FEATURES

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BCL2 Protein Regulation 3

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All aspects of cellular biology somehow impinge on the process of programmed cell death, or apoptosis. Furthermore, disruption of apoptosis is a causative event in many human pathologies, especially cancer. Therefore, a comprehensive understanding of all signaling pathways that interact with and affect the function of direct apoptotic regulators will increase our knowledge of basic cellular functions, as well as the etiologies of many diseases. One family of proteins that can regulate cellular death following apoptotic stimuli is the BCL2-family of proteins. The basic mechanism by which BCL2 family members regulate apoptosis has been known for well over a decade, but nuances and subtleties are constantly coming to light. This Prospect article focuses on the non-canonical regulators of the BCL2-family of proteins, especially the void in our understanding of such interactions and the controversy that surrounds such interactions. Only when we completely understand how BCL2 proteins are regulated will we be able to modulate their activities for positive clinical outcomes.

PTH-Induced Osteoblast Regulation 70

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Parathyroid hormone (PTH) is a potent anabolic agent for the treatment of osteoporosis. Studies aimed at the characterization of downstream signals induced by PTH in bone, have identified activating transcription factor 4 (ATF4) as essential for the anabolic effects of PTH. ATF4 contributes to PTH-induced bone formation partially through its positive regulation of *osteocalcin,* an osteoblast-specific gene. To identify novel regulators of ATF4 function, Danciu et al, have focused on Twist proteins, Twist1 and Twist2, known inhibitors of *osteocalcin* transcription. The authors determined that PTH stimulation dramatically decreased Twist1 transcription in osteoblasts. Since ATF4 is a major regulator of the PTH response in *osteoblasts,* the authors investigated the mutual regulation between Twist and ATF4 and determined that these proteins interact in a manner that affects ATF4 DNA binding function. The interaction domain of Twist proteins is the C-terminal "box" domain and that of ATF4 is the N-terminus. Twist1 overexpression attenuated ATF4 binding to the osteocalcin promoter in response to PTH suggesting that the positive regulation of PTH-induced *osteocalcin* transcription is also due, in part, to the ability of PTH to decrease the levels of ATF4 inhibitors. Collectively, these results provide a novel insight into PTH-induced osteoblast regulation.

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mTOR Signaling and Bone Formation

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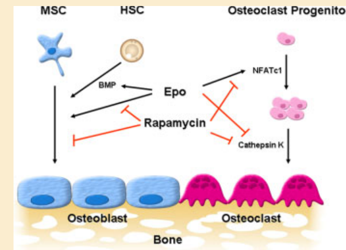
Recently, emerging evidence demonstrates that erythropoietin (Epo) plays an important role in bone formation and fracture healing. While the role of Epo and Epo/Epo receptor (EpoR) signaling pathways for production of red blood cells are well established, little is known about Epo/EpoR signaling in non-hematopoietic cells. Here, Kim et al investigated the effects of mTOR signaling on Epo-mediated osteoblastogenesis and osteoclastogenesis. Epo directly induces the differentiation of human bone marrow stromal cells (hBMSCs) into osteoblasts. mTOR inhibition by rapamycin blocks Epo-dependent and -independent osteoblastic phenotypes in hBMSCs and mouse bone marrow-derived stroma cell line ST2, respectively. Epo in combination with receptor activation of NF-κB ligand (RANKL) increases the number of osteoclasts generated from mouse marrow mononuclear cells (mMMCs) and from mouse macrophage cell line RAW264.7 cells. Rapamycin treatment also inhibits Epo-dependent and -independent osteoclastogenesis in mMMCs and Raw264.7 cells. Furthermore, the authors found that Epo increases NFATc1 expression and decreases cathepsin K expression in an mTOR-independent manner, resulting in an increase of osteoclast numbers and a decrease in resorption activity. These results indicate that the mTOR signaling pathway plays an important role in Epo-mediated bone homeostasis.



Glucose Activates RUNX2: DNA Association

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Transcriptional control of gene expression in vascular endothelial cells (EC) is mediated through specific DNA-binding factors. The Runt-domain family member RUNX2 regulates cytokine, matrix, and metalloproteinase levels to promote angiogenesis. However, the precise mechanisms through which this occurs have not been described. Pierce et al report that glucose activates cell signaling and RUNX2 phosphorylation to promote cell cycle progression. RUNX2 DNA binding in response to glucose was mediated by cyclin-dependent kinase (CDK)4 activity and coincided with pRB phosphorylation in the G1 phase. The $p21^{Cip1}$ protein is a CDK inhibitor that is normally repressed by RUNX2 and is responsible, in part, for restraining cell cycle progression. RUNX2 localized to focal subnuclear regions after glucose treatment and associated with a glucose-responsive RUNX2 binding site in the $p21^{Cip1}$ promoter. A RUNX2 cdk-site mutant expressed in EC exhibited dominant negative activity. It inhibited EC proliferation, reduced monolayer wound healing, and disrupted tubulogenesis (*in vitro* model of angiogenesis). Therefore, the studies by Pierce et al have begun to define both the mechanisms regulating RUNX2 phosphorylation in response to glucose and its relevance to endothelial cell function. These findings may lead to the identification of novel cellular targets regulating tumor angiogenesis, which could be exploited for therapeutic benefit.