FEATURES

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Hypoxia-Inducible Factor-1: A Critical Player in the Survival Strategy of Stressed Cells

Shuyang Chen and Nianli Sang

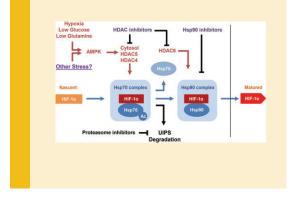
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HIF-1 activation has been well known as an adaptive strategy to hypoxia. Recently it became clear that hypoxia was often accompanied by insufficient supply of glucose or amino acids as a common result of poor circulation that frequently occurs in solid tumors and ischemic lesions, creating a mixed nutrient insufficiency. In response to nutrient insufficiency, stressed cells elicit survival strategies including activation of AMPK and HIF-1 to cope with the stress. Particularly, in solid tumors, HIF-1 promotes cell survival and migration, stimulates angiogenesis, and induces resistance to radiation and chemotherapy. Interestingly, radiation and some chemotherapeutics are reported to trigger the activation of AMPK. Here we discuss the recent advances that may potentially link the stress responsive mechanisms including AMPK activation, ATF4 activation and the enhancement of Hsp70/Hsp90 function to HIF-1 activation. Potential implication and application of the stress-facilitated HIF-1 activation in solid tumors and ischemic disorders will be discussed. A better understanding of HIF-1 activation in cells exposed to stresses is expected to facilitate the design of therapeutic approaches that specifically modulate cell survival strategy.

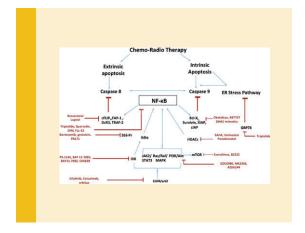
Control of Apoptosis in Treatment and Biology of Pancreatic Cancer

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Pancreatic cancer is estimated to be the 12th most common cancer in the United States in 2014 and yet this malignancy is the fourth leading cause of cancer-related death in the United States. Late detection and resistance to therapy are the major causes for its dismal prognosis. Apoptosis is an actively orchestrated cell death mechanism that serves to maintain tissue homoeostasis. Cancer develops from normal cells by accruing significant changes through one or more mechanisms, leading to DNA damage and mutations, which in a normal cell would induce this programmed cell death pathway. As a result, evasion of apoptosis is one of the hallmarks of cancer cells. PDAC is notoriously resistant to apoptosis, thereby explaining its aggressive nature and resistance to conventional treatment modalities. The current review is focus on understanding different intrinsic and extrinsic pathways in pancreatic cancer that may affect apoptosis in this disease.



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Biology and Treatment of Paget's Disease of Bone

Mahéva Vallet and Stuart H. Ralston

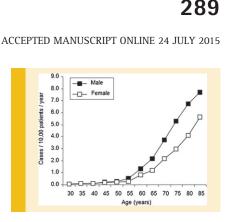
Paget's disease of bone (PDB) is a common skeletal disorder characterized by increased and disorganized bone remodeling affecting one or more skeletal sites. Although some patients are asymptomatic others develop complications such as bone pain, deformity, nerve compression syndromes, and fragility fractures. Genetic factors play an important role in the pathogenesis of PDB and there is strong evidence that susceptibility is determined by variants within or close to genes that regulate osteoclast function. Environmental factors also play a key role but the nature of the environmental triggers is less clear. Bisphosphonates are a highly effective treatment for the elevations in bone turnover that are characteristic of PDB but it is unclear at present if they alter the natural history of the disease. Here, we review the epidemiology, clinical, cellular, and molecular abnormalities in PDB as well as environmental and genetic triggers, and current available treatment options.

Competing Repressive Factors Control Bone Morphogenetic Protein 2 (BMP2) in Mesenchymal Cells

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The amount, timing, and location of bone morphogenetic protein 2 (BMP2) synthesis influences the differentiation of pluripotent mesenchymal cells in embryos and adults. The BMP2 3'untranslated region (3'UTR) contains a highly conserved AU-rich element (ARE) embedded in a sequence that commonly represses gene expression in mesenchymal cells. Computational analyses indicate that this site also may bind several microRNAs (miRNAs). Although miRNAs frequently target AU-rich regions, this ARE is unusual because the miRNAs directly span the ARE. We began to characterize the factors that may regulate Bmp2 expression via this complex site. The activating protein HuR (Hu antigen R, ELAVL1, HGNC:3312) directly binds this ARE and can activate gene expression. An miRNA was demonstrated to reverse HuR-mediated activation. Mutational and RNA-interference evidence also supports an AUF1 (AU-factor-1, HNRNPD, HGNC:5036) contribution to the observed repressive activity of the 3'UTR in mesenchymal cells. A limited number of studies describe how miRNAs interact with ARE-binding proteins that bind adjacent sites. This study is among the first to describe protein/miRNA interactions at the same site.



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