FEATURES

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Hypoxia-Mediated Biological Control

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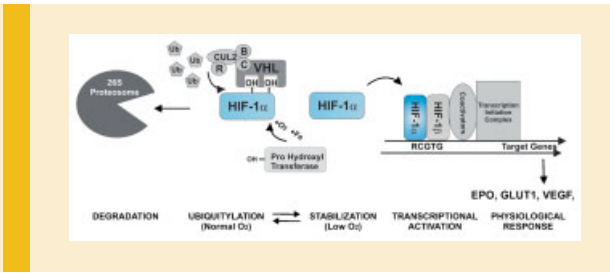

When oxygen demand is greater than oxygen supply, cells need to rapidly adjust their metabolism in order for the tissue to survive. Oxygen sensing by an organism influences a host of processes including growth, development, metabolism, pH homeostasis, and angiogenesis. Hypoxia also contributes to a wide number of human diseases including vascular disease, inflammatory conditions and cancer. Recently, major advances have been made in understanding the response of cells and tissues to hypoxia with the goal of providing mechanistic insight and novel therapeutic targets. In this article Cassavaugh and Lounsbury review both the normal biological effects of hypoxia as well as the alterations that occur in specific disease conditions with an emphasis on the cell signaling and gene transcription mechanisms that underlie the changes associated with chronic hypoxia. Comparisons of studies in the fields of cardiac ischemia and tumor angiogenesis reveal the complexities within the microenvironment that control responses to hypoxia. It is clear that more interaction between researchers in these fields will improve the development of therapies that either promote or prevent hypoxic responses.

RUNX2 Signaling Networks in Bone

Toshihisa Komori

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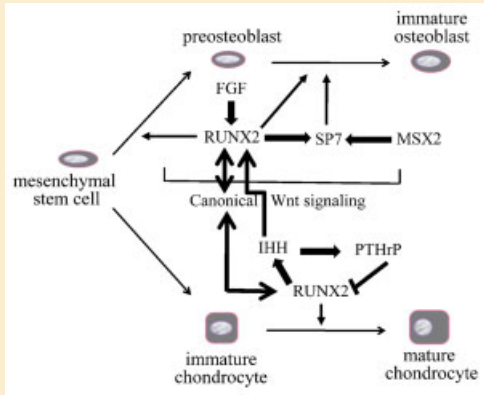

RUNX2 plays important roles in bone development by regulating the differentiation of osteoblasts and chondrocytes. The major issue is how RUNX2 regulates differentiation of the two different lineages at an appropriate time and space during bone development. Komori proposes that reciprocal regulations among RUNX2 and SP7 (another essential transcription factor for osteoblast differentiation), and major signaling pathways, (including FGF, Wnt, and IHH), form a crucial signaling network for the regulation of osteoblast and chondrocyte differentiation. RUNX2 and canonical Wnt signaling are required for *Sp7* expression at an early stage of osteoblast differentiation. FGF2 upregulates *Runx2* expression and activates RUNX2, and Runx2 expression is upregulated in gain-of-function mutations of FGFRs. Canonical Wnt signaling upregulates *Runx2* expression and activates RUNX2, and RUNX2 induces *Tcf7* expression. *Runx2* also interacts with TCF/LEF transcription factors and regulates transcription. In the process of endochondral ossification, reciprocal regulation of RUNX2 and IHH coordinates chondrocyte maturation and proliferation in the growth plates and regulates osteoblast differentiation at the perichondrium. Komori indicates that the key molecules and signaling pathways control the process of bone development by regulating each other and that further elucidation of reciprocal regulations would reveal why RUNX2 plays critical roles in both osteoblasts and chondrocytes.

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Roscovitine Treatment for ER-Positive Breast Cancer

Józefa Węsierska-Gądek, David Gritsch, Nora Zulehner, Oxana Komina, and Margarita Maurer

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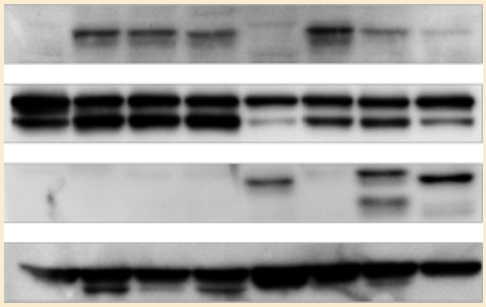

The growing incidence of breast cancers is a matter of great concern. Approximately 70% of breast cancers are estrogen receptor positive and hormones are known to be important in promoting breast carcinogenesis. ER-α, the major estrogen receptor, controls the expression of multiple genes involved in cell proliferation and survival. Its activity is regulated by phosphorylation; estrogen promotes its phosphorylation at Ser118. Wesierska-Gadek et al. examined the impact of two CDK inhibitors (roscovitine and DRB) on the phosphorylation of ER-α in non-stimulated and ligand-stimulated human MCF-7 breast cancer cells. They found that roscovitine but not DRB abolished the basal phosphorylation of ER-α at Ser118 in non-stimulated cells and also prevented the activation of ER-α after stimulation with estrogen in a time- and concentration-dependent manner. The abolition of ER-α phosphorylation at Ser118 coincided with the inhibition of CDK7 activity. Moreover, the authors investigated the use of roscovitine in conjunction with tamoxifen for the treatment of ER-positive breast cancers. The combination enhanced roscovitine's anti-proliferative effects; the two drugs interacted synergistically. These data indicate that simultaneous inhibition of cell cycle progression, transcriptional elongation, and ER-signaling by pan-specific CDK inhibitors such as roscovitine might prove advantageous in the treatment of ER-positive breast cancers.

Cdk1: Self Renewal of ES Cells

Wei Wei Zhang, Xiao Jie Zhang, Hui Xian Liu, Jie Chen, Yong Hong Ren, Deng Gao Huang, Xiang Hong Zou, and Wei Xiao

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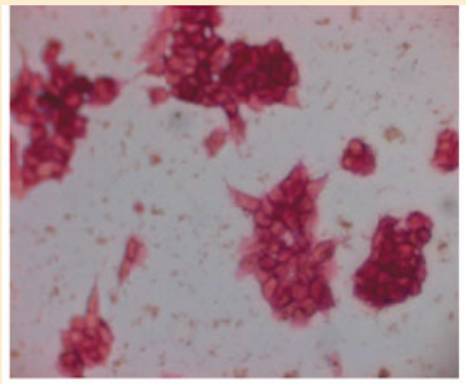

Understanding the molecular mechanisms underlying the maintenance of undifferentiated embryonic stem (ES) cells is a hot topic in stem cell biology. The study by Zhang et al. provides new insights into how the cell cycle regulator Cdk1 is involved in maintaining this "stemness" state. They show that the level of expression of *Cdk1* correlates closely with the undifferentiated state of ES cells. Moreover, ES cell-specific transcription factors, Oct4 and Nanog, are involved in maintaining *Cdk1* expression. Depletion of *Cdk1* by RNA interference abrogates the self-renewal of ES cells. They further demonstrate that Cdk1 regulates *Sox2, Tcl1, Nanog,* and *Esrrb.* These genes are key factors required to maintain the self-renewal of ES cells. On the other hand, differentiation marker genes, such as *Cdx2* and *Hand1,* are generated upon *Cdk1* depletion. These results suggest a role for Cdk1 in maintaining the unique undifferentiated and self-renewal state of the mouse ES cells.