

FEATURES

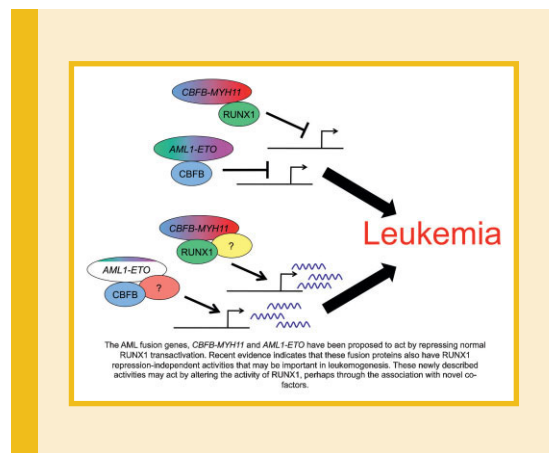
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RUNX1 and CBF Leukemias

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1039

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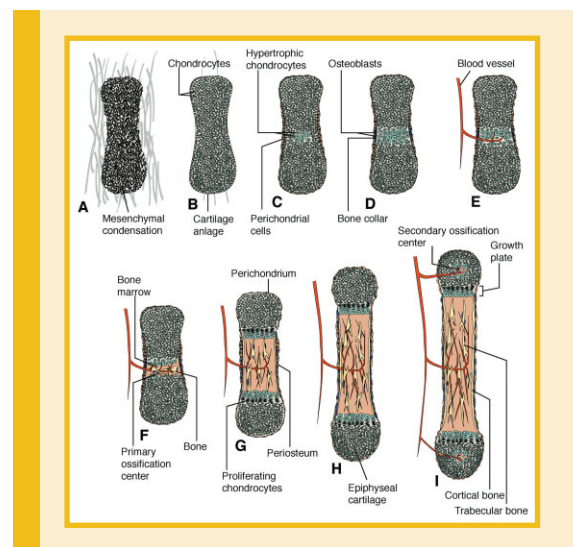
A hallmark of acute myeloid leukemias (AMLs) is the presence of recurrent chromosomal rearrangements. Two common rearrangements, *inv(16)* and *t(8;21)*, generate fusion genes with members of the Core Binding Factor (CBF) family of transcription factors, *CBFB* and *RUNX1*, respectively. Because these fusion genes, *CBFB-MYH11* and *AML1-ETO* (aka *RUNX1-RUNX1T1*), are required for leukemogenesis, and are expressed exclusively in AML cells, they are attractive targets for the development of new therapies. However, the design of such therapies requires a good mechanistic understanding of the fusion genes' activities. It has been proposed that both fusion genes act by inhibiting *RUNX1*. However, recent publications have indicated that the fusion genes may have *RUNX1*-repression independent activities as well. This article describes these recent findings and their potential implications for the treatment of CBF leukemias.

FGFs in Endochondral Skeletal Development

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1046

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FGFs and their cognate receptors (FGFRs) are important cell fate regulators of development and homeostasis as evidenced by the causative roles of FGFR mutations in disorders of skeletal development and human cancer. Understanding the mechanisms through which FGFs act to bring about these effects has historically lagged behind their recognition as players in these pathways; however, as Degnin et al point out in a comprehensive review, the mechanisms relevant to endochondral skeletal development are emerging. The authors examine the developmental expression patterns of the FGFs and FGFRs against the backdrop of cartilage-mediated skeletal development and linear growth. They inspect the molecular interactions between FGF ligands, receptors and cofactors and tissue-specific proteoglycans that activate signaling pathways that regulate chondrocyte proliferation and differentiation in the growth plate. The central roles of FGF18 and FGFR3 are highlighted and explored in the contexts of established circuits mediated by IHH, PTHrP and other regulators of skeletal development. Degnin et al also raise several fundamental questions that remain unanswered, such as how are FGF signals propagated through cartilage to distant cells, how are FGF-initiated signals integrated with other regulatory circuits in developing bone and how might aberrant FGF signals associated with disease be countered therapeutically?

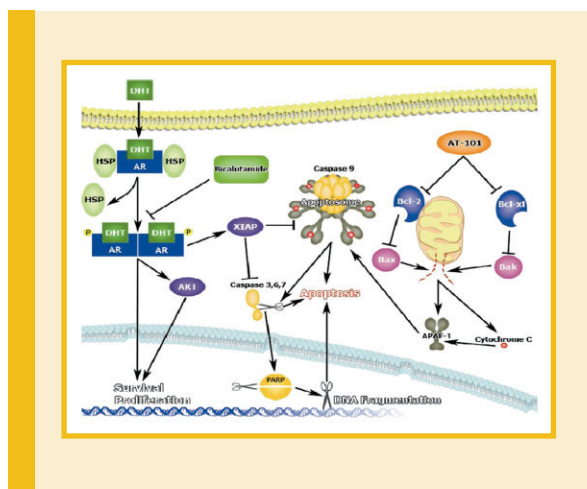
Inhibiting Prostate Cancer Progression

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1187

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Prostate cancer remains a leading cause of cancer death in American men. Androgen deprivation therapy (ADT) is the most common treatment for advanced prostate cancer patients; however, ADT fails in nearly all cases resulting in castration resistant or androgen insensitive (AI) disease. In many cases, this progression results from dysregulation of the pro-survival Bcl-2 family proteins. Inhibition of pro-survival Bcl-2 family proteins, therefore, may be an effective strategy to delay the onset of AI disease. Gossypol, a small molecule inhibitor of pro-survival Bcl-2 family proteins, has been demonstrated to inhibit AI prostate cancer growth. This study by McGregor et al was undertaken to better understand the *in vitro* effects of androgen receptor (AR) on AT-101 induced apoptosis. Upon AR activation in combination with AT-101 treatment, apoptosis is reduced, cell survival increases, and caspase activation is attenuated. Akt and X inhibitors of apoptosis (XIAP) are downregulated in the presence of AT-101, and AR stimulation rescues protein expression. Combination treatment of bicalutamide and AT-101 increases apoptosis by reducing the expression of these prosurvival proteins. These data suggest that combination therapy of AT-101 and androgen deprivation therapy may further delay the onset of androgen insensitive disease, resulting in prolonged progression free survival of prostate cancer patients.



Adiponectin and Hepatic Fibrosis

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1195

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Recently adipocytokines, primarily produced by white adipose tissue (WAT), have been implicated as molecular mediators of liver fibrogenesis. The biological basis for the molecular interplay of leptin and adiponectin in the regulation of matrix production is timely as non-alcoholic fatty liver disease has become so widespread. In this article Handy, et. al. extend recent findings that adiponectin is protective against hepatic fibrosis. In this report they demonstrate that adiponectin upregulates matrix metalloproteinase 1 while conversely inhibiting available TIMP-1 protein availability in cultured hepatic stellate cells. More compelling are *in vivo* data revealing that adiponectin knockout mice are more vulnerable to develop liver fibrosis in the setting of leptin and carbon tetrachloride co-administration, and liver tissue expression of the Suppressors of Cytokine Signaling 3 (SOCS3) mRNA protein in these mice are markedly suppressed. Handy and colleagues demonstrate that adiponectin down-regulates leptin-mediated phosphorylation of Stat3 proteins—a downstream effector in the leptin signaling cascade which may be the result of activation of adenosine monophosphate kinase (AMPK)-related stabilization of SOCS-3 protein expression and a bi-phasic increase in SOCS-3mRNA. Their findings suggest adiponectin has hierarchical control of upstream leptin-signaling events, since both *in vivo* and *in vitro* adiponectin overrides the pro-fibrotic effects of leptin.

