FEATURES

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The Search for Tumor Suppressor Genes

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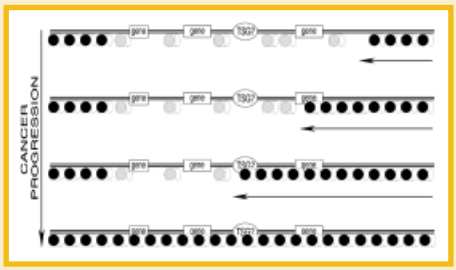

Genes with tumor suppressor function are generally inactivated in at least some cancers, and this inactivated state is often the first experimental indicator of a gene's potential function in cancer control. Bradley et al. review recent advances showing that spontaneously-occurring large scale deletions are highly clustered, and these clusters, or hotspots, coincide with some of the regions where deletions are reported in tumors. Deletion frequencies are so high that individuals carrying knockout deletions have been identified, but there is no known effect on cancer incidence; thus, more deletions documented may actually reflect less chance of the affected gene being an authentic tumor suppressor. Similarly, epigenetic inactivation can arise from spreading of chromatin with closed conformation, generating new domains of silent DNA stretching for a megabase or more. Again, the frequency of this spreading can be relatively high, whether or not cancer-related genes or indeed any genes at all, are turned off in the process. In both inactivation processes, therefore, the argument is made that some genes which are thought of as tumor suppressors may only be victims of collateral damage and their roles in cancer suppression should be reevaluated.

Transcriptional Repression in ES Cells

Clara Y. Cheong and Thomas Lufkin

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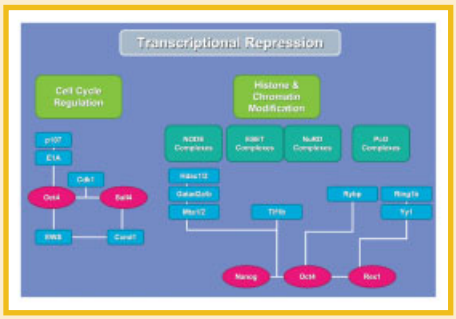

With the power of both pluripotency and self-renewal encapsulated in a single cell, the workings of ES cells are a fascination of nature. While genes involved in self-renewal are active in ES cells, other genes for differentiation to other cell fates must be repressed, but readily accessed and activated on developmental cues. Work in this field has pointed towards the role of chromatin modifications, particularly the unique presence of bivalent chromatin domains, in preparing ES cells for potentially imminent differentiation cues. In this feature, the authors review the associations between key ES cell transcription factors and chromatin modifying repressive complexes that may serve to establish and maintain ES cell identity. Tight links between the transcriptional and epigenetic machinery, as well as the cell cycle enables controlled transitions of multiple developmental genes into self-renewal or differentiation. In addition to Oct4, an essential ES cell transcription factor, other transcription factors with co-occurring binding sites or protein complexes suggest that transcriptional regulation occurs through a modular system. In this light, further extensive DNA-protein and protein-protein interaction studies are important to derive further insight on ES cell regulation.

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Osteoblastic Cell Fate

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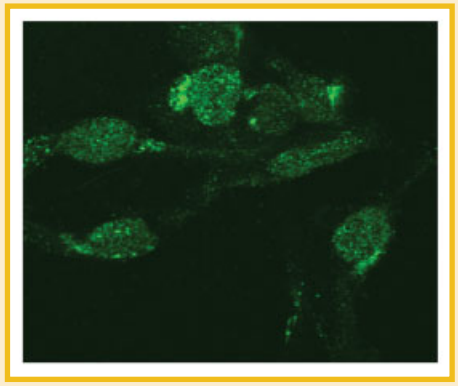
Connective Tissue Growth Factor (CTGF) induces osteoblastic differentiation, but the mechanisms involved are unknown. CTGF enhances the transactivating activity of the nuclear factor of activated T cells (NFAT), a nuclear factor that regulates osteoblastogenesis. NFAT is dephosphorylated by calcineurin, inducing its nuclear translocation, and NFAT is phosphorylated by glycogen synthase kinase 3β (GSK3β), resulting in its nuclear export. Smerdel et al. explore the mechanisms by which CTGF enhances NFAT transactivation, and demonstrate that CTGF induces the expression of *protein kinase cyclic GMP dependent type 2* (*Prkg2*), the gene encoding the cyclic GMP dependent protein kinase II (cGKII). As a consequence, cGKII phosphorylates GSK3β, favoring its degradation. Therefore, CTGF reduces the pool of active GSK3β available to phosphorylate NFAT so that NFAT remains dephosphorylated and localized to the nucleus of osteoblastic cells. Downregulation of *Prkg2* reverses the stimulatory effect of CTGF on NFAT transactivation confirming that *Prkg2*/cGKII is central to the mechanism of CTGF action. Since GSK3β also phosphorylates β-catenin, this mechanism could play a role in regulating Wnt signaling. Smerdel et al. provide novel insights into the regulation of GSK3β and NFAT transactivation by CTGF. The evidence suggests that GSK3β is a critical checkpoint in intracellular events controlling osteoblastic cell fate and function.



IGF1R IRES and Gene Regulation

Zheng Meng, Nateka L. Jackson, Oleg D. Shcherbakov, Hyoungsoo Choi, and Scott W. Blume

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Genes involved in the control of cellular proliferation and survival are often specifically regulated at the translational level, through structural features and regulatory protein binding sites contained within the 5'-untranslated region of the mRNA. Associated with a number of these mRNAs is a highly specialized translation-regulatory feature known as an internal ribosome entry site (IRES). In this issue, data presented by Meng et al provide insight into the fundamental molecular mechanisms by which one of these IRESs operates. Utilizing site-directed mutagenesis to dissect the IGF1R IRES, they have discovered that the sequence most critical for IRES function is potentially capable of direct Watson-Crick base-pairing interaction with the 18S rRNA component of the 40S ribosomal subunit. This finding is reminiscent of the mechanism utilized in prokaryotic organisms for translation initiation within polycistronic messages. Intriguingly, this same sequence element is also recognized by a specific group of RNA-binding proteins which differentially modulate IRES-mediated translation initiation. An adjacent homopolymeric loop serves to restrict access of these regulatory proteins to the critical sequence element, thereby governing the activity of the IRES. These results have implications for understanding how gene-specific translational regulation is accomplished in the cell.