FEATURES

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AKT as Locus of Cancer Phenotype 1

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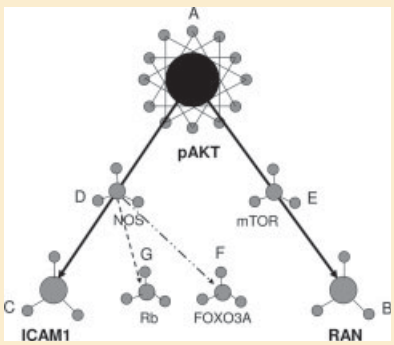
Cancer robustness is generated by the positive feedback loops. The positive loops hyperactivate AKT locus forming a cancer phenotype in leukemia, lymphoma, myeloma, plasmocytoma, sarcoma and carcinoma. The positive loops inducing AKT hyperphosphorylation increase activity of the AKT locus and the nodal associated and interconnected signaling genes. Only genes expressed above the threshold in the AKT signaling interactome networks, participate in the formation of the complex cancer phenotype. AKT is the switching locus for the cancer phenotype. The phenotype formation and maintenance is regulated by the AKT locus through entropy/enthalpy processes. Targeting the AKT by locus chemotherapy, changing redox balance (antioxidant/oxidant), affects phosphorylation and activity of the AKT, inducing conversion of the positive feedback loops and disappearance of the malignant phenotype.



The Bone Marrow Endosteal Niche: How Far from the Surface? 6

Eric Cordeiro-Spinetti, Russell S. Taichman, and Alex Balduino

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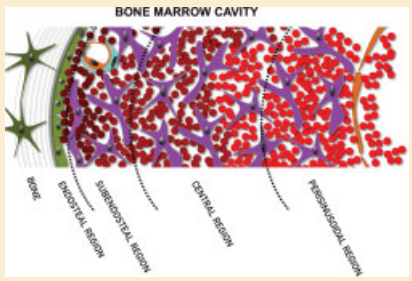
Hematopoietic stem cells (HSC) self-renewal takes place in the same microenvironment in which massive hematopoietic progenitor proliferation, commitment, and differentiation will occur. Histological and functional assays indicated that HSC and multipotent progenitors preferentially colonize the endosteal and subendosteal regions, in close association with the bone surface. Conversely, committed progenitors and differentiated cells are distributed in the central and perisinusoidal regions, respectively. Over the last decade, many investigative teams sought to define which cell types regulate the HSC niche, how they are organized, and to what extent they interface with each other. System dynamics requires different stromal cells to operate distinct functions over similar HSC pools rather than a single stromal cell type controlling everything. The focus of the prospect article is to depict the players in the endosteal niche in order to better understand the interactions of the HSC within the niche, and to identify potential targets to manipulate and/or modulate normal and malignant HSC behavior.



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The Presence of Androgen Receptor Elements Regulates ZEB1 Expression in the Absence of Androgen Receptor

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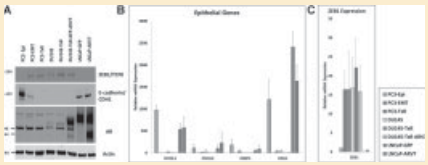

Zinc finger E-box binding homeobox 1 (ZEB1) is a transcription factor that plays a central role in the epithelial to mesenchymal transition (EMT) of cancer cell lines. Studies on its regulation have mostly focused on the negative 3'UTR binding of miR200c. Interestingly, it has been previously reported that androgen receptor (AR) regulates ZEB1 expression in breast and prostate cancers. To validate the findings, various ZEB1 promoter deletions were cloned into a luciferase reporter system to elucidate the contribution of two putative androgen response elements (AREs). The in vivo contribution of AR was also assessed in cell lines after R1881 treatment using qPCR with prostate specific antigen (PSA) as the positive control. The authors discovered that AR upregulates the levels of expression of ZEB1 10-fold on a luciferase promoter that only contains the distal ARE. However, when the proximal ARE is included, no additional activation is apparent with AR or its hormone independent variant, AR-V7. Furthermore, a promoter construct containing both AREs activates transcription of ZEB1 even in the AR-null cell lines DU145 and PC3. Incubation of the AR-positive cell line, LNCaP with R1881, failed to substantially increase the expression levels of ZEB1. Despite the presence of AREs in the promoter region, it appears that ZEB1 expression can be induced even without AR. In addition, the region around the distal ARE is a potent repressor in AR-null cell lines.

PTH Regulates β2-Adrenergic Receptor Expression in Osteoblast-Like MC3T3-E1 Cells

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Shuichi Moriya, Tadayoshi Hayata, Takuya Notomi, Smriti Aryal, Testuya Nakamaoto, Yayoi Izu, Makiri Kawasaki, Takayuki Yamada, Jumpei Shirakawa, Kazuo Kaneko,Yoichi Ezura, and Masaki Noda

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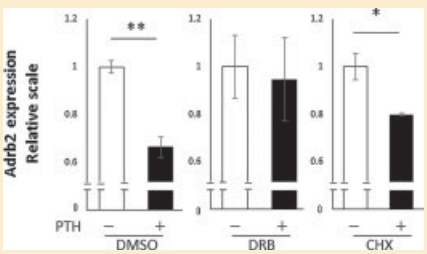

The authors investigated the effects of parathyroid hormone (PTH) on beta2 adrenergic receptor gene expression in osteoblast-like MC3T3-E1 cells. PTH treatment immediately suppressed the expression levels of beta2 adrenergic receptor mRNA. PTH effect was dose-dependent starting as low as 1 nM. PTH action on beta2 adrenergic receptor gene expression was inhibited by a transcriptional inhibitor, DRB, but not by a protein synthesis inhibitor, cycloheximide suggesting direct transcription control. Knockdown of beta2 adrenergic receptor promoted PTH-induced expression of *c-fos*, an immediate early response gene. Knockdown of beta2 adrenergic receptor enhanced PTH-induced transcriptional activity of cyclic AMP response element-luciferase construct in osteoblasts. Knockdown of beta2 adrenergic receptors also enhanced forskolin-induced luciferase expression, revealing that adenylate cyclase activity is influenced by beta2 adrenergic receptor. Knockdown of beta2 adrenergic receptor enhanced PTH-induced phosphorylation of cyclic AMP response element binding protein (CREB). The data reveal that beta2 adrenergic receptor is one of the targets of PTH and acts as a suppressor of PTH action in osteoblasts.