FEATURES

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Wnt-Centric Epigenetic Signaling in Stem Cells

Bingnan Gu, Kazuhide Watanabe, and Xing Dai

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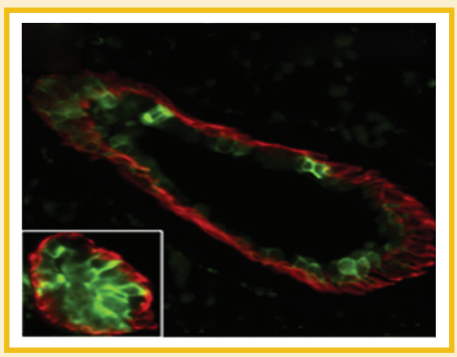

The recent elucidation of DNA methylation and histone modification landscapes of embryonic stem (ES) cells have shed light onto a unique epigenetic strategy used to support homeostasis of ES cells. However, whether and how such epigenetic modifications function in tissue-specific epithelial stem cells is less clear. Mounting evidence suggests an interesting and critical connection between canonical Wnt signaling and epigenetic regulation of epithelial stem cells. For example, it has been shown that Pygo2, a chromatin effector acting downstream of Wnt/β-catenin signaling, opens the chromatin of and expands mammary epithelial stem and progenitor cells. In this invited "Prospect" article, Gu et al. focus their discussion on leading epithelial stem cell models, namely skin, intestine, and mammary gland, and review recent studies implicating epigenetic control mechanisms, particularly those linked to Wnt/β-catenin signaling, in mammalian epithelial stem cell development and homeostasis. The authors anticipate that epigenetic and epigenomic studies of epithelial stem cells will continue to rise, and that an analysis of the effect of Wnt signaling on the epigenomes of these will be highly beneficial to both basic stem cell biology and the design of therapeutic tools to manipulate the epigenetic state of these cells.

Twist-ing Cell Fate

D. Cakouros, R.M. Raices, S. Gronthos, and C.A. Glackin

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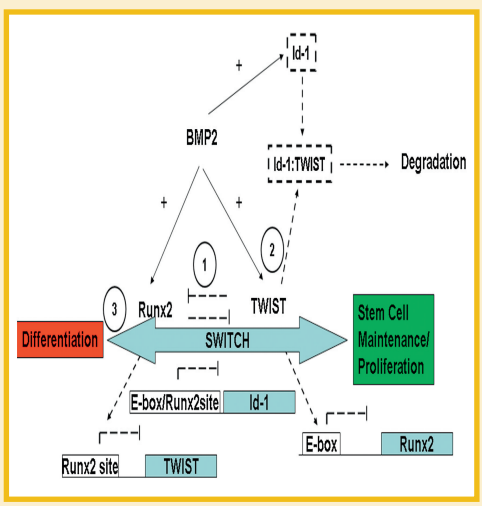

One of the difficulties in stem cell biology is understanding the transcriptional regulation of important factors that regulate self-renewal and stem cell maintenance in embryonic development as well as aging and cancer. In addition, a key problem in the use of stem cells for tissue regeneration and repair is the efficiency of these cells to engraft and fully regenerate damaged tissues. Therefore, to optimize this process, a comprehensive understanding of the key regulators of mesenchymal stem cell (MSC) self-renewal and maintenance is critical to the success of future cell therapy, as well as other clinical applications. The basic helix loop helix transcription factor Twist plays a master regulatory role in all of these processes of epithelial to mesenchymal transition (EMT); therefore, fully understanding the mechanistic role of Twist in lineage specification/differentiation and tumorigenesis is vital to the success of future therapeutic uses of MSCs. This article provides background on the basic mechanisms and signaling pathways that are important to stem cell maintenance and tumor initiation, which involve similar EMT pathways. This information will contribute to a broader understanding of stem cell biology and will help to provide novel molecular targets for cancer and to generate novel stem cell based therapeutics.

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GRP78 in Physiology and Cancer

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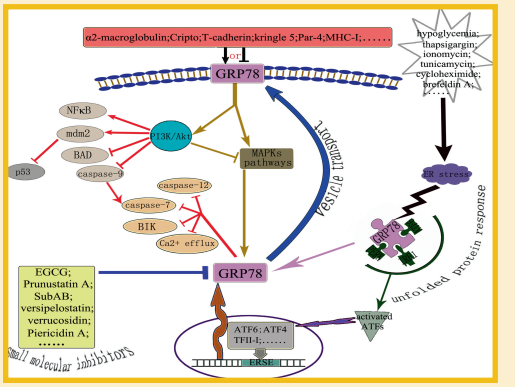
Belonging to the family of heat shock proteins, GRP78 can act as a molecular chaperone, facilitating folding of nascent polypeptides, participating in the degradation of misfolded products, and influencing transportation of membrane or secretary proteins. However, unlike its homologues, GRP78 has the property of multifaceted subcellular positioning. In the endoplasmic reticulum, it sustains cytosolic calcium homeostasis and serves as the hub for an unfolded protein response. At the mitochondria, it directly interacts with and suppresses the activation of pro-apoptotic molecules. On the cell surface, it can be bound by extracellular ligands and can transduce proliferative signals to the cytoplasm. In a variety of tumors, some of these physiological actions are deregulated, or at least exaggerated. The close correlation between GRP78 and neoplasm sheds light on the mystery of carcinogenesis and cancer cell chemo resistance. This review summarizes and analyzes GRP78's related molecular mechanisms, especially complex signaling. Targeting GRP78 has already achieved success at the experimental level, presenting the possibility of clinical utilization, including prognostic prediction and cancer treatment.



UV Light: Cancer Killing Strategies

Hiroaki Kimura, Claudia Lee, Katsuhiro Hayashi, Kensuke Yamauchi, Norio Yamamoto, Hiroyuki Tsuchiya, Katsuro Tomita, Michael Bouvet, and Robert M. Hoffman

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A major problem in cancer surgery is minimal residual disease remaining after tumors or metastases are resected. The report by Kimura et al in this issue demonstrates that UVC irradiation can ablate tumors in a mouse model of minimal residual lung cancer. In the current study, the cancer cells were labeled with green fluorescent protein (GFP) in the nucleus and red fluorescent protein (RFP) in the cytoplasm allowing fluorescence-guided UV light irradiation of the tumor in nude mice. The dual-color cells allow imaging of cancer cell dynamics, including apoptosis in vivo as well as in vitro. Previous findings by these investigators demonstrated that tumors can be labeled in situ with a telomerase-specific adenovirus containing the GFP gene. Future experiments will utilize the combined approach of labeling the tumors in vivo with GFP with the adenovirus, subsequent fluorescence-guided surgical resection and then fluorescence-guided UVC irradiation of any MRC. This strategy could advance cancer surgery.