

FEATURES

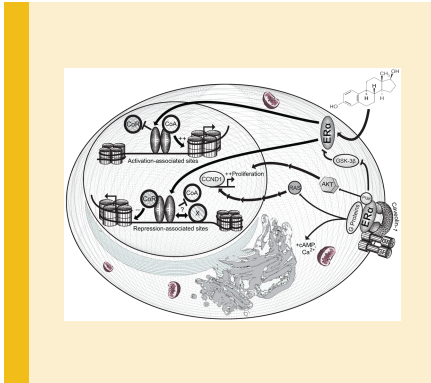
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Estrogen Receptor Alpha: Molecular Mechanisms and Emerging Insights

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2203

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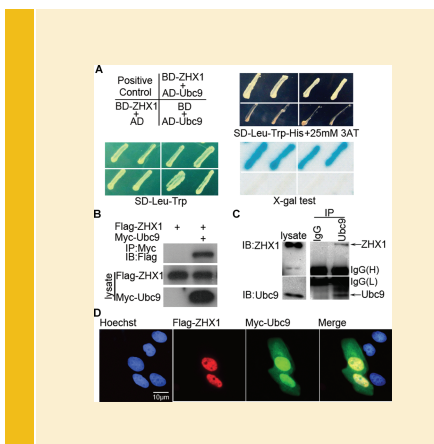
Estrogen receptor alpha (ER α) is a cellular receptor for the female sex hormone estrogen and other natural and synthetic ligands and play critical roles in normal development and physiology and in the etiology and treatment of endocrine-related diseases. ER α is a member of the nuclear receptor superfamily of transcription factors and regulates target gene expression in a ligand-dependent manner. It has also been shown to interact with G-protein coupled receptors and associated signaling molecules in the cytoplasm. Transcriptionally, ER α either binds DNA directly through conserved estrogen response element sequence motifs or indirectly by tethering to other interacting transcription factors and nucleate transcriptional regulatory complexes which include an array of co-regulator proteins. Genome-scale studies of ER α transcriptional activity and localization have revealed mechanistic complexity and insights including novel interactions with several transcription factors, including FOXA1, AP-2g, GATA3, and RUNX1, which function as pioneering, collaborative, or tethering factors. The major challenge and exciting prospect moving forward is the comprehensive definition and integration of ER α complexes and mechanisms and their tissue-specific roles in normal physiology and in human diseases.

The SUMOylation of Zinc-Fingers and Homeoboxes 1 (ZHX1) by Ubc9 Regulates Its Stability and Transcriptional Repression Activity

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Zinc-fingers and homeoboxes protein 1 (ZHX1) belongs to the ZF (zinc-fingers) class of homeodomain transcription factors, and its function remains largely unknown. ZHX1 has been previously found to interact with the activation domain of the nuclear factor Y subunit A (NFYA) and to have a transcriptional repression activity. Here, it is reported that the SUMO-E2 conjugating enzyme Ubc9 was identified to interact with ZHX1 by an interaction screen using a yeast two-hybrid system. This interaction was confirmed by co-immunoprecipitation and co-localization assays. Further study showed that ZHX1 is SUMOylated by Ubc9 with SUMO1 at the sites K159, K454, and K626. Furthermore, it is demonstrated that the SUMOylation of ZHX1 regulated the stability, ubiquitination and transcriptional activity of ZHX1.

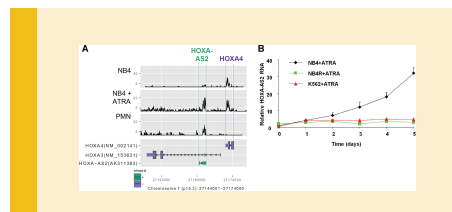
HOX Antisense lincRNA HOXA-AS2 is an Apoptosis Repressor in all *Trans* Retinoic Acid Treated NB4 Promyelocytic Leukemia Cells

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HOXA cluster antisense RNA 2 (HOXA-AS2) is a long non-coding RNA located between the HOXA3 and HOXA4 genes in the HOXA cluster. Its transcript is expressed in NB4 promyelocytic leukemia cells and human peripheral blood neutrophils, and expression is increased in NB4 cells treated with all *trans* retinoic acid (ATRA). Knockdown of HOXA-AS2 expression by transduced shRNA decreases the number of viable cells and increases the proportion of apoptotic cells, measured by annexin V binding and by activity and cleavage of caspases-3, -8, and -9. The increase in death of HOXA-AS2 knockdown cells was accompanied by an elevated TNF-related apoptosis-inducing ligand (TRAIL) levels, but ATRA-induced NB4 cells treated with TRAIL did show an increase in HOXA-AS2 expression. These results demonstrate that ATRA induction of HOXA-AS2 suppresses ATRA-induced apoptosis, possibly through a TRAIL-mediated pathway. HOXA-AS2-mediated negative regulation thus contributes to the fine-tuning of apoptosis during ATRA-induced myeloid differentiation in NB4 cells



Biomarkers of Sensitivity to Potent and Selective Antitumor 2-(4-Amino-3-Methylphenyl)-5-Fluorobenzothiazole (5F203) in Ovarian Cancer

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2-(4-Amino-3-methylphenyl)-5-fluorobenzothiazole (5F203, NSC 703786) lysylamide belongs to a novel mechanistic class of antitumor agents. It elicits activity against ovarian, breast, kidney and colorectal cancer models. In sensitive breast cancer cells, 5F203 activates aryl hydrocarbon receptor (AhR) signaling. Herein, the role of AhR in 5F203 activity in two ovarian cancer cell lines: IGROV-1 (sensitive to 5F203), SKOV-3 (resistant to this agent) is evaluated. In addition, cancer cells have been isolated from ascites fluid of ovarian cancer patients; sensitivity to 5F203 and concurrent AhR signal transduction has been examined in ascites-isolated ovarian cancer patients' cells. 5F203 induced enhanced CYP1A1 expression, AhR translocation and ROS formation in IGROV-1 cells and ascites-isolated ovarian cancer cells that were sensitive to 5F203. In IGROV-1 cells 5F203-induced ROS formation was accompanied by JNK, ERK and P38MAPK phosphorylation, DNA damage and cell cycle arrest prior to apoptosis. In contrast, 5F203 failed to induce CYP1A1 expression, AhR translocation or oxidative stress in 5F203-resistant SKOV-3 cells, or in ovarian cancer ascites cells inherently resistant to this agent. It is proposed that AhR may represent a new molecular target in the treatment of ovarian tumors and 5F203 may exemplify a potential novel treatment. Furthermore, putative biomarkers of sensitivity to this agent have been Identified.

