ESTROGEN RECEPTOR AND ESTROGEN RELATED RECEPTOR MAY CORPORATELY REGULATE HYPOXIC GENE EXPRESSION

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Tumor cells can undergo adaptation to the hypoxia environment created by rapid growth of tumor cells to persist growing. A main regulator of hypoxia induced gene expression is hypoxia-inducible factor (HIF), and HIF can bind to the promoter of hypoxia target gene, such as VEGF and PGK1. Orphan nuclear receptor estrogen related receptor (ERR) can form protein complex with HIF heterodimer and regulate hypoxia induced gene expression through association with the promoter of target gene. Estrogen receptor (ER)-beta can form protein complex with Endothelial Nitric Oxide Synthase (eNOS), HIF1alpha and HIF2alpha and regulate hypoxia induced gene expression in hypoxia or E2 induced manner. These evidences lead to the hypothesis that ERR and ER can corporately regulate HIF induced gene expression. It is seen that some hypoxia target genes are also targets of sonic hedgehog signaling, Yamazaki reported that mRNA levels of VEGF were significantly increased in endothelial progenitor cells (EPC) isolated from human peripheral blood after cultured with sonic hedgehog peptide, indicating hedgehog signaling and nuclear receptor ER and ERR can co-regulate the expression of hypoxic genes and thus influence the tumor angiogenesis.