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Loss of estrogen responsiveness under hypoxia occurs through hypoxia inducible factor-1 induced proteasome-dependent down regulation of estrogen receptor

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Estrogen receptor is a ligand-activated transcription factor. Its action depends on the receptor, its ligand, and its coactivator proteins. As a consequence, the concentration of the receptor is a major component that governs the magnitude of the estrogen response. Despite the extensive knowledge on mechanism of estrogen receptor action, regulation of estrogen receptor itself is not very well understood. Estrogen receptor is known to be downregulated under hypoxia leading to inhibition of estrogen receptor mediated transcription activation. We have studied mechanism of loss of estrogen responsiveness under hypoxia. We found that Hif-1α, a major transcription factor regulating hypoxic response, inhibited transcription of estrogen response element driven luciferase gene by expression of HIF-1α/vp16 construct designed to contain transcription activity under normoxia. This loss of estrogen responsiveness appears to be the result of ERα downregulation. ERαwas downregulated at the levels of ligand-biding and protein within 12-24h, and the response was blocked by the proteasome inhibitor MG132, protein synthesis inhibitor cyclohexamide, and tyrosine kinase inhibitor Genistein. These results demonstrate that Hif-1α downregulates ERα by proteasome dependent pathway.