HIF-1とSp1の相互作用による低酸素に応答したRORα4遺伝子の転写活性化

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Hypoxia-induced activation of the retinoic acid receptor-related orphan receptor α4 gene by an interaction between hypoxia-inducible factor-1 and Sp1

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ABSTRACT : Hypoxia plays a key role in the pathophysiology of many disease states, and expression of the retinoic acid receptor-related orphan receptor α (RORα) gene increases under hypoxia. We investigated the mechanism for this transient hypoxia-induced increase in RORα expression. Reverse transcription-coupled PCR (RT-PCR) analysis revealed that the steady-state level of mRNA for the RORα4 isoform, but not the RORα1 isoform, increased in HepG2 cells after 3 hr of hypoxia. Transient transfection studies showed that the hypoxia-induced increase in RORα4 mRNA occurs at the transcriptional level, and is dependent on a hypoxia responsive element (HRE) located downstream of the promoter. A dominant-negative mutant of hypoxia inducible factor-1α (HIF-1α) abrogates the transcription activated by hypoxia as well as the transcription activated by exogenously expressed HIF-1α, demonstrating the direct involvement of HIF-1α in the transcriptional activation. However, HIF-1 alone was not sufficient to activate transcription in hypoxic conditions, but rather required Sp1/Sp3, which binds to a cluster of GC-rich sequences adjacent to the HRE. Deletion of one or more of these GC Boxes reduced or eliminated the HIF-1-dependent transcription. Together, these results suggest that the hypoxia-responsive region of the RORα4 promoter is composed of the HRE and GC-rich sequences, and that the transcriptional activation under hypoxia is conferred through the cooperation of HIF-1 with Sp1/Sp3.

抄録　核内オーファンレセプターRORα4遺伝子の発現が低酸素により増大しすることをRT-PCRで示し、さらにトランスフェクション実験でこの増大が転写レベルで起こることを示した。低酸素に応答した転写活性化はRORαの他のプロモーターでは起こらず、RORα4アイソフォーム特異的であること、プロモーター下流に局在する低酸素応答配列への低酸素誘導因子（HIF-1）の結合により起こることを明らかにした。さらに、HIF-1依存的な転写活性化に構成的な転写制御因子Sp1が協調的に作用していることも示した。