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Targeting the HIF system

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Keywords

HIF-1, hypoxia, p300/CBP, tumors

Context

Cellular hypoxia is a hallmark of many tumors and is involved in key aspects of tumor biology such as angiogenesis, invasion and altered energy metabolism through induction of the transcription factor hypoxia inducible factor-1 (HIF-1). The aim of the present study was to investigate whether inhibition of the HIF-1 pathway can reduce tumor growth.

Significant findings

Interaction of the HIF heterodimer with the p300/CBP coactivator is essential for transactivation of HIF-1 regulated genes such as insulin-like growth factor-2, transforming growth factor-?3, vascular endothelial growth factor (VEGF) and the VEGF receptor FLT-1. Transfection of Hep3B cells with expression plasmids for polypeptides corresponding to the p300/CBP-binding domain of HIF-1a resulted in a significant attenuation of hypoxia-inducible reporter activity due to competitive binding inhibition. When hepatoma cells were infected with retroviruses encoding these polypeptides, VEGF mRNA abundance was reproducibly reduced. To assess the effects of HIF-1 blockade *in vivo*, retrovirally infected tumor cells were implanted into nude mice. Tumor growth and vessel density were reduced compared to values in control experiments.

Comments

Previous reports on whether targeting HIF would be a possible antitumor strategy revealed contradictory results. In this paper, proof is provided that in tumorigenic cell lines blockade of the interaction between HIF-1a and the coactivator p300 is able to reduce tumor growth significantly in a nude mice xenograft tumor model. Considering that the HIF system is activated in a broad range of cancers (see Additional information), these findings may open new perspectives for antitumor strategies.

Moreover, similar strategies may also be suitable for other diseases with increased angiogenesis, such as rheumatoid arthritis. However, there are some limitations (see Additional information). The role of HIF in rheumatoid arthritis has not yet been examined. As the p300 coactivator also interacts with many other transcription factors, untoward effects might be expected. In this study, experiments were performed with colon and breast cancer cell lines. Future studies have to address whether the growth of other tumors can be reduced by disrupting HIF signaling.

Methods

In vitro protein binding assays, luciferase reporter assays, ssDNA mutagenesis, thioredoxin-constrained expression vectors, immunoblot, ribonuclease protection, xenograft nude mice tumor model

Additional information

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