TUMOR HYPOXIA AND ITS CLINICAL SIGNIFICANCE

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ABSTRACT – In the light of intense cancer research, the tumor microenvironment has become a matter of great interest as it can influence many different aspects of tumor progression including growth, metastatic potential and response to treatment. In that field, low oxygen pressure (hypoxia), which evolves from uncontrollable growth and poor vasculature, plays a significant role. The main executer of tumor cell responses to hypoxia is a transcription factor HIF-1 (hypoxia-inducible factor 1), which triggers molecular adjustments helping cells to overcome those unfavorable conditions. It is also known that hypoxia renders cells resistant to treatment and in consequence affects patient outcome. This review focuses on HIF-1-dependent adaptations to insufficient oxygen delivery as well as describing clinical problems arising from hypoxia. Lastly, it highlights importance of targeted therapy aiming at hypoxic pathways.

INTRODUCTION

Insufficient oxygen delivery together with high metabolic demands lead to the formation of poorly oxygenated (hypoxic) areas within tumor tissue. Hypoxic regions pose a serious clinical problem as they are resistant to commonly used therapies and require a deeper understanding in order to set individual patient treatment. The key regulator of cellular adaptation to hypoxic conditions is a transcriptional factor named hypoxia inducible factor 1 (HIF-1), which modulates different molecular pathways in order to switch into more favorable phenotype (Hrstka *et al.*, 2012).

CELLULAR ADAPTATION TO HYPOXIC CONDITIONS

HIF-1 is a heterodimer composed of an oxygen-dependent α-subunit and a constitutively expressed β-subunit. Under normoxia, HIF-1α is hydroxylated on two prolines by enzymes of the prolyl hydroxylase family (PHDs), enabling recognition by von Hippel Lindeu protein (pVHL), which in consequence leads to HIF-1α proteasomal degradation (Ivan *et al.*, 2001). On the other hand, low oxygen pressure prevents HIF-1α hydroxylation resulting in its stabilization, nuclear translocation and dimerization with the β-subunit, thus activation (Ratcliffe *et al.*, 1998). Active HIF-1 binds to promoters of target genes, triggering the molecular machinery allowing cells to survive the unfavorable conditions. There are three isoforms of the α-subunit: HIF-1α, HIF-2α and HIF-3α, but the best described ones are HIF-1α and HIF-2α, which have divergent influence on tumor growth and progression (reviewed by Keith *et al.*, 2012).