ADENOSINE MODULATES VASCULAR ENDOTHELIAL GROWTH FACTOR EXPRESSION VIA HYPOXIA-INDUCIBLE FACTOR-1 IN HUMAN GLIOBLASTOMA CELLS

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Hypoxia appears to induce a program which shifts the cellular phenotype toward an increase in extracellular adenosine. Hypoxia-inducible factor-1 (HIF-1) is a key regulator of genes crucial to many aspects of cancer biology. Since in gliomas there is a strong correlation between HIF-1alpha expression, tumor grade and tumor vascularization, the aim of this study was to investigate whether adenosine may regulate HIF-1 in human glioblastoma cell lines. The results indicate that in the human hypoxic A172 and U87MG glioblastoma cell lines adenosine up-regulates HIF-1alpha protein expression via the A_3 receptor subtype. In particular, we investigated the effect of A_3 receptor antagonists on HIF-1 and vascular endothelial growth factor (VEGF) expression. We found that A_3 antagonists inhibit adenosine-induced HIF-1alpha and VEGF protein accumulation in the hypoxic cells. Investigations in the molecular mechanism showed that A_3 receptor stimulation activates p44/p42 and p38 MAPKs that are required for A_3-induced increase of HIF-1alpha and VEGF. Further studies are required to demonstrate the in vivo relevance of these observations with regard to the proposed role for adenosine as a key element in hypoxia and in tumors.