HYPOXIA REGULATION OF SENSITIVITY TO THE MECHANISTIC TARGET OF RAPAMYCIN KINASE INHIBITION (mTORki) IN GLIOBLASTOMA MULTIFORME

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Aim: Hypoxia is a marker of advanced cancer progression frequently correlated with treatment refractory tumors. The role that hypoxia exerts in determining cancer treatment resistance has not been clarified yet. In the present study we evaluated the hypoxia dependency of mTORki resistance in glioblastoma multiforme (GBM).

Methods: We performed in vivo tests aimed at developing an mTORki resistance model. We assessed an intra-tumoral hypoxia index, quantified as the ratio between total HIF-1-alpha and hydroxy-HIF-1-alpha. Then we recapitulated in vitro the mTORki resistance growing GBM cells in hypoxia.

Results: The molecular signature associated with mTORki resistance in GBM reveals the emergence of a putative nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) dependent reactivation of the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (PKB) pathway. Further, the onset of the resistance phenotype was hypoxia-inducible factor-1-alpha (HIF-1-alpha) independent.

Conclusions: These data provide for the first time the evidence that hypoxia induced mTORki resistance potentially relies on an NF-kB mediated reactivation of the PI3K/PKB signaling. Additional pre-clinical studies will be needed to confirm the clinical implications of our insights.

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