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Int6/eIF3e is essential for proliferation and survival of humanglioblastoma cells

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Based on the World Health Organization classification, Glioblastoma Multiforme (GBM) are grade IV astrocytic brain tumors and are one of the most deadly human cancers. GBM are very aggressive, with frequent relapses despite an appropriate treatment combining surgery, chemotherapy and radiotherapy. In GBM, hypoxia is a characteristic feature and activation of Hypoxia Inducible Factors (HIF-1α and HIF-2α) has been associated with resistance to anti-cancer therapeutics. Int6, also named eIF3e, is the "e" subunit of the translation initiation factor eIF3, and was identified as novel regulator of HIF-2α. Eukaryotic initiation factors (eIFs) are key factors regulating total protein synthesis, which controls cell growth, size and proliferation. The functional significance of Int6/eIF3e and the effect of *Int6/EIF3E* gene silencing on human brain GBM has not yet been described and its role on the HIFs is unknown in glioma cells. In the present work, we show that Int6/eIF3e suppression affects survival of various GBM cells. We highlight that Int6 inhibition induces decreased proliferation through cell cycle arrest and increased autophagy and caspase-dependent and capase-independent cell death. Surprisingly, these phenotypes do not correlate with decreasedglobal cell translation, but could be, in part, explained by the decrease of HIF and HIF target expression in GBM cells. Indeed, isolation of polysome-bound mRNA reveals modulation of specific mRNA translation, such as *HIF* mRNA, when Int6 is silenced. Although a deeper understanding of the molecular mechanisms involved in this Int6/eIF3e-HIFs pathway is necessary, Int6 could become a new therapeutic option for these aggressive tumors.

Biography

Julie Sesen is a PhD applicant at the Paul Sabatier University in Toulouse, France. She completed a Master degree in Oncology and is now in her 2nd year of PhD. She works in the team of Pr. Elizabeth Moyal under the direction of Dr. Nicolas Skuli and Dr. Cathy Seva within the Cancer Research Center of Toulouse. Her research was awarded fellowships from the Ligue Contre le Cancer, Cancéropôle GSO and Association pour la Recherche contre le Cancer, and should allow us to identify new therapeutic options to improve the treatment of glioma patients. Her work was recently published in the *International Journal of Molecular Sciences*.

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