Epigenetic Regulation by Notch Signaling in Glioma

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Abstract

In the neural stem cell, the Notch signaling pathway plays a dominant role in inhibiting differentiation through the activities of its downstream effectors, such as Hairy and enhancer of split 1/5 (Hes1/5), which repress the implementation of neurogenic programs. In the context of glioma tumorigenesis, Notch signaling has been shown to promote glioma stem cell (GSC) self-renewal and to suppress GSC differentiation. However, the mechanism by which Notch signaling and its downstream effectors maintains the stemness properties of GSCs through the function of a certain set of genes, such as SOX2, MYC and Nestin, remains unresolved. Here, we found that a specific Notch-regulated long non-coding RNA, TUG1, the expression of which is regulated by the Notch signaling pathway, was highly expressed in GSCs. TUG1 coordinately promotes self-renewal by sponging miR-145 in the cytoplasm and recruiting polycomb to repress differentiation genes by locus-specific methylation of histone H3K27 via YY1 binding activity in the nucleus. Furthermore, we developed new antisense oligonucleotides targeting TUG1 coupled with a potent drug delivery system, which can be used intravenously to provide efficient and selective delivery to glioma cells at sufficient concentrations to acquire anti-tumor effects. Our observations indicate that Notch-directed TUG1 is an effective epigenetic modulator that regulates the cancer stem cell population.