QKI deletion enhances self-renewal of glioma stem cells and promotes gliomagenesis

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Glioma stem cells (GSCs) have higher self-renewal capacity than neural stem cells (NSCs). However it is still not clear how GSCs enhance their self-renewal and whether or not enhanced self-renewal alone without affecting cell proliferation can promote gliomagenesis. Here we report the generation of a novel conditional KO allele of QKI, a tumor suppressor in GBM with RNA binding motif. When QKI was deleted in NSCs isolated from subventricular zone of *Nestin-CreERT2 QKI*$^{L/L}$ mice, multiple NSC markers were dramatically increased, including Notch1, Sox2, beta-catenin, ID1 and BLBP. When QKI was deleted in adult *Nestin-CreERT2 QKI*$^{L/L}$ mice, the NSC population, which is characterized by long-term BrdU retention and GFAP+/Nestin+ double positive staining, was greatly increased, indicating that deletion of QKI enhances NSC self-renewal. Surprisingly, we found that deletion of QKI also decreases cell proliferation rate of NSCs/GSCs, suggesting that QKI deletion makes NSCs/GSCs more quiescent. When *QKI*$^{-/-}$ NSCs were cultured in differentiation medium, they were not able to differentiate like *QKI*$^{+/+}$ NSCs, indicating that QKI is required for NSC lineage determination. To determine whether QKI KO promotes gliomagenesis, we generated a *Nestin-CreERT2 QKI*$^{L/L}$ *Pten*$^{L/L}$ *P53*$^{L/L}$ cohort, in which 92% of the mice developed glioblastoma starting at 2 months. However, the *Nestin-CreERT2 Pten*$^{L/L}$ *P53*$^{L/L}$ cohort did not develop any glioma up to a year; therefore QKI deletion greatly promotes gliomagenesis. Transcriptomic and proteomic profiling coupled with PAR-CLIP (Photoactivatable-Ribonucleoside-Enhanced Crosslinking and Immunoprecipitation) analyses revealed that genes involved in receptor trafficking were greatly enriched by QKI deletion. Specifically, 34% of the genes up-regulated by QKI deletion are involved in receptor delivery, and 39% of the genes down-regulated by QKI deletion are subunits of receptor degradation machineries such as endosomes and lysosomes. High level of receptor delivery and low level of receptor degradation concomitantly enrich receptors on the membrane and enhance the activity of the receptors that are involved in maintaining stemness, including RTK, Notch1 and Frizzled. Inhibition of the activity of receptors such as EGFR can diminish the enhanced self-renewal and decreased differentiation caused by QKI deletion. Taken together, our data suggest that QKI deletion increases receptor delivery and decreases endocytosis-mediated degradation, consequently enhancing the receptor activity and self-renewal capacity. Therapeutically, because QKI deletion greatly reduces lysosome level and protein degradation capacity, QKI-low cells are under much higher ER-stress compared with QKI-high cells; hence high level of ER-stress may provide an Achilles' heel for QKI-low glioblastoma, and pharmacologically inducing more ER-stress could render cytotoxicity to QKI-low glioma cells while keep normal cells intact.