miR 451

MiR-451a is best known for its role in erythropoiesis and for its tumor suppressor features.

Trattnig et al. showed a role for miR 451a in neuronal differentiation through analysis of endogenous and ectopically expressed or silenced miR-451a in Ntera2/D1 cells during neuronal differentiation. Furthermore, they compared neuronal differentiation in the dentate gyrus of hippocampus of miR 451a-/- and wild type mice. MiR-451a overexpression in lentiviral transduced Ntera2/D1 cells was associated with a significant shifting of mRNA expression of the developmental markers Nestin, βIII Tubulin, NF200, DCX and MAP2 to earlier developmental time points, compared to control vector transduced cells. In line with this, accelerated neuronal network formation in AB.G.miR-451a transduced cells, as well as an increase in neurite outgrowth both in number and length was observed. MiR-451a targets genes MIF, AKT1, CAB39, YWHAZ, RAB14, TSC1, OSR1, POU3F2, TNS4, PSMB8, CXCL16, CDKN2D and IL6R were, moreover, either constantly downregulated or exhibited shifted expression profiles in AB.G.miR-451a transduced cells. Lentiviral knockdown of endogenous miR-451a expression in Ntera2/D1 cells resulted in decelerated differentiation. Endogenous miR-451a expression was upregulated during development in the hippocampus of wildtype mice. In situ hybridization revealed intensively stained single cells in the subgranular zone and the hilus of the dentate gyrus of wild type mice, while genetic ablation of miR-451a was observed to promote an imbalance between proliferation and neuronal differentiation in neurogenic brain regions, suggested by Ki67 and DCX staining. Taken together, these results provide strong support for a role of miR-451a in neuronal maturation processes in vitro and in vivo [1)].

Studies have shown that miR-451 regulates downstream molecules including AMPK/CAB39/MARK and mTOR to determine the balance between rapid proliferation and invasion in response to metabolic stress in the harsh tumor microenvironment. Surgical removal of the main tumor is inevitably followed by recurrence of the tumor due to inaccessibility of dispersed tumor cells in normal brain tissue. In order to address this complex process of cell proliferation and invasion and its response to conventional treatment, Kim et al. propose a mathematical model that analyzes the intracellular dynamics of the miR-451-AMPK- mTOR-cell cycle signaling pathway within a cell. The model identifies a key mechanism underlying the molecular switches between proliferative phase and migratory phase in response to metabolic stress in response to fluctuating glucose levels.

They showed how up- or down-regulation of components in these pathways affects the key cellular decision to infiltrate or proliferate in a complex microenvironment in the absence and presence of time delays and stochastic noise.

Glycosylated chondroitin sulfate proteoglycans (CSPGs), a major component of the extracellular matrix (ECM) in the brain, contribute to the physical structure of the local brain microenvironment but also induce or inhibit glioma invasion by regulating the dynamics of the CSPG receptor LAR as well as the spatiotemporal activation status of resident astrocytes and tumor-associated microglia. Using a multi-scale mathematical model, we investigate a CSPG-induced switch between invasive and non-invasive tumors through the coordination of ECM-cell adhesion and dynamic changes in stromal cells. We show that the CSPG-rich microenvironment is associated with non-invasive tumor lesions through LAR-CSGAG binding while the absence of glycosylated CSPGs induce the critical glioma invasion. We illustrate how high molecular weight CSPGs can regulate the exodus of local reactive astrocytes from the main tumor lesion, leading to encapsulation of non-invasive tumor and inhibition of tumor invasion. These different CSPG conditions also change the spatial profiles of ramified and activated

microglia. The complex distribution of CSPGs in the tumor microenvironment can determine the nonlinear invasion behaviors of glioma cells, which suggests the need for careful therapeutic strategies [2].

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2)
Kim Y, Kang H, Powathil G, Kim H, Trucu D, Lee W, Lawler S, Chaplain M. Role of extracellular matrix and microenvironment in regulation of tumor growth and LAR-mediated invasion in glioblastoma. PLoS One. 2018 Oct 4;13(10):e0204865. doi: 10.1371/journal.pone.0204865. eCollection 2018. PubMed PMID: 30286133.