Glioma angiogenesis

Brain tumors exhibit marked and aberrant blood vessel formation indicating angiogenic endothelial cells as a potential target for brain tumor treatment. The brain tumor blood vessels are used for nutrient delivery, and possibly for cancer cell migration. The process of angiogenesis is complex and involves multiple players. The current angiogenesis inhibitors used in clinical trials mostly target single angiogenic proteins and so far show limited effects on tumor growth. Besides the conventional angiogenesis inhibitors, RNA-based inhibitors such as small-interfering RNAs (siRNAs) are being analyzed for their capacity to silence the message of proteins involved in neovascularization.

A family of non-coding RNAs, named AngiomiRs [microRNAs (MicroRNAs) involved in angiogenesis] has emerged. These small RNAs have the advantage over siRNAs in that they have the potential of silencing multiple messages at the same time and therefore they might become therapeutically relevant in a “one-hit multiple-target” context against brain tumor angiogenesis [1].

Angiogenesis is required for tumor progression; thus, its investigation can be useful to identify strategies for potential cancer treatments.

Tripartite motif 47 (TRIM47) is involved in the progression of multiple cancers. However, its role in glioma angiogenesis is largely unknown.

Wang et al. first showed that TRIM47 is frequently upregulated in gliomas, and increased TRIM47 levels are correlated with microvascular density. They then examined the role of TRIM47 in cellular functions related to angiogenesis in vitro and observed that TRIM47 knockdown significantly reduced human umbilical vein endothelial cell proliferation, migration, and tube formation. They also found that TRIM47 silencing reduced vessel density and tumor volume in glioma xenografts. Mechanistically, TRIM47 negatively regulated Smad4 expression in glioma cells, and SMAD4 knockdown rescued the suppressive effects of TRIM47 silencing. Taken together, the results indicate that TRIM47 promotes angiogenesis in gliomas by downregulating SMAD4. Therefore, targeting the TRIM47/SMAD4 axis may offer an innovative approach to glioma treatment [2].

Yang et al. aimed to explore the role of connexin 43 on exosome uptake and angiogenesis in glioma under hypoxia. U251 cells were exposed to 3% oxygen to achieve hypoxia, and the expression levels of HIF-1α and Cx43, involved in the colony formation and proliferation of cells were assessed. Exosomes were isolated by differential velocity centrifugation from U251 cells under normoxia and hypoxia (Nor-Exos and Hypo-Exos), respectively. Immunofluorescence staining, along with assays for CCK-8, tube formation, and wound healing along with a transwell assay were conducted to profile exosomal uptake, proliferation, tube formation, migration, and invasion of HUVECs, respectively. Our results revealed that Hypoxia significantly up-regulated the expression of HIF-1α in U251 cells as well as promoting proliferation and colony number. Hypoxia also increased the level of Cx43 in U251 cells and in the exosomes secreted. The uptake of Dio-stained Hypo-Exos by HUVECs was greater than that of Nor-Exos, and inhibition of Cx43 by 37,43gap27 or lenti-Cx43-shRNA efficiently prevented the uptake of Hypo-Exos by recipient endothelial cells. In addition, the proliferation and total loops of HUVECs were remarkably increased at 24 h, 48 h, and 10 h after Hypo-Exos, respectively. Notably, 37,43gap27, a specific Cx-mimetic peptide blocker of Cx37 and Cx43, efficiently alleviated Hypo-Exos-induced proliferation and tube formation by HUVECs. Finally, 37,43gap27 also significantly attenuated

Hypo-Exos-induced migration and invasion of HUVECs. These findings demonstrate that exosomal Cx43 contributes to glioma angiogenesis mediated by Hypo-Exos, and suggest that exosomal Cx43 might serve as a potential therapeutic target for glioblastoma [3].

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