Glioblastoma pathogenesis

Glioblastomas originates either from astrocytes that have accumulated mutations and de-differentiated or from neural stem cells within the subventricular zone (SVZ) in close contact with the vasculature.

A deeper understanding of the pathogenesis of these tumors has presented opportunities for newer therapies to evolve and an expectation of better control of this disease. Lately, efforts have been made to investigate tumor resistance, which results from complex alternate signaling pathways, the existence of glioma stem cells, the influence of the blood-brain barrier as well as the expression of O6 methylguanine DNA methyltransferase [1].

Presence in glioblastomas of cancer cells with normal neural stem cell (NSC) properties, tumor-initiating capacity, and resistance to current therapies suggest that glioblastoma stem cells (GSCs) play central roles in glioblastoma development.

IDH Mutation

IDH Mutation in glioblastoma.

Notch signaling pathway

Notch signaling pathway in glioblastoma.

Polymorphisms of VEGF could potentially play a role in the pathogenesis of GBM, as the allele and genotype distributions of rs3025039 and rs2010963 SNPs were significantly associated with GBM occurrence [2].

Some evidence about the role of the androgen receptor (AR) in glioblastoma pathogenesis has been reported.

Molecular and clinical data from The Cancer Genome Atlas database were used. The AR-expression at the protein level was obtained from reversed-phase protein array (RPPA) assays. The AR activity was determined by calculating the AR-score, an index calculated by using the expression (at RNA level) of 13 androgen-responsive genes. Univariate and multivariate Cox regression analyses were performed. Finally, a correlation analysis was conducted between protein expression data and the AR score.

Two hundred and thirty-three patients were included. RPPA data showed a mean AR abundance of 0.027(Statistical Deviation = 0.38) in GB. The univariate Cox regression analysis showed that the AR-Score was associated with a worse prognosis (Hazard Ratio (HR) = 1.070) while the AR-expression did not show any relationship with survival (HR = 0.869). The association of the AR-score with worse overall survival (OS) was still significant in the multivariate analysis (HR = 1.054). The highest

correlation coefficients between the AR-score and RPPA were identified in a group of proteins involved in apoptotic process regulation.

GB patients with a high AR activity present a worse prognosis in terms of OS. Thus, the activity of the AR may have a pathogenic role in GB. In this regard, the activation of the AR in GB may be associated with a dysregulation of apoptosis [3].

The EGFRvIII mutation has emerged as the central driver of the classic subtype of glioblastomas [4]

EGFRvIII-STAT3 signaling is important in glioblastoma pathogenesis. Jahani-Asl et al., identified the cytokine receptor OSMR as a direct target gene of the transcription factor STAT3 in mouse astrocytes and human brain tumor stem cells (BTSCs). They found that OSMR functioned as an essential co-receptor for EGFRvIII. OSMR formed a physical complex with EGFRvIII, and depletion of OSMR impaired EGFRvIII-STAT3 signaling. Conversely, pharmacological inhibition of EGFRvIII phosphorylation inhibited the EGFRvIII-OSMR interaction and activation of STAT3. EGFRvIII-OSMR signaling in tumors operated constitutively, whereas EGFR-OSMR signaling in nontumor cells was synergistically activated by the ligands EGF and OSM. Finally, knockdown of OSMR strongly suppressed cell proliferation and tumor growth of mouse glioblastoma cells and human BTSC xenografts in mice, and prolonged the lifespan of these mice.

The findings identify OSMR as a critical regulator of glioblastoma tumor growth that orchestrates a feed-forward signaling mechanism with EGFRvIII and STAT3 to drive tumorigenesis [5].

1)
Alifieris C, Trafalis DT. Glioblastoma multiforme: Pathogenesis and treatment. Pharmacol Ther. 2015 Aug;152:63-82. doi: 10.1016/j.pharmthera.2015.05.005. Epub 2015 May 2. Review. PubMed PMID: 25944528.
2)
Hanaei S, Mojtahedi H, Namvar M, Iranmehr A, Safaei R, Razavi A, Esmaeili M, Sadr M, Rezaei A, Edalatfar M, Khayat Kashani H, Sadeghi-Naini M, Darbeheshti F, Gharehdaghi J, Forouzesh M, Ebrahimi A, Rezaei N. VEGF gene polymorphisms in Iranian patients with intracranial glioblastoma. J Neurosurg Sci. 2023 Jan 18. doi: 10.23736/S0390-5616.22.05832-5. Epub ahead of print. PMID: 36651322.
3)
Fariña-Jerónimo H, de Vera A, Medina L, Plata-Bello J. Androgen Receptor Activity Is Associated with Worse Survival in Glioblastoma. J Integr Neurosci. 2022 Apr 22;21(3):86. doi: 10.31083/j.jin2103086. PMID: 35633167.
4)
Nagane M, Lin H, Cavenee WK, Huang HJ. Aberrant receptor signaling in human malignant gliomas: mechanisms and therapeutic implications. Cancer Lett. 2001;(162 suppl):S17–S21.
5)
Jahani-Asl A, Yin H, Soleimani VD, Haque T, Luchman HA, Chang NC, Sincennes MC, Puram SV, Scott AM, Lorimer IA, Perkins TJ, Ligon KL, Weiss S, Rudnicki MA, Bonni A. Control of glioblastoma tumorigenesis by feed-forward cytokine signaling. Nat Neurosci. 2016 Jun;19(6):798-806. doi: 10.1038/nn.4295. Epub 2016 Apr 25. PubMed PMID: 27110918; PubMed Central PMCID: PMC4984527.