Review article:

Transforming Growth Factor – β and Glioma

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Abstract:

Transforming growth factor-beta (TGF-β) is a regulatory cytokine secreted by various types of cell such as stromal cell, immune cells and tumor cells. Signaling of TGF-β plays an important role in proliferation, differentiation and apoptosis regulation of various cell, including glial cell. Disruption in the signaling pathway of TGF-β is commonly seen in tumor cells and is believed to contribute to the initiation and progression of cancer cells. Changes in the chromosome accompanied by genetic mutation has been observed which causes TGF-β to act as an oncogene, a substance which promote normal cells to differentiate to cancer cells.Increased level expression of TGF-β molecules has been seen in more malignant gliomas which yields a lower prognosis for the patient compared to those with lower expression of TGF-β. Malignant gliomas are characterized by rapid proliferation, invasion of parenchyma and angiogenic capabilities, are most common type of primary brain tumors. Studies have now implemented specific targeted therapy which act as a treatment for glioma cases. This review will focus on the role of TGF-β in glioma and its application in the treatment of glioma.

Keywords: Signaling pathway, TGF-β, Glioma, targeted therapy

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Introduction

Glioma are neoplasms of the central nervous system (CNS) which originate from glial cell, cells which surround the neurons providing insulation and support to sustain their function. According to the National Cancer Institute, brain tumors account for 85-90% of all CNS tumors. It is estimated that there are 23.880 new cases of brain tumor, with 16.830 deaths in the United States in 2018.[5] Furthermore, in 2012 it was estimated that there were 256.213 of brain tumor, with an estimated death count of 189.382 cases worldwide. Glioma accounts for approximately 30% of CNS tumors and 80% of malignant brain tumor, this shows that glioma has a significant impact with relation to brain tumors.[6]

Etiology

The etiology of brain tumor, similar to many other tumor, is hard to determine. This is due to the rise of tumor cells are multi-factorial and is unique to each case and individuals, and most brain tumors have no known cause. Currently there are little studies to a specific cause of tumors, however there are some factors which can contribute to the development of tumor such as genetics and infections by viruses such as Epstein-Barr virus which has been correlated to lymphoma.[7]

Screening and Diagnosis

Currently there are no effective ways to screen glioma cases especially those that do not present with symptoms. The symptoms of CNS tumors can have a variety of outcome, some can have mild headache while others can have generalized or focal neurologic symptoms.[7] As in other tumors, gliomas are categorized into 4 categories by the World Health Organization (WHO), grades I-IV.[8]

Role of TGF-β.

TGF-β is a cytokine that has various functions to regulate cell proliferation and differentiation along with tissue homeostasis.[1] The important

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aspect of TGF-β is present in all cell, it can affect the differentiation, proliferation, movement, adhesion, communication and death of various types of cell.[9] TGF-β acts as a ligand which binds to two pairs of receptor on the surface of cells, these are transmembrane serine/threonine kinases. The binding of TGF-β to the receptor initiates a sequence of event, starting from the activation of the receptor leading to the phosphorylation of SMAD proteins.[10] Normally SMAD proteins are inactive and shuttle between the nucleus and cytoplasm, when they are phosphorylated they will be activated and accumulate within the nucleus. There, they will bind to loci which will both suppress and activate hundreds of gene, including those which affect cell lineage specification and differentiation.[9]

As TGF-β plays a crucial role in differentiation and specification, it is not a surprise that it plays an important role in cancer tumor progression. TGF-β is famous for having two sided nature which can both aid and suppress the growth and proliferation of cancer cells, specifically it acts as a tumor suppressor in pre-malignant stages of cancer while also a tumor promotor in the later stages of malignant cancer cells.[11-12]

Tumor Suppressor

In normal and early stages of tumor growth TGF-β is able to modulate and regulate tumor via inhibiting proliferation and stimulating apoptosis. TGF-β inhibits proliferation by targeting cell-dependent kinase (CDK), which are molecule needed within the cell cycle allowing cells to progress past the G1 phase. This is action is accomplished by the production of p15, p21 and p27 which has binds to CDK molecule, preventing the cell from moving past the G1 phase thus inhibiting proliferation of the cell.[13]

Mutation in this particular gene can be detrimental which causes a sustained proliferation without inhibition leading to progression of tumor. There is evidence which suggest that restoring the sensitivity to TGF-β molecule through the TGF-β receptor type 2 (TβRII) inhibits the proliferation of human breast cancer.[14]

TGF-β can also help reduce tumor cells by upregulating apoptosis of cell, SMAD protein can also help stimulate the production of pro-apoptotic proteins such as TGF-β induced early response gene (TIEG1), inositol-5-phospate (SHIP), and Death-associated protein kinase (DAPK). Similarly, mutation can also occur here which lead to decrease in apoptosis.[15]

Tumor promotor

Despite the fact that TGF-β can inhibit the initiation of cancer, however when cancer cells are formed it has been noted that there were increased expression of TGF-β ligands in various cancers which include colorectal, gastric, lung, esophageal, breast and pancreatic cancers.[16-17] The increased expression of TGF-β molecules in more advanced cancer has been correlated with increased levels of invasiveness, progression and prognosis. The increased levels of TGF-β can be accounted due to the increased production by the cancer cells themselves or by the cells which make up the microenvironment surrounding the cancer, this can be macrophages, stromal cells and others.[18-19] Despite the tumor suppressive effects mentioned above one might speculate that this will help prevent the formation of more malignant cancer cells, however this not so true due to the fact that most of the more malignant cancer types have lost their sensitivity which makes them unresponsive to the TGF-β signaling. Despite this, normal cells within the microenvironment are still susceptible to the signaling altering them to promote tumor progression. This can be achieved by promoting angiogenesis, changes in extracellular matrix and suppression of immune system towards the cancer cells.[9]

During the process of angiogenesis, the main targeted cells are the endothelial cells. When stimulated, endothelial cells will express an increased level of permeability, proliferation, migration and invasion as they are trying to form new blood vessels.[20] One of the components which help regulate angiogenesis is TGF-β. In an experiment using mice models it was shown that mice which has mutation within the TGF-β receptor type 1 (TβRI) and TβRII have dysregulated angiogenesis.[21] Angiogenesis is a particularly important role in tumor growth, like any other tissue they require a constant supply of blood in order to meet the metabolic demand of an actively replicating tissue. The demand for supplies such as oxygen and nutrient are elevated in tumor cells as they are replicating at a higher rate compared to normal cell, therefore they require more nourishment compared to normal cells. Increased levels of TGF-β within the microenvironment has been shown to increase the vascular density and tumor progression in small cell lung cancer which leads to a worse prognosis.[22]

Another role that TGF-β has in the promotion of cancer cell is the inhibition of immune surveillance. TGF-β has the ability to suppress cytotoxic T-cells, dendritic cells and natural killer cells while simultaneously creating a pro-inflammatory condition by recruiting neutrophils and macrophage. The pro-inflammatory condition creates a positive feedback loop which induces the release of more TGF-β molecule, the summation of this promotes the progression of tumor cells even further.[23]

TGF-β and its application

Due to the increasing amount of evidence which suggest that the increase in TGF-β signaling is prominent in malignant tumors, the clinical application of TGF-β is being investigated further. The implications of using TGF-β inhibitors are being studied, some are now in clinical development. TGF-β inhibition can be accomplished in 3 different levels of the signaling pathway: (1) ligand level, (2) ligand-receptor level and (3) intracellular level.At the ligand level, antisense oligonucleotide (AON) can be given to the patient.[24] A study using a phosphonothioate-modified AON named AP12009 which specifically targets TGF-β2 mRNA sequence has been shown to reduce the expression of TGF-β2 expression by up to 73%.[25] Apart from that, this specific AON has also demonstrated the ability to reduce proliferation, migration and the immune suppression.[26] There has been clinical trials regarding the administration of AP12009 to glioma patients, where administration of the drug was shown to increase the median survival of glioma patient suffering from anaplastic astrocytoma was 39 months when treated with AP12009 as when compared to the median survival of 21 month when treated with chemotherapy. Despite the positive outcome shown from the research due to the limited number of patients, the result was determined to not be statistically significant. Although this effect is not seen in glioblastoma (GB).[27] Another benefit mentioned by research conducted was the reduced amount of side effects when compared to glioma treatment using chemotherapy.[27]

At the ligand-receptor level, an anti-TGF-β neutralizing monoclonal antibody (1D11) which binds to the TGF-β molecules prevent them from interacting with the receptors on the surface of the cells, inhibiting their actions. The drug can be administered intravenously and enters both the subcutaneous and intracranial.[28] However, the results of this experiment showed varying results when tested on immunocompetent and immuno-deficient mice. When 1D11 was administered to the immunocompetent it was observed that the mice experienced complete remission from the drug, however when the same medication was administered, for unknown reasons, to immune-deficient mice the complete opposite effect was observed.[28] Current research has focused on the usage of human analogue of 1D11 antibody, GC1008, for the treatment of glioma has been done.[2989]Zirkonium (Zr)-GC1008 was shown to have excellent and specific uptake toward patients suffering from recurrent glioma, this was determined by using a positron emission tomography (PET) scan.[29] Other compounds such as ligand traps, in the form of soluble receptor, are able to bind to TGF-β molecules which prevent them from binding to the actual receptors on the cell surface. A study conducted by Naumann et al, using adenoviral gene transfer to express TβRII which resulted in reduced Smad2 phosphorylation in the TGF-β signaling pathway along with enhanced natural killer (NK) cell activity against glioma. Mice model which expresses the TβRII was shown to have significantly delayed glioma growth compared to untreated mice.[30]

On the intracellular level, it is possible to reduce the kinase activity by blocking the activity of the TGF-β receptors on the cell. This prevents the formation of TGF-β signaling and thus downregulates the downstream proteins such as R-Smad, it was shown that this can downregulate the proliferation and migration of glioma cells in vitro.[31] The success of kinase inhibitor has been seen in other in vivo cancers such as basal cell carcinoma[32], pancreatic carcinoma[33], melanoma[34], and mammary carcinoma.[35]

Conclusion

Gliomas are malignancies within the CNS which arise from glial cells and are characterized by aggressive proliferation and diffuse infiltration. TGF-β signaling plays a key role in the glioma progression as it can act as both a tumor promotor and tumor suppressor depending on the stage and degree of the malignancy. Due to increasing evidence of increased TGF-β signaling in more advance stages of cancer the therapeutic benefit of inhibiting TGF-β signaling is being studied. The therapeutic benefits of inhibiting TGF-β has been observed in several other malignancies,

and some trials has been conducted for glioma. The inhibition of TGF-β can be accomplished in several different levels which are (1) ligand level, (2) ligand-receptor level and (3) intracellular level.

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Conflict of Interest

[the authors declared no conflict of interest)

Authors's contribution:

Data gathering and idea owner of this study: HH, NSH

Study design: NSH

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