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Review Article

Pathophysiological mechanisms regulated by cytokines in gliomas

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ABSTRACT

Glioma, a neuroglia originated malignancy, consists of one of the most aggressive primary tumors of the central nervous system with poor prognosis and lack of efficient treatment strategy. Cytokines have been implicated in several stages of glioma progression, participating in tumor onset, growth enhancement, angiogenesis and aggressiveness. Interestingly, cytokines have also the ability to inhibit glioma growth upon specific regulation or interplay with other molecules. This review addresses the dual role of major cytokines implicated in glioma pathology, pointing toward promising therapeutic approaches.

1. Introduction

Gliomas refer to the most common primary brain tumors resulting from the deregulated proliferation of neuroglia [1]. Different types of glial cells give rise to gliomas which can be classified according to their origin; astrocytomas, the most aggressive types, oligodendrogliomas, ependymomas and oligoastrocytomas, all of them being further subdivided into several subgroups [2]. Except of the histopathological features, additional factors including genetic and molecular aberrations have been proposed to contribute into glioma classification.

Several different signaling pathways have been implicated in tumor development through regulation of cellular processes such as invasion, migration and proliferation. Dysfunction of many critical signaling molecules like serine/threonine kinase AKT, Ras, Mitogen Activated Protein Kinases (MAPK), Epidermal Growth Factor Receptor (EGFR), Vascular Endothelial Growth Factor Receptor (VEGFR), as well as tyrosine kinase receptors have been shown to contribute to brain tumor formation [3]. The superfamily of cytokines produced exogenously from the stromal cells as well as endogenously by glial cells has been recently recognized as vital regulators of gliomagenesis and valuable therapeutic targets [1].

Cytokines form a large group of peptide molecules, secretory cellular products, acting mainly as paracrine messengers (with several exceptions). Although they are known for their participation in immune response, cytokines play a vital role in the regulation of human body homeostasis by affecting many individual systems including CNS [4]. Regarding their mechanism of action, cytokines bind to transmembrane receptors and activate intracellular pathways through second messengers, thus regulating a wide variety of cellular functions including cell differentiation or proliferation. Noteworthy they can also influence the production of other cytokines and generate a complicated molecular signaling cascade that commonly involves multiple targets and diverse activities.

The regulation of cytokines is based on the strict limitation of their action through negative feedback mechanisms responsible either for the suppression of their expression or positive target responsiveness [5]. These negative feedback mechanisms control the range of cytokine levels in the extracellular fluid. On the other hand, their implication in the majority of body functions inevitably leads to diverse expression. It is widely accepted that the same cytokine may be produced by different cells while it can act as ligand to different targets with a variety of different functions. Aberrant cytokine expression or deregulated action has been associated in the development of an impressive variety of human diseases. In the following sections, we provide evidence on cytokine imbalance that has been observed in human gliomas.

2. Deregulated cytokine network characterizes gliomas

Cytokines have been primarily characterized as essential mediators of brain development [6]. Specific binding to their membrane

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receptors activates intracellular pathways, responsible for microglial and neuronal migration [7]. In addition, several cytokines (IL-6, TGF-β) have been attributed a specific role over synaptogenesis during the developmental stages [8,9].

Except from their impact in the brain development, there is evidence of cytokine activity in the mature nervous system [10]. An important function is their ability to modulate the release of specific neurotransmitters during an inflammatory reaction, regulating further the balance between healthy and non-healthy situations [11]. Moreover, extensive research on cytokine functions reveals specific actions over fundamental cellular processes of glia, including regulation of cytoskeletal activity and cell survival [12].

Therefore, cytokines comprise a major cell communication network affecting critical steps of the cell cycle [13]. Abnormalities in cytokines' network lead to severe disorders of the CNS and many glial malignancies [14,15] (Table 1).

2.1. Transforming growth factor (TGF-β)

TGF-β is a Th1 cytokine with various functions, acting as crucial growth mediator in several organs and systems [16,17]. TGF-β participates in almost every stage of CNS development being implicated in nervous system formation, neurogenesis [18], neuronal migration [19], synapse formation [20], differentiation and proliferation [21,22]. Therefore, not surprisingly altered TGF-β expression has been associated with nervous system diseases and injuries as well as CNS tumors [20].

TGF-β exhibits a multidimensional impact over glioma development by affecting all processes of carcinogenesis. Although it has been identified to both inhibit and stimulate tumor growth, only recently elevated TGF-β levels have been associated with glioma grade and stage [23,24]. More specifically, activated TGF-β acts as tumor growth inhibitor in low grade gliomas while it triggers cell proliferation in high grade tumors (Fig. 1). The tumor suppressing effect of TGF-β is mediated by the SMAD signaling cascade which results in activation of p21, a widely recognized anti-tumor molecule [25,26].

On the other hand, TGF-β also possesses mitogenic properties as it is able to activate Ras protein and induce the MAPK signaling leading to ERK activation. Mutations that have been identified in SMAD2 and SMAD4 gene loci in high grade gliomas shift the balanced expression of the two pathways toward MAPK, confirming the tumor promoting effect of this cytokine [27]. TGF-β1 and β2 isoforms are also able to affect the tumor angiogenesis by regulating VEGF and its receptor, thus controlling the formation of tumor vessels [28]. The latter action is greatly stimulated by Hypoxia Inducing Factor (HIF) activation, indicating the synergistic cooperation of TGF-β with other major mediators such as HIF and basic Fibroblast Growth Factor (bFGF) [29] over tumor growth promotion. TGF-β1 and TGF-β2 isoforms contribute to increased tumor invasion by upregulating the α5β3 integrins [30]. Moreover, a positive correlation exists between TGF-β 1/2 and expression of MMP-2 and -9 at the extracellular area of glial cells plasma membrane (Fig. 1). On the contrary, TGF-β 1/2 downregulates the production of the cell adhesion molecule E-cadherin, restraining the migratory effects of cancer modulators [24]. Aberrations in TGF-β levels may cause severe abnormalities on immune system regulation. High TGF-β levels secreted by gliomas inactivate the immune cytotoxic response via downregulation of Natural Killer Group 2 member D (NKG2D) receptor in their surface [31]. IL-1 has also been indicated to induce the expression of Bim-1, LIF and Notch-2 proteins synergistically with TGF-β [32]. These agents are correlated with increased expression of nestin, indicating an augmented self-renewal rate of glioma stem cells. In association to the increased expression of N-cadherin, SIP-1 and β-integrin which promote the invasiveness of the tumor, this leads to a more aggressive type of cancer and thus a worse prognosis [32].

2.2. Interleukin (IL)-18

Several studies link glioma formation with inflammation generated by activated microglia mainly by focusing on the complicated and dual role of IL-18. This cytokine has been associated with inhibition of tumor development because of its effects on cell motility and immune response. Its importance is further enhanced by the high percentage of innate macrophages found in GBM cultures [33]. On the one hand, IL-18 influences the motility of glial cells, increases their aggressiveness via the regulation of NO/cGMP/PKG and is consequently associated with tumor grade [34]. This action is being held by the autocrine binding of IL-18 to microglia cells which potentiates the migratory effects and the secretory products of microglia over glioma neoplastic cells [35]. It is noticeable that the initial secretion of IL-18 by activated microglia is further enhanced by the presence of extracellular matrix proteins like vitronectin and fibronectin [35]. On the other hand, paradoxically it overpowers the immune response against glioma by stimulating secretion of IFN-γ which in turn causes the proliferation of T cells and at the same time the augmented activity of NK and CD8 cells which mediate cytotoxic immunity [36].

2.3. Tumor necrosis factor (TNF)

The TNF family of chemokines is also an important regulator of the progress of glial malignancies. The effect of TNF family members on gliomas presents high heterogeneity as different mediators are being linked with both the inhibition and enhancement of glioma development. First of all, several studies highlight the role of TRAIL as it has been largely associated with selective suppression of many tumors while protecting normal cells, generating an innate anticancer network. However in the case of glioma, tumor cells seem to develop a resistance mechanism opposing to the TRAIL-induced apoptosis. Glioma cells seem to overexpress a wide variety of antiapoptotic proteins including survivin [37], XIAP [38], c-FLIP short isoform [39] and many others [40] which are able to

Table 1
Major cytokines implicated in glioma formation.

Cytokine	Normal function	Glioma function	References
TGF-β	CNS development neurogenesis, synapse formation, neural migration, proliferation, differentiation	Low levels: tumor inhibitor high levels: positive effect on invasion, angiogenesis and proliferation	6–10, 13–23
IL-1	Increased expression of chemokines, adhesion molecules and MMPs, cell cycle progression	Proliferation, expression of metastatic agents	5, 40–47
TNF	Apoptosis, increased expression of adhesion molecules and endothelin-1	Inability to cause apoptosis but potential increase in proliferation	29–734
IL-6	Proliferation, neurogenesis	Neoangiogenesis, invasion, increased activity of GSCs	48–56
IL-18	Astrocyte hypertrophy, probable inhibitor of neural differentiation	Dual effect, increased aggressiveness, increased immune response	24–28
IL-8	Angiogenesis, cell cycle progression, inhibition of apoptosis	Neoangiogenesis	35–39
IL-10	–	$CD8^+$ mediated cytotoxicity	57–62

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