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Review

Intrinsic protective mechanisms of the neuron-glia network against glioma invasion

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ABSTRACT

Gliomas arising in the brain parenchyma infiltrate into the surrounding brain and break down established complex neuron-glia networks. However, mounting evidence suggests that initially the network microenvironment of the adult central nervous system (CNS) is innately non-permissive to glioma cell invasion. The main players are inhibitory molecules in CNS myelin, as well as proteoglycans associated with astrocytes. Neural stem cells, and neurons themselves, possess inhibitory functions against neighboring tumor cells. These mechanisms have evolved to protect the established neuron-glia network, which is necessary for brain function. Greater insight into the interaction between glioma cells and the surrounding neuron-glia network is crucial for developing new therapies for treating these devastating tumors while preserving the important and complex neural functions of patients.

1. Introduction

Glioma, the most common primary malignant central nervous system (CNS) tumor in adults, is a devastating cancer, with a median survival time of approximately 1.5 years for the most malignant form, glioblastoma [1]. This tumor is highly invasive into surrounding normal brain tissue, extending far beyond the tumor mass. This invasiveness precludes effective surgical removal and limits the efficacy of radiotherapy if neurological deficits are to be avoided [2]. However, the normal brain is non-permissive for axonal or cellular infiltration, mainly because of myelin-associated molecules [3,4]. Understanding the biological relationship between tumor cells and normal cells in the surrounding brain parenchyma is a key issue for understanding the invasive nature of these devastating tumors [5].

Many inhibitory or repelling guidance cues involved in axonal outgrowth during development also restrict axonal regeneration in CNS injury in adults [3,4]. These mechanisms also restrict tumor cell infiltration into the brain parenchyma once the neuron-glia network is established. The main components of this inhibition are myelin-associated inhibitors produced by oligodendrocytes and astrocyte-related extracellular matrix (ECM) proteins [3,4,6]. Such inhibitory mechanisms have evolved to protect the neuron-glia network that is formed during the accumulation of learning, memory, and personal experiences, which are essential for a person's individuality [4]. In addition, the immunosurveillance system, which is another defense mechanism, can work in the brain against gliomas, at least in the initial stage [7].

Clarification of the interaction of glioma cells with the surrounding neuron-glia network is important in developing an appropriate treatment strategy against gliomas. Maintaining host tissue resistance to invasive tumor cells may prevent tumor progression and maintain quality of life of these patients.

2. Myelin-associated inhibitors

The myelin structures formed by oligodendrocytes normally ensheath nerve fibers to enhance the speed of nerve transmission. This function has been essential for vertebrates to evolve into human beings with an intricate nervous system. Another important function of myelin is to preserve the complex neural networks formed during brain development by preventing excessive axonal regeneration, sprouting, and cellular infiltration into the brain parenchyma [3,4,6]. Myelinating oligodendrocytes produce axon guidance molecules, which can inhibit cellular and axonal migration into established brain parenchyma (Fig. 1). The key cell for generating mature oligodendrocytes in adults is the oligodendrocyte type-2 astrocyte progenitor cell, which replaces dying oligodendrocytes. This turnover cycle is essential for adequate oligodendrocyte function.

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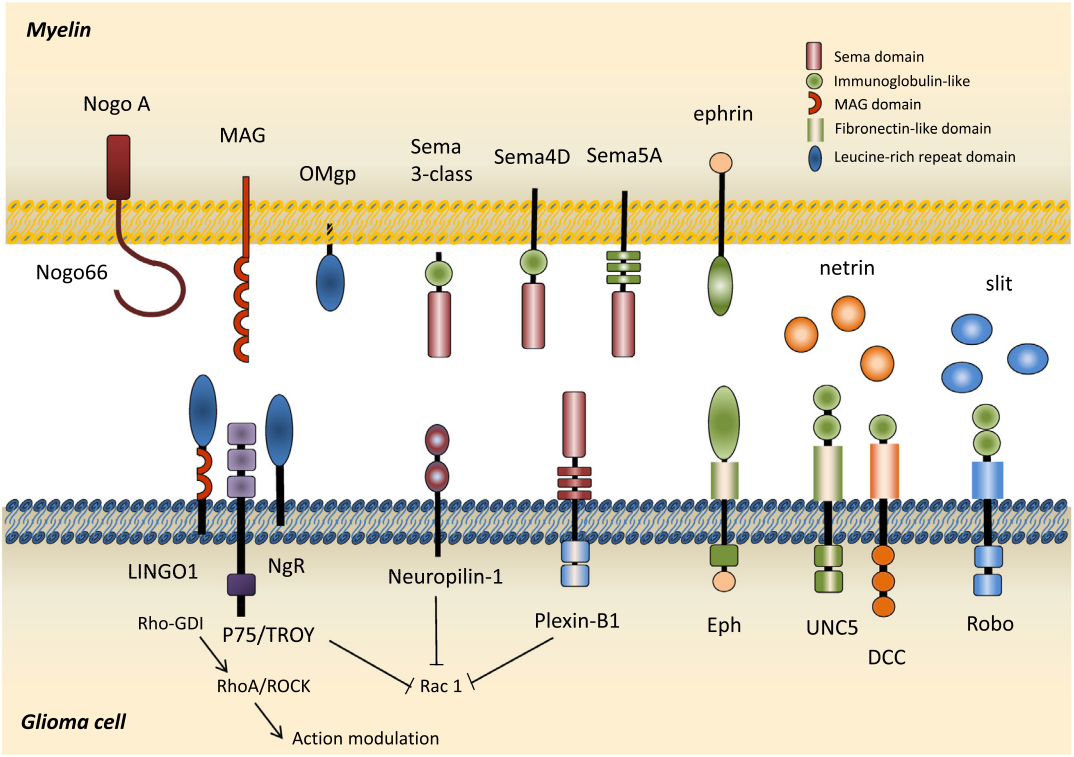

Fig. 1. The molecular inhibitors and intracellular signaling mechanisms of the myelin-associated glial environment against glioma invasion. They interact with specific receptors on glioma cells, which generate intracellular signaling, including Rac1 inhibition and activation of the Rho/ROCK pathways. DCC = deleted in colorectal cancer, MAG = myelin-associated glycoprotein, NgR = Nogo-66 receptor, OMgp = oligodendrocyte myelin glycoprotein.

2.1. Nogo

An antibody to an inhibitory portion of myelin was isolated and named IN-1 in 2000, and Nogo was found to be its antigen [8]. Nogo is an oligodendrocyte-specific member of the reticulon family, in which three isoforms, Nogo-A, Nogo-B, and Nogo-C, are generated by alternative splicing. Nogo-A is highly expressed in CNS oligodendrocytes and has two inhibitory domains: a unique amino-terminal region (amino-Nogo) and a 66 amino acid loop (Nogo-66), which is the extracellular domain of Nogo [9]. The Nogo-66 loop inhibits the growth and migration of glioma cells by acting through the Nogo-66 receptor (NgR), combined with members of the tumor necrosis factor receptor family, such as p75/TROY and LINGO1 [10]. Astrocytic tumors usually express NgR, and its expression decreases both at the protein and mRNA levels with increasing histological grade [11]. In contrast, Nogo-A is highly expressed in oligodendroglial tumors; up to 85.7% of grade II and 93.7% of grade III tumors [12]. The cytoplasmic domain of Nogo may render glioma cells susecptible to apoptosis, which may partly explain the relatively good prognosis of oligodendroglial tumors compared with astrocytic tumors.

2.2. Myelin-associated glycoprotein and oligodendrocyte myelin glycoprotein

Myelin-associated glycoprotein and oligodendrocyte myelin glycoprotein have been reported to bind to the NgR on glioma cells to inhibit infiltration as well as axonal regrowth [10]. A myelin-related gene, epithelial membrane protein 3, has tumor suppressor-like features, including inhibition of colony formation and growth inhibition of neuroblastoma and glioma cells [13]. This gene is frequently hypermethylated in neuroblastomas and gliomas [13].

2.3. Semaphorins

Semaphorins, originally identified as guidance factors that navigate axons in the nervous system, are divided into eight subclasses of secreted, membrane glycosylphosphatidyl-inositol (GPI)-anchored, and transmembrane proteins [14]. Semaphorins are characterized by the presence of a sema domain at the C-terminus, and a PSI (plexin, semaphorin, and integrin) domain at the N-terminus [15]. Most family members harbor the immunoglobulin-like domain, which is a signature feature found in cell adhesion or recognition molecules. Semaphorins play a key role in sculpting normal neural connectivity by inhibiting growth towards inappropriate targets. They have been implicated in many biological processes, including cell migration, immune responses, angiogenesis, and organogenesis [15,16]. In the adult, Sema6A strongly contributes to axonal regrowth inhibition after CNS injury [17]. Additionally, some semaphorins have been characterized as suppressors of tumor progression, including gliomas [17]. Activation of plexin-B1 signaling by the ligand Sema4D triggers its endogenous GTPase-activating protein activity toward R-Ras, and negatively regulates integrin function to suppress glioma invasion and metastasis [17]. Sema5A contributes to the impediment of glioma cell invasion through a marked reduction in Rac1 activity [18]. Class-3 semaphorins, such as Sema3D and Sema3E, display strong inhibitory effects on the tumor formation of U87 or U373 glioblastoma cell lines, primarily due to angiogenesis inhibition [19]. All of these reports indicate that semaphorins inhibit the proliferation and invasion of plexin-expressing glioma cells [16].

2.4. Ephrins

Ephrins are expressed in myelin as membrane GPI-bound molecules. They bind to erythropoietin-producing human