

Editorial

Extracellular Microenvironment Components of Glioblastoma as Possible Therapeutic Targets

Marzenna Wiranowska*

*Corresponding author: Marzenna Wiranowska Ph.D., Department Pathology and Cell Biology, Morsani College of Medicine, University of South Florida, Tampa, Florida, USA, E-mail: mwiranow@health.usf.edu

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Introduction

Glioblastoma multiforme (GBM), is a highly invasive primary brain tumor representing more than half of all gliomas with an average patient survival time of only 12 to 15 months [1]. Unlike tumors derived from peripheral tissues, GBM is known to rarely metastasize outside its original location in the central nervous system (CNS). This characteristic is attributed to both a limited survival time of GBM patients as well as the specific and unique composition of the extracellular matrix (ECM) in the brain supportive for migration and invasion by glioma cells into the normal brain tissue.

Data generated by The Cancer Genome Atlas Research Network [2] resulted in an integrated genomic analysis of GBM. It identified clinically relevant subtypes of GBM such as classical, proneural, neural and mesenchymal [3]. Also certain genomic abnormalities associated with GBM that relate to several ECM-related signaling pathways were revealed [4]. Despite these significant findings in the molecular characterization of GBM, more attention still needs to be devoted to understanding the heterogeneous nature of these tumors and their complex and unique interaction with the microenvironment components of the brain ECM.

Glioma cells are capable of invading deep into the brain through the barriers of the CNS which normally prevent the movement [5]. In contrast to glioma, other highly invasive peripheral tumors rarely invade adjacent neural tissues [5,6]. In addition, the peripheral tumors which metastasized into the CNS do not truly infiltrate the brain, but instead, they rather “push” the nervous tissue away or infiltrate only perivascular tissue [7].

GBM however, shows diffused infiltration into the normal brain parenchyma and interacts with the ECM components in the brain. Despite standard GBM therapies such as surgery, radiation and chemotherapy, a single glioma cells still may migrate through ECM and establish new recurrent tumor foci elsewhere in the normal brain tissue escaping early detection [8]. Recently, it was reported that glioma associated microglia/macrophages may also support infiltration and invasion of glioma cells into the normal brain tissue through increased expression of certain ECM degrading metalloproteinases (MMPs) [9]. In fact, GBM is known to show a high level of infiltration by macroglia and macrophages [10]. Another characteristic of GBM is the increased ECM rigidity found in the vicinity of the tumor in contrast to normal brain. This higher ECM rigidity was found to promote glioma cell migration [4]. Further research toward understanding the intricate interactions between glioma cells and the brain ECM may reveal new targets and new pathways for more effective therapies for glioma patients.

Extracellular Matrix Molecules in the Normal Brain and in GBM

The extracellular space in the CNS (approximately 15-25% of CNS volume) is filled with ECM molecules while rest of the CNS volume consists of cellular elements including neurons, glia, astrocytic processes and blood vessels [11]. Some normal brain regions such as the subarachnoid space, superependymal packets, and perivascular space around arterioles and venules are especially rich in ECM. The main ECM component in the normal brain include space-filling carbohydrate, a large glycosaminoglycan (GAG), hyaluronan (HA), also called hyaluronic acid, the production of which is increased in glioma [12]. In addition its CD44 receptor is also overexpressed in

glioma cells [13-15] and found in vivo at the leading edge of glioma, at the brain-tumor interface [16].

Other prominent ECM components include proteoglycans (PGs), protein-bound carbohydrate molecules, which consist of a core protein attached to a GAG chain. These complexes of HA and PGs form the ECM domains called perineuronal nets first described by Camillo Golgi in 1893. They enwrap the neuronal cell bodies and proximal dendrites and fill the space between neurons and glial processes. The PGs which are present at high levels in the normal brain include sulfated proteoglycans: chondroitin sulfate proteoglycans (CSPGs) and heparan sulfate proteoglycans (HSPGs). Both CSPGs and HSPGs play a major role in regulation of cell signaling and migration providing an essential support in interactions between the tumor and its microenvironment [17]. Interestingly, CSPG proteoglycan, also known as neuroglial protein-2 (NG2) is a characteristic marker of oligodendrocyte progenitor cells and often expressed by gliomas [16]. Based on expression of NG2 these cells have been suggested to be the originating cells for glioma [18].

In the ECM of the normal brain there are also low levels of fibrous proteins associated with the basement membranes of the brain's vasculature. These fibrous proteins include collagens, fibronectin, and laminin [19-21]. However, in GBM, these fibrous proteins may be expressed at high levels and correlated with the glioma grade [22,23]. In addition, some types of fibrous proteins such as collagen XVI only known as a minor component of the connective tissue may actually play a significant role in GBM invasion through modification of the beta-1 integrin [24].

The lining of blood vessels by basal laminae rich in HSPGs was suggested to serve as a storage site of growth factors and cytokines [25]. The basal laminae of blood vessels as well as myelinated nerve fibers of white matter tracts exhibit a higher mechanical rigidity and serve as the infiltrative path of glioma into the normal brain parenchyma [26,27]. In addition, the microenvironment of glioma vasculature establishes a niche in which cancer stem cells (CSCs) can transmit and receive signals from the ECM. This vascular niche can shield CSCs cells and therefore interfere with radiation and chemotherapy resulting in the resistance to treatments as shown recently [28].

Other important molecules within the ECM are proteases, MMPs, and their inhibitors (TIMPS) essential in remodeling of ECM in the normal brain and highly expressed in glioma [7,29]. The MMPs expressed by gliomas mainly include the MMP class of gelatinases: MMP2 and MMP9 [26,30]. It has been shown recently that MMP9 is predominantly expressed by glioma-associated macroglia/macrophages [9]. Glioma cells actively modify their ECM through proteolytic degradation of the normal brain

matrix providing for a stiffer and rigid tumor-like ECM microenvironment which supports glioma cell invasion [4].

Therapeutic Targets in the extracellular environment of GBM

It has been proposed to use invasion as a target for therapy for GBM specifically focusing on targeting the infiltrative behavior of glioblastoma cells in the modified ECM [31].

In the past, MMPs essential in ECM modification, tumor cell migration and invasion and initiation of angiogenesis were considered a potential target for anti-cancer therapies. However, due to highly pleiotropic activities of MMPs the initial use in clinical studies of broad spectrum MMP inhibitors interfered with multiple functions of these enzymes and led to disappointing results and termination of these studies [32]. However, based on MMPs' role in tumor progression, more specific approaches in inhibiting MMPs derived from glioma and microglia should be used for therapeutic interventions [7,9]. Other suggested therapeutic ECM targets include blocking of tumor-associated proteoglycans [17], interference with HA-CD44 ligand receptor [12,14,15] or targeting glioma associated fibronectins using peptide-conjugated nanoparticles [33]. Therefore, ECM molecules within the GBM microenvironment may have an important potential in the development of new therapeutic strategies which aim to disrupt the tumor-microenvironment interactions and halt invasiveness of GBM cells.

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