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Review article

The extracellular matrix niche microenvironment of neural and cancer stem cells in the brain

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ABSTRACT

Numerous studies demonstrated that neural stem cells and cancer stem cells (NSCs/CSCs) share several overlapping characteristics such as self-renewal, multipotency and a comparable molecular repertoire. In addition to the intrinsic cellular properties, NSCs/CSCs favor a similar environment to acquire and maintain their characteristics. In the present review, we highlight the shared properties of NSCs and CSCs in regard to their extracellular microenvironment called the NSC/CSC niche. Moreover, we point out that extracellular matrix (ECM) molecules and their complementary receptors influence the behavior of NSCs/CSCs as well as brain tumor progression. Here, we focus on the expression profile and functional importance of the ECM glycoprotein tenascin-C, the chondroitin sulfate proteoglycan DSD-1-PG/phosphacan but also on other important glycoprotein/proteoglycan constituents.

Within this review, we specifically concentrate on *glioblastoma multiforme* (*GBM*). *GBM* is the most common malignant brain tumor in adults and is associated with poor prognosis despite intense and aggressive surgical and therapeutic treatment. Recent studies indicate that *GBM* onset is driven by a subpopulation of CSCs that display self-renewal and recapitulate tumor heterogeneity. Based on the CSC hypothesis the cancer arises just from a small subpopulation of self-sustaining cancer cells with the exclusive ability to self-renew and maintain the tumor. Besides the fundamental stem cell properties of self-renewal and multipotency, *GBM* stem cells share further molecular characteristics with NSCs, which we would like to review in this article.

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1. Introduction

Building up tissues during development and maintaining a homeostasis of tissue compartments by replacing cells are main features of stem cells in normal physiological processes. But if these processes are disturbed by pathological influences and cells lose specific control mechanisms tumors can arise that lead to fatal consequences for the organism. In the last decades both fields have been studied intensively.

The most obvious similarity of a neural stem cell (NSC) and a cancer stem cell (CSC) is self-renewal. Both cell types achieve a common purpose, which is the production of a huge number of

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daughter cells. The molecular repertoire inherited in the respective cell populations reflects these efforts. Several studies reported largely on the intrinsic signaling of stem cells and CSCs. Indeed, stem cells and CSCs share an overlapping collection of growth factor receptors, cell cycle progression genes and transcription factors (Chen et al., 2012; Denysenko et al., 2010; Rebetz et al., 2008). Also, the influence of epigenetic factors in cancer initiation and progression is well established and resembles what is known from stem cells in the developing tissue (Baylin, 2011; Baylin and Jones, 2011; Imamura et al., 2014; MuhChyi et al., 2013; Pujadas and Feinberg, 2012).

Glioblastoma multiforme (*GBM*) represents the most common malignancy of the brain and is associated with a devastating prognosis despite intense and aggressive surgical and therapeutical treatment. It has been shown that the onset of *GBM* is driven by a subpopulation of cells that display self-renewal and recapitulate tumor heterogeneity: the so-called CSCs (Galli et al., 2004; Singh et al., 2004). Besides the fundamental stem cell properties of self-renewal and multipotency, *GBM* stem cells share further molecular characteristics with NSCs. In addition to the intrinsic cellular properties, NSCs/CSCs favor a similar environment to acquire and maintain their characteristics. Similarities and differences of NSCs/CSCs in regard to their extracellular microenvironment, called the NSC/CSC niche have also been reported. Extracellular matrix (ECM) molecules as well as their complementary receptors contribute to cell behavior and brain tumor progression. For instance, CD133 (also known as prominin-1)—a marker for NSCs and neural progenitor cells—is the classical glycoprotein for cell sorting to obtain pure CSC cultures from *GBM*. Additionally, it is known that the expression of CD133 inhibits the differentiation of neuroblastoma cells (Takenobu et al., 2011).

Similar to stem cells, CSCs are supported by the tumor microenvironment, which contributes to tumor development and cell behavior (reviewed by Filatova et al., 2013). The ECM represents one major part of this “niche”. Basically, the stem cell niche comprises the stem cell itself, its progeny, a variety of supporting cells, the vascular supply, and surrounding ECM components (for review see Kazanis and ffrench-Constant, 2011; Rojas-Rios and Gonzalez-Reyes, 2014; Scadden, 2006). Tumor cells exhibit an extensive overexpression of various matrix components to design their own ECM. This matrix in consequence supports the CSCs and tumor cells in their behavior but it is also known that the ECM is involved in alterating the diffusion of therapeutic drugs and other neuroactive molecules. The latter property counts for one of the huge problems in the therapy of glioma (Zamecnik, 2005).

2. The specialized extracellular matrix compartment of the embryonic and adult neural stem cell niche

Neuroepithelial cells of the developing neural tube represent veritable neural stem cells (Merkle and Alvarez-Buylla, 2006). They divide symmetrically to expand the number of cells in the early phase of neural development. At the onset of forebrain neurogenesis the neuroepithelial cells are replaced by radial glia cells (RGCs) (Gotz and Huttner, 2005; Kriegstein and Alvarez-Buylla, 2009). RGCs display long processes that stretch the entire thickness of the cortical tissue extending from the ventricular zone (VZ) towards the pial surface. In gyrencephalic primates, so-called outer radial glia cells have been discovered in the outer subventricular zone and are considered responsible for the expansion and folding of the cortex (Fietz et al., 2010; Hansen et al., 2010). In contrast to RGCs, these extend solely a basal process towards the surface of the cortex (Taverna et al., 2014). Neuroepithelial cells and RGCs share common characteristics like the expression of the intermediate filament nestin. However, RGCs express additional glial markers such as the brain lipid binding protein (BLBP), the glutamate aspartate transporter (GLAST), S100 and vimentin (Mori et al., 2005). RGCs mainly divide asymmetrically, undergo self-renewal and generate a differentiated progeny, namely a neuron or a glia cell. Moreover, RGCs give rise to intermediate progenitor cells of the subventricular zone (SVZ). These divide symmetrically to generate two daughter neurons or two novel intermediate progenitors. This transit amplifying precursor mode increases the number of daughter cells and leads to high cell numbers in a short time frame. The progenitor cells in the developing brain also differentiate into glial cells. In general, oligodendrocytes and astrocytes originate from distinct intermediate progenitor cells. Later during development, RGCs detach from the ventricle, migrate into the cortical plate and convert into glial cells. A minor fraction of RGCs keeps contact with the ventricular surface and leads to neurogenic astrocytes, called type B cells and ependymal cells that constitute the adult SVZ, which represents the adult neural stem cell niche of the brain. Restricted neurogenic regions, where stem cells have been localized during adult stages, share several characteristics with stem cell compartments in the developing tissue. The adult NSC niche consists of slowly dividing astrocytes/type B cells—the late RGC descendants, leptomeningeal cells, blood vessel-forming endothelial cells and the cerebrospinal fluid (Ihrie and Alvarez-Buylla, 2011; Riquelme et al., 2008). Slowly dividing type B cells produce transient amplifying type C precursor cells. These type C cells rapidly proliferate and increase the number of descendent lineage cells by the generation of neuroblasts.

It is well accepted that the ECM creates a niche compartment for NSCs (reviewed in Faissner and Reinhard, 2015; Kazanis and ffrench-Constant, 2011; Theocharidis et al., 2014; Wiese and Faissner, 2015). Here, environmental micro-heterogeneity, termed environmental asymmetry, enforces self-renewal or differentiation properties of NSCs. The interaction of the stem cell itself with surrounding molecules and other cells is integrated via membrane receptors and their consecutive signaling cascades. A variation of interaction partners can result in different lineage decisions of daughter cells arising from a cell division. It is evident that proliferation, differentiation, and migration processes are not only cell-intrinsic decisions but often crucially determined by the cells' environment.

Indeed, systematic comparative screenings for a variety of ECM components enriched in the human inner and outer SVZ revealed major expression differences, which suggest that the matrix is crucial for NSC proliferation and maintenance (Fietz et al., 2012; Pollen et al., 2015). Collagens, glycoproteins and proteoglycans as well as integrins interacting with specific growth factors and morphogens keep the stem cells in their proliferative and self-renewing state, or drive them to lineage progression and differentiation.

In general, the neural ECM forms a complex interactive network of glycoproteins and proteoglycans. ECM constituents are structural components of the neurogenic stem cell niche as initially reported by Gates and Steindler for the glycoprotein tenascin-C and its complementary ligand and chondroitin sulfate proteoglycan (CSPG) DSD-1-PG, called phosphacan (Garwood et al., 1999; Gates et al., 1995; Steindler et al., 1996). Both molecules interact with each other, form regulatory networks with other ECM proteins and play a pivotal role during neural development, plasticity, and regeneration (Garcion et al., 2001; Sirko et al., 2010a; von Holst et al., 2006).

During the neurogenic and gliogenic phases of embryonic neural development the glycoprotein tenascin-C and phosphacan are detectable in RGCs in vivo (Garcion et al., 2001, 2004; Sirko et al., 2010a; von Holst et al., 2006) (Fig. 1A–H). Neurospheres generated from embryonic brain tissue express the mRNA of at least 20 tenascin-C isoforms, which are generated by alternative splicing Interestingly, overexpression of the transcription factor and radial glia determinant Pax6 induces the expression of large tenascin-C