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Review

The role of stem cells and progenitors in the genesis of medulloblastoma

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ABSTRACT

Cancer results from dysregulation of growth and survival pathways in normal stem cells and progenitors. Identifying the cells from which a tumor arises can facilitate the development of animal models and point to novel targets for therapy. Medulloblastoma is an aggressive tumor of the cerebellum that occurs predominantly in children. Recent genomic studies suggest that medulloblastoma consists of 4 major subgroups, each with distinct mutations and signaling pathway deregulations, and each potentially arising from distinct populations of stem cells and progenitors. Here we review the major types of progenitor cells in the cerebellum and discuss their role in the genesis of medulloblastoma.

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Introduction

Medulloblastoma (MB) is the most common malignant brain tumor in children. Current treatments for MB include surgical resection followed by irradiation of the entire neuraxis and high-dose chemotherapy. Many patients die despite these treatments, and those who survive often suffer from cognitive deficits and endocrine disorders as a consequence of therapy (Mulhern et al., 2005). New therapies are urgently needed to improve patients' survival and quality of life.

The World Health Organization (WHO) currently classifies MB based on histology and recognizes several subtypes of the disease: classic, large cell/anaplastic (LCA), nodular/desmoplastic and MB with extensive nodularity (Louis et al., 2007). Patients with nodular/desmoplastic histology tend to have favorable outcomes, while those with large cell and anaplastic histology have the worst prognosis (Eberhart et al., 2002; McManamy et al., 2007). Recent advances in microarray and genomic sequencing technologies have enabled a deeper understanding of MB. Based on such analysis, MBs have now been divided into 4 major molecular subgroups: WNT, Sonic Hedgehog (SHH), Group 3 and Group 4 (Jones et al., 2012; Northcott et al., 2012; Pugh et al., 2012; Robinson et al., 2012; Taylor et al., 2012).

WNT-associated tumors, which occur in children and teenagers as well as in adults, normally have disrupted WNT signaling genes, including activating mutations in Ctnnb1 (β-catenin) which activates canonical

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WNT signaling, and inactivating mutations in the adenomatous polyposis coli (APC) gene, a negative regulator of the WNT pathway (Hamilton et al., 1995; Zurawel et al., 1998). WNT MBs typically have classic histology, with LCA observed only rarely. WNT signaling signatures usually predict favorable outcomes compared to other subgroups of MB, and with current modes of therapy, more than 90% of patients with WNT-associated MB survive for >5 years (Clifford et al., 2006; Ellison et al., 2005).

SHH-associated MB is characterized by activation of the Hedgehog signaling pathway, typically resulting from inactivating mutations in the negative regulators PATCHED1 (PTCH1) or Suppressor of Fused (SUFU), activating mutations in the signal transducing molecule SMOOTHENED (SMO), or amplification of the GLI2 transcription factor (Pfister et al., 2010; Taylor et al., 2012). Many SHH-associated MBs have desmoplastic/nodular histology, although classic and LCA histologies are also observed (Taylor et al., 2012). SHH MB occurs in infants, where the prognosis is favorable, as well as in adults, where the prognosis is more variable (Kool et al., 2012).

The majority of MBs do not exhibit activation of the WNT or SHH pathways, and these tumors can be divided into at least two subtypes – Group 3 and Group 4 – based on gene expression, DNA copy number changes and mutations. Group 3 MB patients commonly exhibit amplification or overexpression of the MYC oncogene and have gene signatures resembling those of photoreceptors and gamma-aminobutyric acid expressing (GABAergic) neurons (Taylor et al., 2012). In contrast, Group 4 tumors often exhibit amplification of CDK6 and MYCN or duplication of the Parkinson's Disease-associated gene synuclein alpha interacting protein (SNCAIP), and have expression profiles reminiscent of glutamate-expressing (glutamatergic) neurons (Northcott et al., 2012; Taylor et al., 2012). These disease subtypes also differ with respect to epidemiology and prognosis: Group 3 MB is predominantly found in children, is frequently associated with metastasis and has the poorest prognosis among all subtypes of MB. Group 4 MB, the most prevalent of all the subgroups, is found in both children and adults and has more variable prognosis.

In addition to the molecular distinctions among MB subtypes, a number of signaling pathways are found to be activated across multiple subtypes of the disease. For example, the phosphatidylinositol 3-kinase (PI3K) pathway is activated in WNT (Robinson et al., 2012), SHH (Northcott et al., 2012), and Group 3 MB (Pei et al., 2012b), and genes responsible for histone methylation and chromatin remodeling (MLL2, MLL3, KDM6A, EZH2, ZMYM3) are deregulated in both Group 3 and Group 4 MBs (Pugh et al., 2012; Robinson et al., 2012).

Although different subtypes of MB tumors have distinct histological and molecular characteristics, the current treatment strategy for most MB patients is the same. Given the physical and molecular distinctions among tumor types, it is reasonable to assume that subgroup-specific therapies could be designed to target the dysregulated pathways and intracellular programs intrinsic to each MB subtype, thereby improving the efficacy of treatment and, ultimately, patient survival.

The heterogeneity of MB might be due to distinct cells of origin, different mutations acquired by the same cells, or a combination of these factors. While expression analysis, copy number analysis and sequencing have provided extensive information about the mutations in each of the MB subgroups, the functional role of these mutations remains poorly understood. Likewise, animal models have begun to shed light on the cells from which these tumors arise, but many questions and controversies remain. In order to discuss the current state of knowledge about the cell of origin for MB, it may be helpful to briefly review the program of cerebellar development.

Stem cells and progenitors in the developing cerebellum

MB is a primitive neuroectodermal tumor of the cerebellum. Thus, in considering cells of origin for the disease, it is important to focus on stem cells and progenitors in and around the cerebellum. There are two major germinal zones in the cerebellum: the ventricular zone (VZ) adjacent to the fourth ventricle, which gives rise to the majority of neurons and glia; and the external granule layer (EGL), around the outside of the cerebellum, which generates restricted populations of glutamatergic neurons.

Ventricular zone

During embryogenesis, multipotent stem cells in the VZ undergo active proliferation and then differentiate to produce neuronal and glial progenitors. These cells migrate radially into the cerebellum and give rise to Purkinje, basket, stellate and Golgi neurons, as well as astrocytes and oligodendrocytes. GABAergic neurons all appear to come from a common progenitor (Leto et al., 2006), which expresses the basic helix-loop-helix (bHLH) transcription factor Ptf1a. In the mutant mouse *Cerebelless*, which lacks Ptf1a expression in the cerebellum, glutamatergic neurons develop normally while there is a complete deficiency in GABAergic neurons (Hoshino et al., 2005).

After birth, stem cells from the VZ migrate into the cerebellar white matter. Many of these cells become restricted to neuronal, oligodendroglial and astrocytic fates and ultimately give rise to mature neurons and glia (Milosevic and Goldman, 2002; Zhang and Goldman, 1996), but some retain multipotency. These cells, identified by expression of Prominin1 and lack of neuronal and glial lineage markers, can generate self-renewing neurospheres in vitro and can differentiate into neurons and glia in culture and after transplantation into the mouse cerebellum (Lee et al., 2005). A subset of cells in the white matter also expresses the human GFAP promoter, and these cells have been shown to give rise to cerebellar interneurons and glia in lineage tracing experiments (Silbereis et al., 2009). The relationship between hGFAP+ cells and Prominin1+ Lineage− cells remains unclear. Cerebellar stem cells have intrinsic regional character that distinguishes them from forebrain neural stem cells, and may persist into adulthood (Klein et al., 2005).

External granule layer

During mid-gestation, a subset of VZ progenitor cells migrates laterally to the upper rhombic lip (URL), and under the influence of bone morphogenetic protein (BMP) signaling (Alder et al., 1999), initiates expression of the bHLH transcription factor Atoh1 (Math1) and becomes restricted to the neuronal lineage. The majority of URL progenitors then migrates around the outside of the cerebellum to form the EGL. Progenitor cells in the EGL (granule neuron precursors, or GNPs) proliferate extensively in response to SHH secreted by neighboring Purkinje cells (Dahmane and Ruiz i Altaba, 1999; Wallace, 1999; Wechsler-Reya and Scott, 1999). Ultimately (in response to signals that are poorly understood), GNPs exit the cell cycle, migrate inward to the internal granule layer (IGL), and differentiate into mature granule neurons, the most abundant type of neuron in the brain.

In addition to GNPs, a small population of URL progenitors expresses the T-box transcription factor Tbr2/Eomes. Instead of migrating around the outside of the cerebellum, these cells migrate radially through the white matter and give rise to unipolar brush cells (UBCs) in the internal granule layer (IGL). Notably, the production of UBCs is Atoh1 dependent (Englund et al., 2006). An additional group of URL progenitor cells migrates toward the deep cerebellar nuclei (DCN), the main output centers of the cerebellum, to form DCN neurons (Fink et al., 2006; Machold and Fishell, 2005; Wang et al., 2005). Finally, a unique class of progenitor cells resides in the lower rhombic lip (LRL) of the cerebellum and in the dorsal brainstem; these cells migrate away from the dorsal brainstem to the pontine grey nucleus (PGN), which is involved in motor activity (Gibson et al., 2010).

The diverse array of stem cells and lineage-restricted progenitors described above all represent candidates for MB cells of origin. Investigating whether each of these cell types can actually give rise to tumors requires targeted expression of putative MB oncogenes in