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Biochimica et Biophysica Acta 1776 (2007) 125–137
Biochimica et Biophysica Acta
BBA
www.elsevier.com/locate/bbacan

Review

Neural stem cells, tumour stem cells and brain tumours: Dangerous relationships?

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Received 21 May 2007; received in revised form 20 July 2007; accepted 30 July 2007
Available online 16 August 2007

Abstract

Neural stem cells (NSC) have been implicated not only in brain development and neurogenesis but also in tumourigenesis. Brain tumour stem cells (BTSC) have been isolated from several paediatric or adult human brain tumours, however their origin is still disputed. This review discusses the normal role of NSC in the adult mammalian brain and their anatomical location. It compares the molecular characteristics and the biological behaviour of NSC/BTSC, and describes the molecular pathways involved in controlling self-renewal and maintenance of adult NSC/BTSC and brain tumour development. It also assesses the current hypotheses about the origin of BTSC and the clinical consequences.

Keywords: Neural stem cell; Tumour stem cell; Brain tumour; Neurogenesis; Molecular pathway; Mouse model

Contents

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doi:10.1016/j.bbcan.2007.07.006

1. Introduction

In the last few years our view of the regenerative capacity of the adult mammalian brain has changed considerably. The traditional way of perceiving the adult brain as a static organ composed of postmitotic, fully differentiated cells has been challenged and several pivotal studies have shown how neurogenesis is retained during adult life, therefore conferring a certain degree of plasticity to the adult central nervous system (CNS).

Although a few reports in the 1960s [1–3] described mitotic activity and neurogenesis in the postnatal rodent brain, it has only recently been convincingly shown by seminal work of Luskin [4] in rats, Lois and Alvarez-Buylla [5] in mice, that neurogenesis occurs in the adult rodent subventricular zone (SVZ).

The brain is therefore no more an exception to general rules governing most of the other adult tissues, where the presence of a reservoir of self-renewing and multipotent cells involved in the generation/repair of differentiated and specialised cells is well accepted [6–8].

This new concept of brain development is very intriguing from a neuro-oncological point of view as it provides a novel interpretation frame to understand the pathogenesis of brain tumours. Indeed it was puzzling that brain tumours with morphological features often recapitulating undifferentiated neural progenitor cells could arise from fully differentiated postmitotic cells, which could hardly accumulate enough genetic mutations to undergo neoplastic transformation. Moreover, brain tumours are rather heterogeneous lesions, which often contain immature, undifferentiated cells as well as more differentiated areas, strikingly resembling a somewhat disorganised brain tissue. It is therefore an interesting emerging concept that similar cellular and molecular mechanisms involved in regulating development/plasticity of the adult brain can also be contributing to tumour formation and maintenance when deregulated.

In this review we will focus (i) on the relationship between neural stem cells (NSC) and brain tumours, (ii) on the contribution of tumour stem cells to tumourigenesis, (iii) on molecular mechanisms involved in self-renewal and proliferation of NSC in the pathogenesis of brain tumours and (iv) on the clinical and therapeutical implications of these concepts (Table 1).

Table 1

Stem cell	An undifferentiated cell which can either produce daughter cells with equal developmental potential or generate daughter cells with more restricted properties.
Progenitor cell/ precursor cell	An intermediate cell which is not capable of self-renewal, but can divide and has the capacity to differentiate.
Tumour stem cell	Self-renewing cell which can sustain a tumour and produce more differentiated daughter cells that form the bulk of the tumour. For details see Fig. 2.
Self-renewal	Ability of a stem cell to generate daughter cells that are equivalent to the mother cell.
Stemness	Hypothesis that in different stem cells the regulation of self-renewal and the ability to generate differentiated daughter cells is based on common genes and mechanisms.

2. Neural stem cells in the adult mammalian brain

2.1. Anatomical location and phenotype of neural stem cells in the adult mammalian brain

Adult stem cells are defined as cells giving rise to daughter cells with equal developmental potential (self-renewal) and capable to generate all differentiated cell types in a given tissue (multipotency in most cases; unipotency e.g. in a spermatogenic stem cell). In the adult mammalian brain the stem cells are termed neural stem cells (NSC, also known as B cells in the SVZ) and they can give rise to neurons, oligodendrocytes and astrocytes through generation of more committed transiently amplifying intermediate progenitors (termed C cells in the SVZ) [9,10]. Their origin is still unclear, however a recent hypothesis suggests that they might originate from radial glial cells, primary embryonic stem cells derived from neuroepithelial cells (reviewed in [11]).

Cells with stem cell properties have been identified in four distinct anatomical areas of the postnatal mammalian brain: (i) the subventricular zone (SVZ) beneath the lateral wall of the lateral ventricles [9], (ii) the subgranular zone (SGZ) in the dentate gyrus of the hippocampus [12], and more recently also (iii) in the subcallosal zone (SCZ) between the hippocampus and the corpus callosum [13] and (iv) in the cerebellum at the boundary between internal granular layer (IGL) and white matter [14] (Fig. 1). While the SVZ and the SCZ harbour cells which fulfill all criteria of NSC, some controversies still exist concerning the other two locations. The self-renewal capacity of SGZ cells seems rather limited according to the experimental data available to date [12] and in the cerebellum, cells fulfilling all criteria of NSC have been isolated only from p7 mice but not yet from adult mice [14].

The NSC persist during adult life through asymmetric self-renewing divisions and they are a source of more differentiated/specified cells through transient amplification of more committed progenitors. They are also called neurogenic astrocytes as they share with them several properties such as morphological appearance and expression of glial fibrillary acidic protein (GFAP) [9,15]. It is interesting that the fraction of astrocytes potentially capable of behaving as NSC might be higher than expected. Sharif and coworkers have recently shown in mice that cultures of mature astrocytes depleted of NSC can revert to a radial glial phenotype or even to an NSC phenotype if treated sufficiently long with TGFα [16], therefore implying a crucial role of the microenvironment in determining the "stemness" of an astrocytic cell. Indeed there is compelling evidence of a crucial role played by the so-called niche or immediate microenvironment composed of more differentiated cells in conditioning stem cell behaviour. Histological and *ex vivo* cell culture studies on mouse tissue have shown that NSC reside within a neurovascular niche in which endothelial cells regulate stem cell self-renewal by direct cell contacts and secreted factors [17–19].

NSC can be isolated from various areas of the adult mammalian brain by cell sorting with stem cell markers (e.g. CD133 or its murine homologue prominin 1) [14,20] and culturing in a serum-free medium on a nonadhesive substrate in the presence of the mitogens βFGF and EGF [21]. Under these conditions they give rise to three-dimensional floating round cell clusters, named