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Review

The vasculature as a neural stem cell niche

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ABSTRACT

Neural stem cells (NSCs) are multipotent, self-renewing progenitors that generate progeny that differentiate into neurons and glia. NSCs in the adult mammalian brain are generally quiescent. Environmental stimuli such as learning or exercise can activate quiescent NSCs, inducing them to proliferate and produce new neurons and glia. How are these behaviours coordinated? The neurovasculature, the circulatory system of the brain, is a key component of the NSC microenvironment, or 'niche'. Instructive signals from the neurovasculature direct NSC quiescence, proliferation, self-renewal and differentiation. During ageing, a breakdown in the niche accompanies NSC dysfunction and cognitive decline. There is much interest in reversing these changes and enhancing NSC activity by targeting the neurovasculature therapeutically. Here we discuss principles of neurovasculature-NSC crosstalk, and the implications for the design of NSC-based therapies. We also consider the emerging contributions to this field of the model organism *Drosophila melanogaster*.

Contents

1. Introduction

Neural stem cells (NSCs) are multipotent progenitors that self-renew and give rise to cells that differentiate into neurons and glia. NSCs proliferate rapidly during embryogenesis, when they generate

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the functional nervous system. In adult mammals, in contrast, NSCs are relatively quiescent and are restricted to two regions of the brain – the ventricular-subventricular zone (V-SVZ) of the lateral ventricles and the subgranular zone (SGZ) of the dentate gyrus in the hippocampus (Doetsch et al., 1999a; Morshead et al., 1994; Seri et al., 2001). Physiological or pathological processes such as learning, exercise or injury stimulate proliferation and neurogenesis (Gould et al., 1999; Gould and Tanapat, 1997; Kempermann et al., 1997; Rochefort et al., 2002; van Praag et al., 1999a, 2005; Zhang et al., 2001). New neurons integrate functionally into existing circuitry in the V-SVZ and SGZ and allow adaptive responses to environmental changes, for example by increasing odour discrimination (Carleton et al., 2003; Livneh et al., 2014; van Praag et al., 2002) or spatial pattern separation (Clelland et al., 2009; Sahay et al., 2011; Tronel et al., 2012). NSCs therefore play essential roles in development, homeostasis and behavioural plasticity in the nervous system.

Each of the NSC behaviours – quiescence, proliferation, self-renewal and differentiation – must be precisely balanced to avoid pathology. Excessive self-renewal at the expense of differentiation, for example, can result in brain tumour formation (Palm and Schwamborn, 2010; Sanai et al., 2009). In contrast, premature differentiation can deplete the stem cell pool.

NSCs reside in specialised microenvironments, or 'niches', in the V-SVZ and SGZ, which tightly regulate their behaviour (Bjornsson et al., 2015; Bond et al., 2015; Fuentealba et al., 2012; Silva-Vargas et al., 2013). The vascular system is a prominent feature of both niches (Gómez-Gaviro et al., 2012a; Licht and Keshet, 2015). Blood vessels distribute oxygen, hormones and metabolites around the body, performing essential support and signalling functions. Pericytes and niche astrocyte end feet associate closely with the walls of blood vessels and control their development and functional properties. NSCs and their progeny frequently divide in the vicinity of blood vessels (Mirzadeh et al., 2008; Palmer et al., 2000; Shen et al., 2008; Tavazoie et al., 2008). In the V-SVZ, NSCs further away from blood vessels extend long processes to contact the vasculature (Mirzadeh et al., 2008; Shen et al., 2008; Tavazoie et al., 2008). It is now clear that the vasculature not only supports but directly controls NSC behaviours. Several diffusible and non-diffusible vascular signals control NSCs and their progeny. Importantly, blood vessels are intimately associated with stem cells in many other organs (Gómez-Gaviro et al., 2012a). It is likely that the principles of NSC regulation discovered in the brain also apply to other stem cell compartments, such as muscle and bone marrow, and *vice versa*.

Here we review our understanding of the vasculature as a NSC niche, focussing on the V-SVZ, the largest germinal zone in the adult mammalian brain. NSC number and activity decline during ageing, accompanied by drastic reductions in the neurovascular network (Ahlenius et al., 2009; Farkas and Luiten, 2001; Katsimpardi et al., 2014; Maslov et al., 2004; Riddle et al., 2003; Tropepe et al., 1997). What factors cause these changes and, importantly, are they reversible? Simpler organisms, such as *Drosophila melanogaster*, are emerging as powerful models to study the neurovascular niche. We consider how the principles learnt from rodents and *Drosophila* could shape future therapies targeting human NSCs.

2. NSCs: a lifetime of neurons and glia

NSCs in the adult V-SVZ, also known as Type B cells, are a subpopulation of astrocyte glia residing in the walls of the lateral ventricles

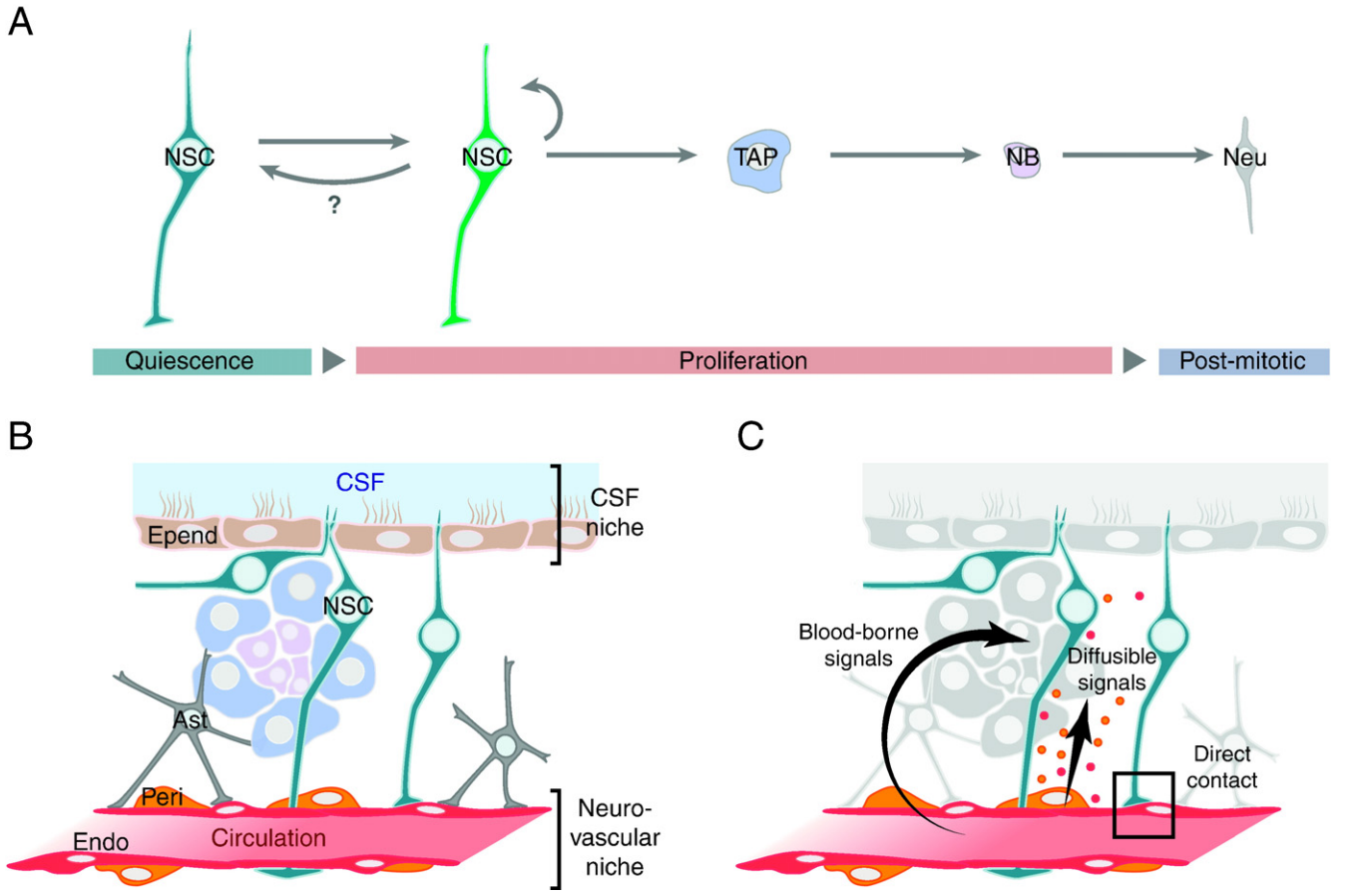

Fig. 1. The adult mammalian V-SVZ niche. A: The lineage of adult V-SVZ neural stem cells (NSCs). Quiescent NSCs become activated and generate, in sequence, transit amplifying progenitors (TAPs), migratory neuroblasts (NBs) and neurons (Neu). It is unclear whether activated NSCs can return to a quiescent state. B: The anatomy of the V-SVZ, illustrating the neurovascular and CSF niches. Abbreviations – Epend: ependymal cell, Ast: niche astrocyte, Peri: pericyte, Endo: endothelial cell. C: Three routes for neurovascular signalling to NSCs.