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Review

Endogenous neurogenesis following ischaemic brain injury: Insights for therapeutic strategies☆

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ABSTRACT

Ischaemic stroke is among the most common yet most intractable types of central nervous system (CNS) injury in the adult human population. In the acute stages of disease, neurons in the ischaemic lesion rapidly die and other neuronal populations in the ischaemic penumbra are vulnerable to secondary injury. Multiple parallel approaches are being investigated to develop neuroprotective, reparative and regenerative strategies for the treatment of stroke. Accumulating evidence indicates that cerebral ischaemia initiates an endogenous regenerative response within the adult brain that potentiates adult neurogenesis from populations of neural stem and progenitor cells. A major research focus has been to understand the cellular and molecular mechanisms that underlie the potentiation of adult neurogenesis and to appreciate how interventions designed to modulate these processes could enhance neural regeneration in the post-ischaemic brain. In this review, we highlight recent advances over the last 5 years that help unravel the cellular and molecular mechanisms that potentiate endogenous neurogenesis following cerebral ischaemia and are dissecting the functional importance of this regenerative mechanism following brain injury.

This article is part of a Directed Issue entitled: Regenerative Medicine: the challenge of translation.

Contents

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1. Introduction

Cerebral ischaemic injury is the most common form of stroke and accounts for a major percentage of neurological disease worldwide (Johnston et al., 2009; Feigin et al., 2014). At present, there is no reparative treatment and patients can experience a permanent loss of brain function. Approaches to reduce the burden of disease in patients who have suffered a stroke seek to limit and reverse neurological damage by reducing CNS injury and promoting neural regeneration. The normal course of disease in stoke patients includes an acute ischaemic period in which focal areas subject to ischaemic injury are vulnerable to cell death. In the subacute phase, tissue adjacent to the ischaemic core known as the ischaemic penumbra is vulnerable to further injury.

A number of processes contribute to recovery following ischaemia including neuroplasticity, angiogenesis and neurogenesis. The role that neuroplasticity and angiogenesis play in mediating recovery following stroke have been recently reviewed (Ergul et al., 2012; Hermann and Chopp, 2012). Understanding the cellular and molecular processes that underlie post-ischaemic neurogenesis are important to establish the extent to which this contributes to neural regeneration after stroke and whether interventions can be developed to potentiate neural regeneration in stroke patients.

2. Cerebral ischaemic injury

Cerebral ischaemic injury is a pathological event caused by temporary or permanent occlusion/blockage of vascular structures within the CNS. Focal (stroke) and global (*e.g.* cardiac arrest) cerebral ischaemia arise from a transient or permanent impairment of blood supply to the brain, causing a local or generalised oxygen and glucose deprivation, respectively. As a consequence, vast numbers of neurons in the brain rapidly die due to the induction of complex pathological processes initiated by excessive glutamate release which is excitotoxic (reviewed by Broughton et al., 2009). The resultant overproduction of free radicals, which cause local and acute tissue injury, is followed by an inflammatory reaction marked by the activation of local microglial cells and the infiltration of peripheral leukocytes. The acute inflammation and oxidative stress that accompany early stages of stroke can result in the activation of detrimental transcription factors (*e.g.* nuclear factor kappa-B (NF-κB)) and disruption the blood-brain barrier (BBB), a physical barrier within the brain providing protection and regulation of homeostasis.

The prevalence of ischaemic stroke in the community has prompted the development of animal models in various species to aid in the investigation of ischaemic and reperfusion injuries. The most common model is the middle cerebral artery occlusion (MCAO) in which the artery is either transiently or permanently occluded *via* ligation or internal physical obstruction (Tamura et al., 1981). An alternative approach involves the injection of endothelin-1 next to blood vessels to induce transient vasoconstriction to block vascular flow, which can be applied to various brain regions for a more focal injury (Teo et al., 2012). Another less commonly used method to induce focal ischaemia is Rose bengal cerebrocortical photothrombotic infarction (Watson et al., 1985).

The regions of the brain that are affected by ischaemic stroke depend considerably on the animal model and experimental paradigm utilised, which has led to much debate and potentially contributed to significant failures in translation of research findings. To this end, there still remain very few treatment options for stroke and as such there is a pressing need to realise the potential of cellular and molecular approaches that may augment repair following such an injury. In this regard, there is considerable interest in understanding how the neurogenic niches in the adult mammalian brain are influenced by cerebral ischaemic injury and whether these responses could be optimised to provide therapeutic benefit.

3. Neurogenic niches of the adult central nervous system

Most of our current understanding of adult neural stem/progenitor cell biology and the mechanics of adult neurogenesis is based upon experiments conducted using rodent models. Neurogenesis has been conclusively demonstrated to persist in two germinal niches in the adult rodent central nervous system (CNS), namely the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone (SGZ) of the hippocampal dentate gyrus (reviewed by Ming and Song, 2011). Neural stem cells located in these regions are relatively quiescent, dividing infrequently to produce heterogeneous populations of rapidly dividing neural precursor cells (NPCs). Under normal physiological conditions, NPCs in the SVZ and SGZ differentiate into cells destined to become interneurons in the olfactory bulb and granule neurons in the dentate gyrus, respectively (Lois and Alvarez-Buylla, 1994; Seri et al., 2001).

In vitro characterisation of cells isolated from the SVZ and dentate gyrus provided additional experimental evidence to define both regions as persistent neurogenic niches in the adult rodent CNS (Reynolds and Weiss, 1992; Richards et al., 1992; Walker et al., 2008). When cultured at low density in the presence of epidermal growth factor (EGF) and/or fibroblast growth factor-2 (FGF-2), neural stem/progenitor cells isolated from the SVZ and dentate gyrus generate clonally derived spheres of cells known as neurospheres. A subset of neurospheres exhibit the cardinal properties of stem cells including the ability to proliferate, self-renew and undergo multipotential differentiation, generating neurones, astrocytes and oligodendrocytes (reviewed by Pastrana et al., 2011). Long-term examination of single cells within the adult neurogenic niches also support the existence of multipotent neural stem/progenitor cells *in vivo* (Bonaguidi et al., 2011).