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Ageing stem and progenitor cells: implications for rejuvenation of the central nervous system

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Summary

The growing burden of the rapidly ageing global population has reinvigorated interest in the science of ageing and rejuvenation. Among organ systems, rejuvenation of the central nervous system (CNS) is arguably the most complex and challenging of tasks owing, among other things, to its startling structural and functional complexity and its restricted capacity for repair. Thus, the prospect of meaningful rejuvenation of the CNS has seemed an impossible goal; however, advances in stem cell science are beginning to challenge this assumption. This Review outlines these advances with a focus on ageing and rejuvenation of key endogenous stem and progenitor cell compartments in the CNS. Insights gleaned from studies of model organisms, chiefly rodents, will be considered in parallel with human studies.

Key words: CNS rejuvenation, CNS stem cells, Disease

Introduction: the burden of ageing and age-related CNS disease

"But age, with his stealing steps, hath claw'd me in his clutch"
Shakespeare, *Hamlet*, Act 5, Scene 1 (graveyard scene)

According to a recent report by the United Nations Population Fund, the number of people in the world aged 60 or above is projected to increase from 810 million in 2012 to a staggering 2 billion by 2050 (UNFPA Report, 2012). Ageing is a leading risk factor for the major causes of chronic disease and disability, and health care expenditure increases significantly with advancing age (Meerding et al., 1998; Alemayehu and Warner, 2004). Accordingly, there is a compelling socioeconomic imperative for interventions to prevent or reverse age-related CNS disease. One such approach centres on harnessing the regenerative potential of endogenous stem cell populations to rejuvenate the ageing CNS. This Review will provide an overview of the current state of knowledge of stem cell ageing and the implications of ageing on CNS rejuvenation. Interventions centred on the transplantation of exogenous progenitor cells are beyond the scope of this work and have been reviewed elsewhere (Marr et al., 2010; Dunnett and Rosser, 2011).

CNS stem and progenitor cells: significant players in CNS function?

The discovery that the adult mammalian CNS contains populations of stem cells that contribute to CNS function took decades to gain traction (Altman and Das, 1965; Altman, 1969; Kaplan and Hinds, 1977; Lois and Alvarez-Buylla, 1994; Kirschenbaum et al., 1994; Eriksson et al., 1998). Neurogenic stem cells are principally concentrated in two spatially and functionally distinct zones in the human brain: the subventricular zone (SVZ), lining the walls of the lateral ventricles; and the subgranular zone (SGZ) of the hippocampal dentate gyri (Fig. 1). The cellular, architectural and signalling milieus of these zones, or niches, are specialised to support stem cell function (Marr et al., 2010), in contrast to the relatively inhospitable microenvironment of the remainder of the brain. A third population of progenitor cells, known as oligodendrocyte progenitor cells (OPCs), are diffusely distributed in the brain and spinal cord. OPCs are multipotent, giving rise chiefly to myelinating oligodendrocytes, but also to Schwann cells, astrocytes and possibly neurons (Box 1), but the question of whether they constitute bone fide stem cells is a subject of ongoing debate (Franklin and ffrench-Constant, 2008; Zawadzka et al., 2010; Richardson et al., 2011). A fourth group of putative neural progenitor cells are reportedly scattered throughout the CNS in regions classically considered to be non-neurogenic (Palmer et al., 1999; Arsenijevic et al., 2001; Richardson et al., 2006; Bennett et al., 2009). Although it appears that these cells may have neurogenic potential when cultured *in vitro*, it is not clear whether this capacity is realised *in vivo* and it is uncertain how these cells differ, if at all, from OPCs. As the functional relevance of these dispersed progenitor cells in humans is unclear, they will not be discussed further in this Review. The neurogenic potential of parenchymal astrocytes in humans is also uncertain and has been reviewed elsewhere (Robel et al., 2011). Key attributes of the SVZ and SGZ stem cell and OPC populations and the contributions they make to CNS function will be reviewed in brief below.

The subgranular zone of the hippocampal dentate gyrus (SGZ)

The hippocampi reside in the medial temporal lobes of the human brain where they constitute part of the limbic system and play important roles in spatial learning and the consolidation of memory as well as the regulation of emotions. The SGZ resides between the granule cell layer and hilus of the hippocampal dentate gyrus and is arguably the most important of the neurogenic zones in the adult human CNS. Although the intricacies of SGZ neurogenesis (reviewed by Kempermann et al., 2004; Ming and Song, 2011) are beyond the scope of this Review, key steps in the process include the asymmetric division of radial glia-like stem cells to yield intermediate progenitor cells (alternatively named transient amplifying progenitor cells), which migrate towards the granule cell layer. Here, they undergo several rounds of division and differentiation to yield a population of post-mitotic immature granule cells that establish nascent network connections. A minority of these neurons subsequently mature into terminally differentiated excitatory granule cells. Several caveats to this simplified scheme of hippocampal neurogenesis warrant consideration [discussed in detail by Kempermann et al.

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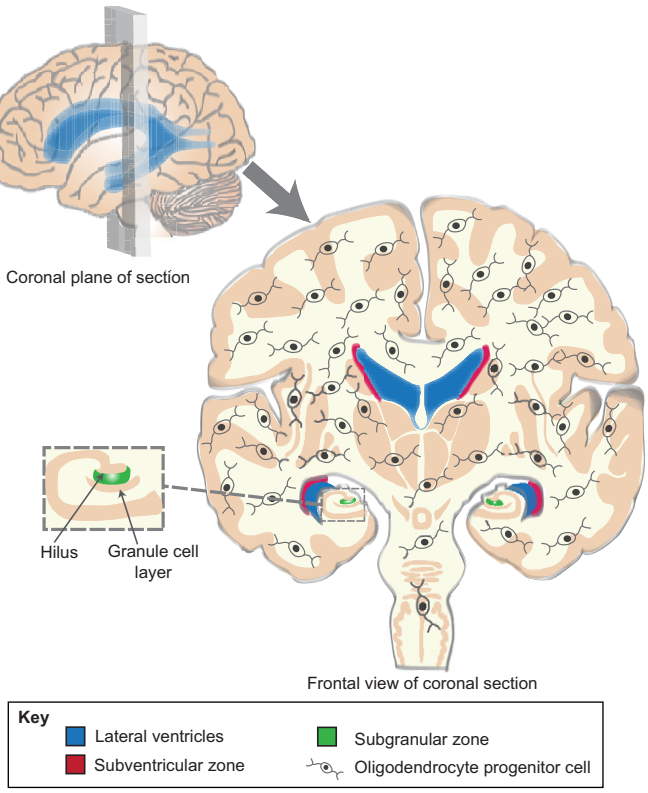

Fig. 1. Location of CNS stem and progenitor cell niches. The subventricular zones line the walls of the lateral ventricles, whereas the subgranular zones reside between the hilus and granule cell layer of each hippocampus. Oligodendrocyte progenitor cells are widely distributed in the white and grey matter of the brain and spinal cord.

(Kempermann et al., 2004)]: the process is continuous and thus the population of dividing cells is heterogeneous; a large proportion of cells die prior to maturation and integration into the neural circuitry; levels of neurogenesis in the adult are orders of magnitude lower than those during development (Ben Abdallah et al., 2010; Kronenberg et al., 2006; Knoth et al., 2010); and the extent of neurogenesis that occurs in the adult human hippocampus is far lower than that in rodents, on which the majority of our knowledge of the process is based (Eisch and Petrik, 2012).

Newborn neurons integrate into the hippocampal circuitry and contribute to hippocampal function. They receive functional afferent connections, spike in response to excitatory inputs and release glutamate onto their post-synaptic neurons (Song et al., 2002; Mongiat et al., 2009; Schmidt-Hieber et al., 2004; Faulkner et al., 2008; Toni et al., 2008). Although the number of adult-born neurons in the granule cell layer is dwarfed by those that form during early development (Schlessinger et al., 1975; Altman and Bayer, 1990), these cells are well equipped to make significant functional contributions: they make synaptic connections prior to attaining maturity and exhibit enhanced excitability, optimising them for synaptic plasticity (Mongiat et al., 2009; Schmidt-Hieber et al., 2004; Laplagne et al., 2006). Adult-born hippocampal neurons exert modulatory effects on the established neural circuitry and thus on brain function (reviewed by Deng et al., 2010; Ming and Song, 2011).

The progeny of adult neurogenesis play numerous important roles in learning and behaviour (reviewed by Deng et al., 2010; Kim et al., 2012; Kempermann, 2012). Chief among these is pattern separation, the capacity to differentially encode memories of similar events on the basis of their precise temporal and spatial attributes (Clelland et al., 2009; Nakashiba et al., 2012). This 'time-stamping' of memories is central to accurate spatial and episodic memory (Kempermann, 2012). Hippocampal neurogenesis has been implicated in other aspects of learning and memory (Kitamura et al., 2009; Kim et al., 2012), including the long-term retention of spatial memory and object recognition memory (Jessberger et al., 2009). Furthermore, hippocampal neurogenesis plays a role in regulating emotions, and impairments in the process are implicated in the pathogenesis of depression and other affective disorders (reviewed by Small et al., 2011; Eisch and Petrik, 2012; Fotuhi et al., 2012).

The subventricular zone (SVZ)

The subventricular zones line the walls of the lateral ventricles of the brain and contain a population of stem cells with neurogenic potential. The bulk of our understanding of this population of cells is derived from rodent studies. In the rodent SVZ, radial glia-like stem cells with morphological features similar to those in the SGZ undergo asymmetric division to yield transient amplifying cells, which in turn give rise to neuroblasts. Chains of neuroblasts migrate in streams along a well-defined pathway to the olfactory bulb, known as the rostral migratory stream (RMS). Once in the olfactory bulb, the neuroblasts migrate in a radial fashion and differentiate into several types of interneurons, integrating with the granule cell and periglomerular layers (Luskin, 1993; reviewed by Yao et al., 2012; Ming and Song, 2011). These adult-born neurons maintain the structural integrity of the olfactory bulb and contribute to olfactory memory, olfactory fear-conditioning and pheromone-linked behaviour (Ming and Song, 2011; Lazarini and Lledo, 2011). The process continues throughout life in the rodent, albeit at a declining rate with advancing age (Enwere et al., 2004; Ahlenius et al., 2009). In addition, stem cells of the SVZ give rise to oligodendrocyte progenitor cells, which migrate chiefly to the corpus callosum and striatum (Levison and Goldman, 1993; Nait-Oumesmar et al., 1999; Menn et al., 2006).

The existence of SVZ neurogenesis in the adult human brain remains a matter of controversy. Although it is clear that a ribbon of astrocyte-like stem cells with *in vitro* neurogenic capacity lines the walls of the lateral ventricles (Kirschenbaum et al., 1994; Pincus et al., 1998; Johansson et al., 1999; Sanai et al., 2004; Curtis et al., 2007; Ayuso-Sacido et al., 2008; Kam et al., 2009), current evidence suggests that the extent of neurogenesis in this zone is negligible beyond late infancy (Wang et al., 2011; Sanai et al., 2011). A clearly defined RMS, replete with cells bearing the morphological and immunohistochemical attributes of migrating neuroblasts, has been characterised in the human brain in early post-natal life (Sanai et al., 2011). These cells are thought to populate the olfactory bulb and an area of the developing prefrontal cortex (Sanai et al., 2011). However, the proliferative activity of the SVZ and the number of neuroblasts in the RMS decline significantly during infancy such that neuroblasts are found infrequently in the adult brain (Sanai et al., 2011; Wang et al., 2011). Accordingly, the functional significance of SVZ neurogenesis in the adult human brain remains in question and as such it may be inappropriate to consider human SVZ and SGZ neurogenesis in the same light, as is often done for model organisms (Kempermann, 2012). Whether SVZ-derived neuroblasts are recruited to any meaningful extent in the setting of injury or disease in humans, as appears to occur in rodent models (Arvidsson et al., 2002; Parent et al., 2002; Tattersfield et al.,

Box 1. Are oligodendrocyte progenitor cells neural stem cells?

OPCs exhibit many features of stemness, including (reviewed by Franklin and ffrench-Constant, 2008; Richardson et al., 2011):

Self-renewal

The capacity to maintain the oligodendrocyte lineage (Dawson et al., 2003; Rivers et al., 2008).

Multipotency

In vivo fate-mapping studies confirm that the progeny of OPC differentiation include oligodendrocytes, Schwann cells and astrocytes (Tatsumi et al., 2008; Zhu et al., 2008a; Zhu et al., 2008b; Tripathi et al., 2010; Zawadzka et al., 2010; Tsai et al., 2012; Zhu et al., 2012). Evidence for neural differentiation is mixed and it is possible that OPCs give rise to a subset of neurons in the piriform cortex during development (Guo et al., 2010; Rivers et al., 2008; Kang et al., 2010; Clarke et al., 2012). Cultured OPCs are readily induced to yield neurospheres, which in turn give rise to mixed colonies of oligodendrocytes, astrocytes and neurons (Kondo and Raff, 2000; Nunes et al., 2003).

Asymmetric division

Genetic fate-mapping studies and live cell imaging have confirmed that single OPCs may self-renew or give rise to either two oligodendrocytes, or one OPC and one oligodendrocyte (Zhu et al., 2011). In most instances, the initial division is symmetric with daughter cells subsequently assuming different fates (Zhu et al., 2011). Whether true asymmetric division occurs is unclear. One study demonstrating asymmetric segregation of the proteoglycan NG2 (CSPG4) as well as epidermal growth factor receptor is suggestive of asymmetric division (Sugiarto et al., 2011); however, further evidence is required to prove definitively that OPCs can undergo asymmetric cell division.

2004), is unclear. A recent post-mortem study of human brains suggested that enhanced SVZ neurogenesis may contribute to repair in the setting of vascular dementia (Ekonomou et al., 2011), but the functional significance of this is unknown. Another study of human brains has identified increased SVZ neurogenesis in Huntington's disease (Curtis et al., 2003); however, the regenerative potential of these cells is still to be established.

Oligodendrocyte progenitor cells (OPCs)

OPCs (alternatively named oligodendrocyte precursor cells or NG2-glia) were first isolated from perinatal rat optic nerve in 1983 (Raff et al., 1983) and are now known to be widely distributed in the grey and white matter of the adult brain and spinal cord, constituting ~5% of all cells in the CNS (Pringle et al., 1992). Although the vast majority of adult OPCs are mitotically quiescent at any given point in time, they constitute the largest population of cycling cells in the adult CNS (Horner et al., 2000; Dawson et al., 2003). OPCs arise from the ventral and dorsal neuroepithelium of the developing brain and spinal cord and migrate throughout the CNS. OPCs display a degree of plasticity (Box 1), but their chief progeny, the oligodendrocytes, are the main myelinating cells of the CNS, facilitating efficient axonal conduction and providing axons with metabolic and trophic support (Waxman, 1977; Felts et al., 1997; Nave and Trapp, 2008; Lee et al., 2012; Fünfschilling et al., 2012). OPCs play an essential role in maintaining CNS myelination in health and disease. It is estimated that ~29% of the total number of oligodendrocytes in the adult mouse corpus callosum are the progeny of OPC differentiation after sexual maturity (Rivers et al., 2008), and myelination is known to continue throughout life, albeit at a declining rate beyond middle age (Lu et al., 2011). The loss of myelin in diseases such as multiple sclerosis (MS), the most common disabling neurological disease of young adults, triggers an endogenous regenerative process known as remyelination. During remyelination, OPCs proliferate and migrate to the site of injury where they differentiate into myelinating oligodendrocytes. The process helps to guard against axonal degeneration and is a key mechanism by which functional improvement occurs after episodes of demyelination (Franklin and ffrench-Constant, 2008).

In addition to providing new oligodendrocytes for myelination, a growing body of evidence suggests that OPCs per se might play important roles in information processing and in the maintenance of neuronal homeostasis (Bakiri et al., 2009; reviewed by Franklin and ffrench-Constant, 2008; Richardson et al., 2011). The finding that OPC numbers far exceed the requirements for basal oligodendrocyte turnover points to these additional roles for OPCs, as does the abundance of these cells in grey matter, where the requirement for myelinating oligodendrocytes is minimal. OPCs have been shown to generate action potentials and to communicate with neurons via synapses (Káradóttir et al., 2008), blurring the boundaries between neuronal and glial cell types. The precise nature and functional significance of this communication awaits clarification. One possibility is that neuronal activity triggers localised OPC differentiation and the subsequent myelination of active neuronal circuits (Richardson et al., 2011). It is postulated that activity-dependent myelination may sustain and enhance neuronal circuitry, contributing to learning, memory consolidation and cognitive function (Bakiri et al., 2009; Richardson et al., 2011).

Stem and progenitor cell ageing

Ageing can be defined as the physiological loss of homeostasis over time. The ageing process affects all cells within an organ, including stem cells. The extent to which stem cell ageing contributes to ageing at the organismal level is the focus of ongoing study (reviewed by Sharpless and DePinho, 2007; Sahin and DePinho, 2010). Although neurogenesis and oligodendrogenesis continue throughout life, significant age-related declines in these processes are known to occur and the effects of this on CNS function are now being unravelled. Interventions to delay or reverse age-related declines in these stem cell populations may lie at the heart of CNS rejuvenation therapies. The following sections address CNS stem cell ageing by compartment, the mechanisms of stem cell ageing, as well as interventions aimed at rejuvenating stem cell function in the context of ageing. Given the uncertain relevance of SVZ stem cells in the adult human brain, the ensuing discussion will focus on OPCs and stem cells of the SGZ.

The ageing SGZ

It has long been known that neurogenesis in the rodent SGZ declines significantly with advancing age (Altman and Das, 1965; Seki and Arai, 1995; Kuhn et al., 1996). Studies have demonstrated that the number of proliferating cells and the number of cells immunoreactive for doublecortin, a marker of neurogenesis expressed by neural progenitor cells and young neurons, in the mouse SGZ reach a peak in early post-natal life, before declining rapidly for several months and more slowly thereafter (Seki and Arai, 1995; Kuhn et al., 1996; Kempermann et al., 1998; Ben Abdallah et al., 2010). Conceptually, waning neurogenesis might be the consequence of changes in stem or progenitor cell dynamics, whether by terminal differentiation, prolongation of cell cycle times, quiescence, senescence or death. Changes in the survival and differentiation of their progeny might also be involved.

Studies of rodents variably demonstrate no significant loss (Hattiangady and Shetty, 2008; Lugert et al., 2010) or substantial loss (Olariu et al., 2007; Walter et al., 2011; Jinno, 2011) of stem and progenitor cells from the SGZ with age. These conflicting observations might in part be attributable to the use of different animal models as well as different methods for the quantification of stem and progenitor cell numbers (Artegiani and Calegari, 2012). Many studies have demonstrated marked age-related declines in stem and progenitor cell proliferation in the dentate gyrus (Kuhn et al., 1996; Cameron and McKay, 1999; Bondolfi et al., 2004; McDonald and Wojtowicz, 2005). However, it is not entirely clear whether this is more attributable to cell quiescence (Hattiangady and Shetty, 2008) or to the prolongation of cell cycle times, as data pertaining to the latter are mixed (McDonald and Wojtowicz, 2005; Rao et al., 2005; Olariu et al., 2007). A recent study has indicated that waning neurogenesis in the ageing mouse hippocampus is due to the transition of a subset of proliferating progenitor cells to a quiescent state, under the control of canonical Wnt signalling (Lugert et al., 2010).

Questions remain about the effects of ageing on the fate of cells born by adult neurogenesis, both in terms of their survival and the proportion of cells that undergo neuronal differentiation. Some studies have demonstrated that cell survival does not decrease as a function of age (Bondolfi et al., 2004; McDonald and Wojtowicz, 2005), whereas others have documented a significant decline in cell survival in old age (Kempermann et al., 1998; van Praag et al., 2005). Neuronal differentiation rates have variously been shown to remain relatively constant throughout life (Seki, 2002; Bondolfi et al., 2004; Rao et al., 2005; McDonald and Wojtowicz, 2005) or to decline significantly with age (Kempermann et al., 1998; van Praag et al., 2005). Ageing might also be associated with fate switching of progeny towards glial lineages (van Praag et al., 2005). A consensus appears to have been reached about the phenotypes of newborn SGZ neurons in young and old mice: neurons are morphologically comparable and they exhibit similar dendritic spine densities (an indicator of glutamatergic afferent connectivity) (van Praag et al., 2005; Morgenstern et al., 2008). Furthermore, the newborn granule cells of young and old mice are electrophysiologically indistinguishable (Couillard-Despres et al., 2006), supporting the notion that these neurons are equally equipped to make functional contributions to the hippocampal circuitry.

Rodent studies have variously demonstrated positive correlation (Kempermann et al., 1998; Drapeau et al., 2003; Driscoll et al., 2006) or no correlation (Merrill et al., 2003; Bizon et al., 2004) between the extent of hippocampal neurogenesis and age-related performance declines in selected learning and memory tasks. Nevertheless, interventions to reduce hippocampal neurogenesis have repeatedly resulted in impaired cognitive function that mirrors changes characteristic of ageing (Shors et al., 2001; Montaron et al., 2006). Similarly, interventions that enhance neurogenesis typically improve cognitive function (Kempermann et al., 1998; Kempermann et al., 2002; van Praag et al., 2005; Montaron et al., 2006). Thus, it is clear that aspects of age-related cognitive decline are related to declining hippocampal neurogenesis. However, the relationship between ageing and neurogenesis is complex and hippocampal dysfunction accounts for part of a broader spectrum of changes in cognitive function with age (van Praag et al., 2005; Artegiani and Calegari, 2012; Kempermann et al., 2012).

Although there are few studies on the effects of ageing on human SGZ neurogenesis, it is thought that the process follows a trajectory similar to that observed in rodents and in non-human primates (Leuner et al., 2007). A recent analysis of human brain tissue across a broad age spectrum demonstrated an exponential decline in the number of cells in the dentate gyrus staining positive for doublecortin and several other surrogate markers of neurogenesis (Knoth et al., 2010). These findings are broadly in keeping with those of a study using magnetic resonance spectroscopy to quantify neurogenesis in living human subjects (Manganas et al., 2007), although the methodological rigour of this latter study has been in question (Hoch et al., 2008; Jansen et al., 2008).

Ageing oligodendrocyte progenitor cells

Ageing is associated with the loss of myelin. Imaging studies of the human brain have demonstrated that white matter volume peaks in middle age and declines thereafter (Bartzokis et al., 2003; Fields, 2010; Lu et al., 2011; Bartzokis et al., 2010). In support of this, histopathological studies of human brains have demonstrated that neocortical white matter volumes decline some 28% between the ages of 20 and 80 years (Pakkenberg and Gundersen, 1997) and oligodendrocyte numbers decline in the order of 27% between 20 and 90 years of age, approximately two to three times greater than the extent of neuron loss (Pakkenberg and Gundersen, 1997; Pelvig et al., 2008). The degree to which age-related myelin loss is due to primary oligodendrocyte dysfunction, as opposed to being a consequence of axon loss, remains to be determined. The loss of myelin integrity with age, reflected by ultrastructural changes and characteristic magnetic resonance imaging signatures, has been shown to follow a similar trajectory to a surrogate marker (maximal finger tapping speed) of human cognitive performance (Bartzokis et al., 2010). These alterations, coupled with significant derangements in myelin biochemistry, support the notion that white matter disruption plays a role in age-related cognitive decline (reviewed by Hinman and Abraham, 2007). Accordingly, interventions aimed at rejuvenating CNS myelination may be broadly applicable to ageing human populations. Interestingly, myelin loss and disruption with ageing is not likely to be due to the loss of OPCs as studies in mice have demonstrated that stable numbers of OPCs are maintained well into old age (Sim et al., 2002; Rivers et al., 2008). In keeping with this observation, OPC depletion is not frequently encountered in animal models of recurrent demyelination (Penderis et al., 2003) and it is only thought to play a role in remyelination failure in the context of sustained demyelinating pathology (Ludwin, 1980; Mason et al., 2004). Although the speed of OPC repopulation of experimentally irradiated spinal cord declines with age in rats, it remains an efficient process nonetheless (Chari and Blakemore, 2002; Chari et al., 2003), suggesting that OPC migration is unlikely to be the major limiting factor in age-related myelin loss.

Studies in the mouse demonstrate that OPC cycle times increase significantly with advancing age and this has been associated with reductions in oligodendrocyte production (Psachoulia et al., 2009). Thus, in normal ageing, reductions in oligodendrogenesis might be due in part to declining OPC proliferation. By contrast, although OPC proliferation remains robust in aged rodents following experimental demyelination, impaired OPC differentiation leads to delayed remyelination (Shields et al., 1999; Sim et al., 2002). Similarly, impaired OPC differentiation is a well recognised, and possibly causal, factor in chronically demyelinated MS lesions in humans (Wolswijk, 1998; Kuhlmann et al., 2008) where remyelination failure is a key contributor to the burden of disease. Age-related OPC differentiation failure following experimental demyelination has been attributed to a variety of factors, including

impaired phagocytosis of myelin debris by aged macrophages (Shields et al., 1999; Kotter et al., 2006) and changes in the epigenetic regulation of OPC differentiation (Shen et al., 2008). In young mice, downregulation of OPC differentiation inhibitors normally precedes remyelination and this is associated with the recruitment of histone deacetylases (HDACs) to the promoter regions of these genes. In old mice, HDAC recruitment is inefficient, resulting in the accumulation of transcriptional inhibitors and impaired OPC differentiation (Shen et al., 2008). Furthermore, age-related declines in signalling via the nuclear receptor retinoid X receptor-γ (RXR-γ) have been demonstrated to be important in OPC differentiation failure during remyelination, and aged rats treated with an RXR-γ agonist exhibited increased OPC differentiation and accelerated remyelination relative to young controls (Huang et al., 2011). Interestingly, the decline in RXR signalling in the brains of ageing rodents has also been associated with impairments of memory tasks subserved by the hippocampus (Mingaud et al., 2008).

General mechanisms of CNS stem and progenitor cell ageing

Ageing is a complex phenomenon characterised by a wide range of cellular perturbations including: DNA damage; telomere shortening; cell cycle dysregulation; epigenetic change; protein and lipid modification and dysfunction; protein aggregation; deficient autophagy; bioenergetic impairment and oxidative stress as well as the activation of stress response pathways (Kenyon, 2010; Sharpless and DePinho, 2007; Sahin and DePinho, 2010; Rubinsztein et al., 2011; Artegiani and Calegari, 2012). These perturbations can lead to changes in cell proliferation and differentiation, the induction of senescence, or cell death. The cellular changes of ageing occur in the broader context of age-related alterations in the local environment of the cell and in the systemic environment (reviewed by Artegiani and Calegari, 2012). Examples include changes in cytokine and growth factor profiles, in the composition of the extracellular matrix and in the availability of oxygen and nutrients. Furthermore, ageing may be associated with inflammation and with changes in the function of cells that constitute integral parts of the stem cell niche, such as vascular endothelial cells and astrocytes. These stem cell-extrinsic changes have the capacity to alter stem cell function as well as the differentiation, survival and function of their progeny. A wide range of animal models has provided valuable insights into the mechanisms of CNS ageing (reviewed by Yeoman et al., 2012). Nevertheless, different mechanisms are likely to predominate in different species, or even in different cell populations within a given species. As a case in point, although telomere length is considered to be a significant determinant of ageing in humans, it appears to be far less influential in mice under normal circumstances (Sharpless and DePinho, 2007). Some of the key determinants of CNS stem cell ageing will be addressed below. Although a distinction between cell-intrinsic and extrinsic mechanisms may be reductionist, it provides a convenient framework for this discussion.

Cell-intrinsic mechanisms

The forkhead box O (FoxO) family of transcription factors has been implicated in the regulation of longevity in a wide range of species, including humans (Willcox et al., 2008; Flachsbart et al., 2009; Kenyon, 2010). They are known to influence adult neural stem cell homeostasis both *in vitro* and *in vivo* (Paik et al., 2009; Renault et al., 2009) (Table 1; Fig. 2). For example, FoxO-null mice exhibit Wnt pathway hyperactivity that leads to neural stem cell exhaustion and depletion (Paik et al., 2009). Although there is redundancy within the FoxO family, the loss of FOXO3 appears to be particularly influential on neural stem cell function, leading to a loss of self-renewal and consequent stem cell depletion (Table 1). The regulators of FoxO transcription factors are many and varied and as such they act as a link between internal and external stimuli that impact on ageing.

It is hypothesised that many of the endogenous processes that contribute to declining stem cell function with age constitute defence mechanisms against the increasing risk of neoplasia (reviewed by Sharpless and DePinho, 2007). These defences include growth arrest, senescence and apoptosis. Key regulators of these processes include the tumour suppressors ARF (CDKN2A), p53 (TRP53 in mouse; TP53 in human) and their downstream effectors, including $p21^{CIP}$ (CDKN1A). These and other factors set the balance between senescence or apoptosis versus neoplasia, thereby establishing the temporal basis for stem cell decline (Sharpless and DePinho, 2007). Age-associated changes in the expression of the senescence regulator $p16^{INK4a}$ (CDKN2A), a cyclin-dependent kinase inhibitor, provide a case in point: increasing expression of this factor has been associated with declining proliferation and self-renewal of mouse SVZ stem cells (Molofsky et al., 2006). In addition, mice deficient in this factor show smaller age-related reductions in SVZ stem cell function and neurogenesis at the expense of increased cancer incidence (Molofsky et al., 2006). Notably, $p16^{INK4a}$ deficiency has no appreciable effect on SGZ stem cell function, pointing to regional variation in regulatory mechanisms (Molofsky et al., 2006). Interestingly, caloric restriction, an intervention well known to have anti-ageing effects in a wide range of species, reduces the age-related increase in the expression of $p16^{INK4a}$ and a suite of other senescence factors (Krishnamurthy et al., 2004; Edwards et al., 2007).

A growing body of data implicates telomere shortening in age-related stem cell decline. Telomeres are nucleoprotein caps on the ends of chromosomes that maintain chromosomal integrity (reviewed by Sahin and DePinho, 2010). Telomeres are maintained by the enzyme telomerase; however, most cells lack sufficient telomerase activity to prevent telomere shortening on cell division. Telomerase-deficient mice exhibit an accelerated ageing phenotype and the reactivation of telomerase function in these mice is accompanied by striking CNS rejuvenation: age-related myelin loss is reversed and oligodendrocyte numbers are restored to normal levels, and elevated SVZ neurogenesis leads to improved olfactory function (Jaskelioff et al., 2011). These changes are associated with rapid telomere elongation in SVZ stem cells. Such observations support the notion that, at least in this experimental system, telomere reconstitution can restore endogenous CNS stem cell function leading to robust rejuvenation.

Age-related impairments in mitochondrial function lead to a reduced efficiency of oxidative phosphorylation, and also to a deficiency in cellular energy and the generation of reactive oxygen species (ROS). ROS can directly contribute to DNA damage, accelerate telomere shortening and activate the p53/p21 signalling axis (Fig. 2) (Sahin and DePinho, 2010). FoxOs are known to be important in driving the expression of a range of genes that regulate mitochondrial function and ROS generation, further strengthening the link between FoxOs and stem cell ageing (Tothova et al., 2007; Ferber et al., 2012). In addition to their better-known roles as injurious agents, ROS can also function as intracellular second messengers to regulate normal cellular processes. At least *in vitro*,

Table 1. FoxO transcription factors and the regulation of neural stem cell homeostasis

Action	Evidence	References
Maintenance of neural stem cell (NSC) populations via the preservation of self-renewal	Adult *Foxo3*$^{-/-}$ mice have fewer NSCs in the SVZ and SGZ than do wild-type mice FOXO3 and FOXO1 are highly expressed in NSC niches FOXO3 activity is higher in self-renewing NSCs than in differentiated progeny *Foxo3*$^{-/-}$ and FOXO1/3/4-deficient NSCs exhibit diminished capacity for neurosphere formation *in vitro* *Foxo3*$^{-/-}$ mice and mice with conditional knockout of *Foxo1*, *Foxo3* and *Foxo4* exhibit transient amplification of progenitor cells and stem cell exhaustion/depletion	Renault et al., 2009; Paik et al., 2009
Maintenance of NSC multipotentiality	Loss of FOXO3 renders NSCs similar to committed progenitor cells: secondary neurospheres derived from the culture of adult *Foxo3*$^{-/-}$ NSCs have more restricted cellular fates (skewed towards astrocytic differentiation) than do those from *Foxo3*$^{+/+}$ NSCs	Renault et al., 2009
Regulation of genes important for NSC quiescence	FoxOs control the expression of a wide range of cell cycle regulators, including cyclin G2, ASPM and p27^{KIP1} (CDKN1B), allowing NSCs to enter a state of relative quiescence following division, guarding against NSC depletion Similar actions in a wide range of cell types	Renault et al., 2009; Paik et al., 2009
Enhancement of NSC resistance to oxidative stress and hypoxia	FOXO3 regulates the expression of genes involved in the response to hypoxia and oxidative stress FOXO1/3/4-deficient NSCs have diminished expression of ROS-detoxifying enzymes and increased ROS levels with associated impairment of self-renewal Similar actions in a wide range of cell types	Renault et al., 2009; Paik et al., 2009; Tothova et al., 2007; Ferber et al., 2012
Optimisation of cellular metabolism for self-renewal	FoxOs regulate the expression of genes involved in glucose metabolism and transport Similar actions in a wide range of cell types	Renault et al., 2009
Regulation of autophagy	FOXO3A is a key regulator of autophagy (a determinant of ageing) in haematopoietic stem cells	Warr et al., 2013; Rubinsztein et al., 2011
Regulation of Wnt signalling	FoxOs regulate Wnt signalling at multiple levels. Inhibition of Wnt signalling is important in NSC self-renewal.	Paik et al., 2009
Integration of internal and external stimuli that impact on ageing	FOXO3 is phosphorylated and inactivated by AKT. The PI3K-AKT pathway is activated by a wide range of extrinsic and intrinsic signals, including insulin and growth factors such as IGF1. Oxidative and nutrient stress (as encountered in caloric restriction) activate numerous signalling cascades, culminating in the post-translational modification of FoxOs by factors such as AMPK (AMP-dependent kinase), JNK (Jun-N-terminal kinase), SLK (mammalian Ste20-like kinase) and CBP (CREB-binding protein), which facilitate FoxO action. FoxOs also interact with the deacetylase sirtuin 1, which is a key mediator of the longevity-promoting effects of caloric restriction.	

This list of functions is not exhaustive (for reviews, see Salih and Brunet, 2008; Greer and Brunet, 2008). It is important to note that the specific targets of FoxOs vary significantly between cell compartments (Miyamoto et al., 2007; Tothova et al., 2007), resulting in tissue-specific expression profiles (Paik et al., 2007; Paik et al., 2009; Renault et al., 2009).

intracellular redox state influences the balance between neural stem cell self-renewal and differentiation, with an oxidised environment generally favouring differentiation (Le Belle et al., 2011; reviewed by Huang et al., 2012). Moreover, in the setting of differentiation, redox state is implicated in cell fate determination: a reduced intracellular environment appears to favour neural differentiation of SGZ stem cells, whereas an oxidised environment favours glial differentiation (Prozorovski et al., 2008). The maintenance of low intracellular levels of ROS appears to be important in OPC self-renewal and the maintenance of an undifferentiated state (Smith et al., 2000; Power et al., 2002; Li et al., 2007). Accordingly, age-associated increases in the generation of ROS might influence CNS stem cell proliferation, differentiation and fate determination.

It is clear that complex inter-relationships exist between the many determinants of stem cell ageing. A recent unifying hypothesis proposed by Sahin and DePinho (Sahin and DePinho, 2010; Sahin and DePinho, 2012) identifies a central axis of ageing whereby DNA damage and telomere shortening converge on p53 activation and the suppression of mitochondrial biogenesis [via PGC1α (PPARGC1A) and PGC1β (PPARGC1B)]. The consequent bioenergetic deficiency, ROS accumulation and further DNA damage lead to cellular adaptations and ultimately to survival, growth arrest, senescence or apoptosis, depending on the specific cellular context.

Alternative ageing paradigms place greater emphasis on nutrient-sensing pathways and regulators of cell growth and metabolism, such as the mechanistic target of rapamycin (mTOR) (reviewed by Johnson et al., 2013) and the sirtuins (reviewed by Finkel et al., 2009; Imai and Guarente, 2010). mTOR is activated by a diverse array of extrinsic cues, including hormones and growth factors, such as insulin and insulin-like growth factor 1 (IGF1), as well as metabolites and nutrients. These factors converge to drive a wide

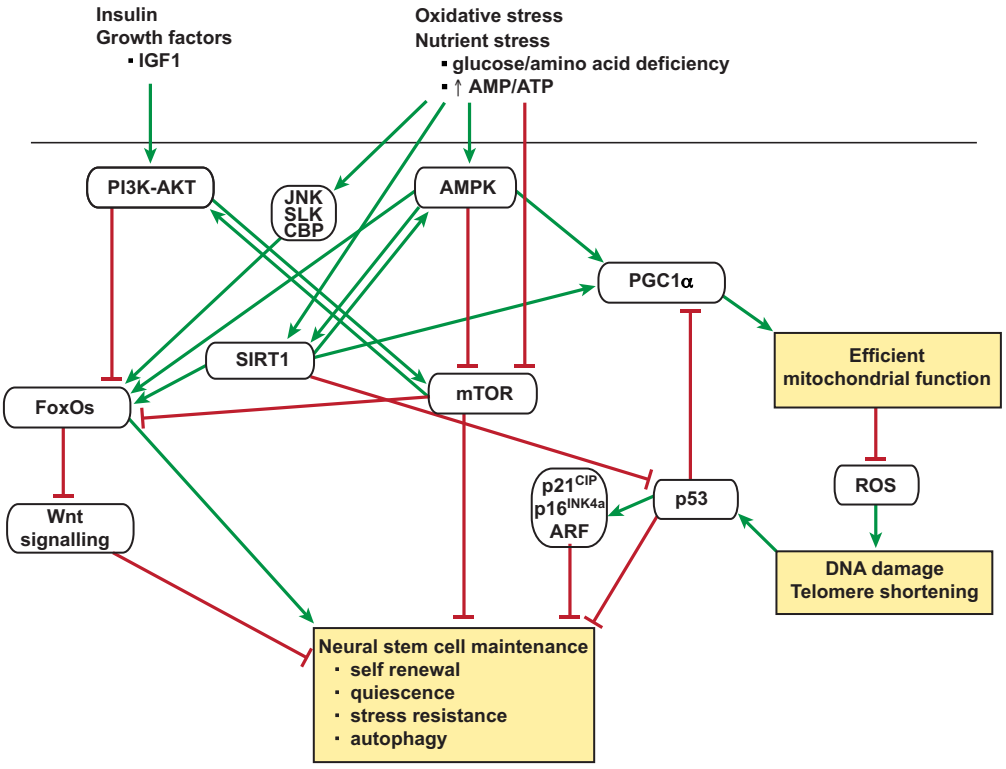

Fig. 2. Key signalling pathways in CNS stem cell ageing. This simplified model highlights some of the key interactions between signalling pathways thought to be important in CNS stem cell ageing. Green arrows represent activation and red bars represent inhibition. Nutrient and oxidative stress activate a host of signalling pathways, including AMP-dependent kinase (AMPK), sirtuin 1 (SIRT1), Jun-N-terminal kinase (JNK; also known as MAPK8), mammalian STE20-like kinase (SLK) and CREB-binding protein (CBP; also known as CREBBP), which collectively activate catabolic cellular processes. These pathways converge on the FoxO transcription factors and PPARγ co-activator 1α (PGC1α). FoxOs are of central importance in maintaining neural stem cell homeostasis and self-renewal. PCG1α triggers mitochondrial biogenesis and improves mitochondrial function, reducing the generation of reactive oxygen species (ROS) and slowing stem cell ageing. DNA damage and telomere shortening act via p53 to inhibit PCG1α expression, with resultant mitochondrial dysfunction, bioenergetic impairment and ROS generation, all of which may contribute to stem cell decline. Furthermore, p53 can induce stem cell apoptosis or senescence. Insulin and a number of growth factors act via phosphoinositide-3 kinase (PI3K) and AKT to trigger a wide range of anabolic cellular processes, some of which are mediated by the mechanistic target of rapamycin (mTOR). mTOR drives stem cells towards proliferation and differentiation, and the inhibition of mTOR signalling has been demonstrated to enhance stem cell self-renewal (reviewed by Johnson et al., 2013). mTOR is found in two complexes, mTORC1 and mTORC2, which have distinct actions (depicted together in this figure for convenience). The relative contributions of the individual pathways to stem cell ageing may vary between niches. These pathways are reviewed in detail by others (Sahin and DePinho, 2007; Sahin and DePinho, 2010; Sharpless and DePinho, 2007; Johnson et al., 2013).

range of anabolic cellular processes, such as lipid and protein synthesis, inhibition of autophagy, and inhibition of FOXO3A (Fig. 2). Interestingly, inhibition of mTOR signalling has longevity-enhancing effects in a wide range of animal models (Johnson et al., 2013). The role of mTOR signalling in the ageing of CNS stem cell compartments is still emerging: mTOR appears to regulate the proliferative activity of transient amplifying progenitor cells in the mouse SVZ, and age-related declines in signalling are thought to contribute to their quiescence (Paliouras et al., 2012). mTOR signalling has also been shown to contribute to oligodendrocyte differentiation (Tyler et al., 2009; Guardiola-Diaz et al., 2012). As such, the mTOR pathway might serve as another link between intrinsic and extrinsic regulators of stem and progenitor cell function in the CNS.

Extrinsic regulators

In addition to the intrinsic mechanisms discussed above, many extrinsic factors, such as psychological stress, physical exercise and diet, regulate stem cell function and ageing. These factors modulate various signalling pathways to effect changes in the proliferation, differentiation and migration of CNS stem cells and their progeny. Their importance is emphasised by the numerous studies that demonstrate positive associations between neurogenesis in rodents and the levels of various soluble growth factors, including IGF1, fibroblast growth factor 2 (FGF2), brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF) (reviewed by Artegiani and Calegari, 2012; Fournier and Duman, 2012). Overexpression or exogenous administration of these growth factors have been shown to enhance neurogenesis, learning and memory in animal models (Aberg et al., 2000; Lichtenwalner et al., 2001; Cao et al., 2004). Reductions in growth factor signalling in the ageing rodent hippocampus are known to occur for each of these factors (Shetty et al., 2005; Hattiangady et al., 2005) and recent studies suggest that waning levels of VEGF and FGF2 expression by astrocytes might be key determinants of declining neurogenesis (Bernal and Peterson, 2011). Furthermore, the inhibition of FGF2 (Zhao et al., 2007) and VEGF (Cao et al., 2004; Pati et al., 2009) signalling has been associated with impaired cognitive function in rodents. In the case of VEGF, this occurred both in the presence of (Cao et al., 2004) and the absence

of (Pati et al., 2009) detectable changes in neurogenesis, pointing to a complex role of the factor in cognition (reviewed by Fournier and Duman, 2012). The actions of these growth factors on stem and progenitor cell dynamics are complex and context dependent. For instance, although insulin and IGF1 signalling enhance stem and progenitor cell proliferation, low levels of these factors promote longevity and cognitive function in a wide range of animal models (reviewed by Rafalski and Brunet, 2011). This apparent paradox points to the importance of a balance between stem cell quiescence and proliferation in maintaining the stem cell population over a lifespan on one hand, and meeting the requirements for new neurons on the other hand (Rafalski and Brunet, 2011).

SVZ neurogenesis has been induced in rodents by intraventricular infusion of FGF2 (Kuhn et al., 1997) or BDNF (Zigova et al., 1998); subcutaneous injection of FGF2 (Jin et al., 2005); or ependymal cell overexpression of BDNF and noggin (Benraiss et al., 2001; Benraiss et al., 2012; Chmielnicki et al., 2004; Cho et al., 2007), resulting in enhanced recruitment of neurons to the olfactory bulb and striatum (reviewed by Benraiss and Goldman, 2011). The addition of striatal neurons by these means improved motor coordination and prolonged lifespan in a mouse model of Huntington's disease (Jin et al., 2005; Cho et al., 2007). Although such work raises the prospect of induced neurogenesis for this and other neurodegenerative disorders, the utility of such an approach in humans is unknown. The observation that neurogenesis might be increased in the human brain in a range of diseases, including Alzheimer's disease (Jin et al., 2004), Huntington's disease (Curtis et al., 2003) and vascular dementia (Ekonomou et al., 2011), attests to the influence of local environmental cues, although many of these cues are as yet unidentified. The neuroprotective and regenerative actions of stem cells are mediated in part by secreted trophic factors (Giusto et al., 2013), which might in turn depend on cross-talk with the immune system, or on the endogenous stem cells themselves (Martino and Pluchino, 2006; Kokaia et al., 2012).

Age-related changes in key extrinsic regulators of neurogenesis may be compounded by psychological stress. Stress may impair hippocampal neurogenesis in rodents, and reduced VEGF signalling as well as elevated glucocorticoid levels are likely to contribute to this (reviewed by Fournier and Duman, 2012; Eisch and Petrik, 2012; Artegiani and Calegari, 2012). Similarly, social isolation, a form of psychological stress, impairs myelination of the prefrontal cortex in young (Makinodan et al., 2012) and adult (Liu et al., 2012) mice, with associated behavioural dysfunction. Social reintegration improves myelination and normalises behaviour in adult mice, but not in young mice. The provision of environmental enrichment to laboratory rodents increases their social interaction and sensorimotor stimulation and enhances their stress resilience (reviewed by Mora et al., 2012). In turn, environmental enrichment enhances SGZ neurogenesis, learning and memory in young and old rodents alike via actions on progenitor differentiation and neuronal survival (Kempermann et al., 1997; Kempermann et al., 1998; Cao et al., 2004). This effect is mediated in part by VEGF produced by neurons and astrocytes (Cao et al., 2004). Enrichment also appears to reduce microglial proliferation and promote OPC differentiation in the mouse amygdala (Ehninger et al., 2011).

Physical exercise provides another example of the influence of extrinsic factors on CNS stem cell function and ageing. Exercise robustly enhances hippocampal neurogenesis and associated cognitive functions in rodents, even in old age (van Praag et al., 1999; van Praag et al., 2005; Kronenberg et al., 2006; reviewed by van Praag, 2008). This effect is mediated in part by upregulation of VEGF (Fabel et al., 2003) and possibly IGF1 (Carro et al., 2000; Trejo et al., 2008; Yau et al., 2012) and BDNF (Adlard et al., 2005; Yau et al., 2012). Exercise has been shown to reduce hippocampal microglial proliferation in aged mice and induce a switch away from a pro-inflammatory phenotype, typical of ageing, to a neuroprotective phenotype that might promote neurogenesis (Kohman et al., 2012). Exercise training can reduce age-related hippocampal astrocyte reactivity (Latimer et al., 2011) and enhance hippocampal blood flow (Pereira et al., 2007), optimising the local microenvironment for stem cell function. In fact, exercise-induced increases in blood flow to the human dentate gyrus have been correlated with the extent of neurogenesis at post-mortem examination (Pereira et al., 2007). Exercise has also been demonstrated to modulate energy metabolism and mitochondrial biogenesis in the brain (Matsui et al., 2012; Zhang et al., 2012). In a mouse model of schizophrenia, physical exercise was demonstrated to enhance telomerase activity and hippocampal function (Wolf et al., 2011). Exercise might also enhance OPC differentiation in the young adult mouse cortex, possibly as a consequence of the increased cortical neuronal activity associated with exercise (Simon et al., 2011).

In a similar vein, dietary restriction, arguably the best characterised and most reproducible non-genetic manipulation to slow the ageing process in mammals, has been demonstrated to influence stem cell function in the ageing brain (reviewed by Park and Lee, 2011). Short-term caloric restriction increases hippocampal neurogenesis in young rats (Lee et al., 2000) and mice (Lee et al., 2002a), by enhancing the survival of newborn neurons without demonstrable effects on progenitor cell proliferation. These actions have been attributed to enhanced BDNF signalling (Lee et al., 2000; Lee et al., 2002a) as well as increased hippocampal expression of neurotrophin 3 (Lee et al., 2002b) and interferon-γ (Lee et al., 2006). It is likely that additional mechanisms are important given the numerous metabolic consequences of caloric restriction, including the activation of AMP-dependent kinase and sirtuin 1 as well as reduced insulin and mTOR signalling (Fontana et al., 2010; Imai and Guarente, 2010; Lu et al., 2011) (Fig. 2). Moreover, it is possible that the effects of caloric restriction on CNS stem cell function may vary over time: one study has suggested that long-term restriction increases the survival of young adult-born glial cells, but not neurons (Bondolfi et al., 2004). Whereas most studies of dietary restriction limit total calorie consumption, recent work points to the importance of dietary composition, namely amino acid balance, in regulating ageing processes (Grandison et al., 2009). This might be particularly true for humans, in whom caloric restriction in the absence of protein restriction does not appear to reduce serum IGF1 levels, as it does in rodents (Fontana et al., 2008). Little is known of the effects of dietary composition on CNS stem cell ageing.

Insights into the relative contributions of CNS-intrinsic and extrinsic determinants of stem cell function in the aged brain have been provided by studies using heterochronic parabiosis, a model in which surgically conjoined young and old mice develop a shared circulatory system (Fig. 3). In this system, young mice exhibit impaired hippocampal neurogenesis, learning and memory when exposed to an aged systemic milieu (Villeda et al., 2011) (Fig. 3A). Elevated serum levels of the chemokine eotaxin (CCL11) in young mice were correlated with this effect. Moreover, the administration of exogenous eotaxin to young mice recapitulated the inhibitory effects of ageing on hippocampal neurogenesis (Villeda et al., 2011). This study provides strong evidence that the ageing systemic

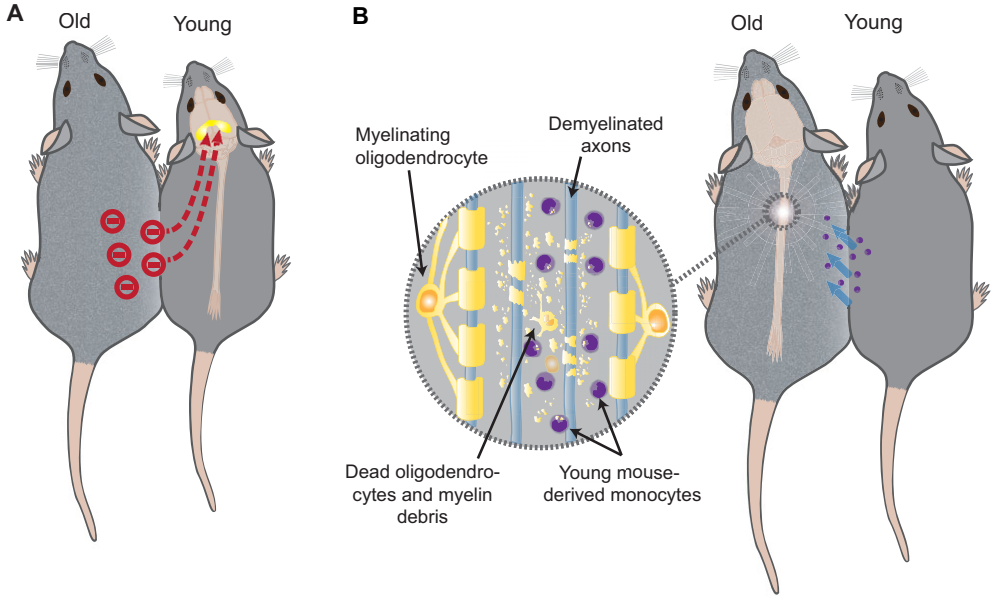

Fig. 3. Heterochronic parabiosis provides insights into ageing and stem cell function. In heterochronic parabiosis, old (left) and young (right) mice develop a shared circulation. (**A**) Hippocampal neurogenesis is impaired in the young mouse owing, in part, to soluble factors from the old systemic circulation (represented as red minus signs) (Villeda et al., 2011; Villeda and Wyss-Coray, 2012). (**B**) Remyelination of the spinal cord of the old mouse is enhanced following experimental demyelination owing to the combined effects of soluble factors and young mouse-derived monocytes, which phagocytose myelin debris (Ruckh et al., 2012).

environment impairs neurogenesis in the brain. In another study, heterochronic parabiosis was used to examine the remyelination of demyelinating spinal cord lesions in mice (Ruckh et al., 2012), a process that normally exhibits a significant age-related decline, largely due to impaired differentiation of OPCs. OPC differentiation and remyelination were significantly enhanced in old mice exposed to a young systemic milieu (Fig. 3B). The effect was mediated in part by the enhanced clearance of myelin debris by monocytes recruited from the young mouse circulation. This work highlights that aged OPCs retain the potential for robust remyelination and that their ability to realise this potential is significantly influenced by the systemic milieu, a finding that is pertinent to the development of treatments for MS.

Perspectives on CNS rejuvenation

Although major advances have been made in our understanding of CNS stem cell ageing, there is much still to be learned before broadly applicable rejuvenating therapies can be developed. Ageing is an extremely complex process with diverse manifestations at multiple levels. Accordingly, it is likely that successful rejuvenation strategies will target multiple aspects of the ageing process. The recent counterintuitive finding that resveratrol, a calorie-restriction mimetic and candidate anti-ageing therapeutic, impairs hippocampal neurogenesis and cognitive function in mice, provides a case in point (Park et al., 2012). In the quest for rejuvenation it is important not to lose sight of the fact that anti-ageing interventions have the potential for harm, especially considering that at a cellular level many ageing processes constitute defences against neoplasia.

The task of bolstering the function of stem cells within their existing niches in the face of advancing age seems to be the most readily achievable objective in CNS rejuvenation. Enhancing hippocampal neurogenesis may go some way to combating age-related cognitive decline; however, hippocampal dysfunction only constitutes part of the broader spectrum of cognitive impairment with age. Other potentially important therapeutic targets of increased hippocampal neurogenesis include depression and schizophrenia (Eisch and Petrik, 2012). Enhanced OPC function may contribute to improved myelin maintenance, which might also guard against some of the cognitive changes of ageing, but the extent of this effect remains to be seen. Strategies for enhancing the efficiency of regenerative remyelination may have a tremendous impact on the management of demyelinating diseases, such as MS (Franklin et al., 2012). OPCs are widely dispersed in the CNS and their ability to migrate to sites of demyelination does not appear to be significantly diminished with age. When these observations are taken together with the finding that aged OPCs retain the capacity for robust remyelination, the therapeutic rejuvenation of remyelination in the ageing CNS seems to be an achievable goal.

Stemming the tide of neurodegenerative diseases and repairing the injured brain and spinal cord are likely to prove significantly more difficult than enhancing remyelination. Key challenges in achieving these therapeutic goals include the large numbers of cells required for repair and reconstruction, as well as the relatively large distances that progenitors might need to travel from the niche to sites of repair. Other major hurdles lie in transforming relatively inhospitable non-niche environments into sites that enable local neurogenesis, cell differentiation and survival as well as facilitating the meaningful integration of newborn neurons into established neural networks. Disease-related local and systemic environmental perturbations might compound these challenges. The progeny of endogenous neurogenesis are ordinarily restricted to a narrow range of fates: granule cells in the dentate gyrus and interneurons in the olfactory bulb. Appropriate fate-specification to meet the requirements of rejuvenation poses a formidable challenge.

Progress in the development of therapies for CNS rejuvenation will inevitably be made as we begin to unravel the complex mechanisms underlying stem cell aging. In the meantime, adherence to the basic tenets of healthy living – eating in moderation, staying physically and intellectually active, and avoiding psychological stress – may constitute the most effective means we have of rejuvenating the CNS. Thus, we end this Review by returning to Shakespeare's *Hamlet*: age may continue to make his stealing steps, but we are beginning to claw back from his clutch, little by little.

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Competing interests statement

The authors declare no competing financial interests.

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