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Chapter 10

Regulation of Basal and Injury-Induced Fate Decisions of Adult Neural Precursor Cells: Focus on SOCS2 and Related Signalling Pathways

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Additional information is available at the end of the chapter

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1. Introduction

Two decades ago it was discovered that the adult mammalian brain contains neural stem cells (NSCs) and neural precursor cells (NPCs) capable of producing new neurons and glial cells [1-3]. This has led to a great deal of research to understand the biology of these cells and to determine signalling pathways that can be targeted to promote repair of the damaged nervous system. There are two primary regions in the adult mammalian brain that contain adult NSCs/NPCs. These are the subventricular zone (SVZ) lining the lateral walls of the lateral ventricles and the subgranular zone (SGZ) of the hippocampal dentate gyrus. NPC fate is regulated by intrinsic (e.g. transcription factors and signalling mediators) and extrinsic (e.g growth factors and extracellular matrix) factors which involve effects on proliferation, migration and differentiation of new neurons and glial cells.

This review will highlight the major signalling cascades involved in neuronal fate from birth to integration. It will begin with a discussion of pathways involved under normal physiological conditions, which will be followed by discussion of changes to these signalling cascades following neural damage due to injury or disease. Finally, there will be a more focused examination of the roles of suppressor of cytokine signalling (SOCS) molecules and related pathways in the context of signalling in adult neurogenesis under basal conditions and following neural damage.

2. Adult neurogenesis

2.1. Hippocampal neurogenesis

NPCs in the SGZ become neurons of the granular cell layer of the dentate gyrus in the hippocampus. In the SGZ, the most immature NPCs (Type 1) are radial and horizontal NPCs that transition to intermediate progenitors (type-2a, 2b and 3) and then to immature granule neurons which become dentate granular neurons. These then make large mossy fibre projections with CA3 pyramidal neurons [4].

2.2. SVZ neurogenesis

The SVZ produces NPCs that form neuroblasts which migrate along the rostral migratory stream and become neurons in the olfactory bulb. These new neurons primarily become GABAergic granule neurons that provide lateral inhibition between mitral and tufted cells. A minority of the new neurons become periglomerular neurons that are involved in lateral inhibition between glomeruli, and a small number of these cells are dopaminergic. Similar to the SGZ, there is a progression of NPC development in the SVZ. Slowly proliferating astrocytes in the SVZ (Type B cells) are the NSCs and these generate the highly proliferative transit-amplifying Type C cells. These then generate post-mitotic neuroblasts (the Type A cells) destined for the olfactory bulb via migration along the rostral migratory stream (RMS) [5-7].

3. Signalling cascades regulating NPC fate under basal conditions

NPCs from the dentate gyrus and SVZ have the potential to differentiate into neurons and glial cells. Multiple signalling pathways are activated to produce a neuron from NSCs. These cascades can involve both intrinsic and extrinsic factors as the NSC is created, migrates, and finally integrates into its final location.

3.1. Proliferation and neuronal fate

Many pathways important for embryonic neural development are conserved in adult neurogenesis. The Wnt pathway, for example, is a key regulator of proliferation and differentiation in development and a key regulator of adult hippocampal neurogenesis [8]. Wnt signalling results in the activation of the GSK3β/β-catenin that leads to the increased expression of NeuroD1 and promotes neuronal differentiation in NSCs [9]. Activation of Wnt, Sonic Hedgehog (Shh), Notch, and the Sox family of genes, in particular *Sox2*, are also important for the formation and proliferation of NSCs [10-12]. At early stages of differentiation, *Sox2* is required for neuronal fate; while downregulation of *Sox9* by miR-124 is required for neuronal differentiation [13, 14]. Other Sox members are important for neuronal specification, including *Sox3, Sox 4* and *Sox 11* [15-19]. Notch signalling is important for maintaining NSCs/NPCs, however this is dependent on the mitotic state of NSCs/NPCs [20]. Bone morphogenic protein (BMP) signalling inhibits neuronal differentiation; however expression of noggin and neurogenin-1 (Ngn1)

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in the SVZ and SGZ can obstruct this cascade [21-23]. Inhibition of the BMP pathway increases neurogenesis initially, however it results in depletion of the NSC pool leading to decreased neurogenesis [24]. In the dentate gyrus, the RNA-binding protein FXR2 regulates neurogenesis by reducing the stability of noggin mRNA leading to an increased activation of the BMP pathway [25]. Proliferation in the SVZ is under epigenetic control via histone HZAX phosophorylation which can limit proliferation and overall neurogenesis [26].

Proneural proteins, basic-helix-loop-helix (bHLH) transcription factors also control neuronal fate commitment of NPCs. Type C cells of the SVZ fated to become GABAergic interneurons in the olfactory bulb express *Ascl1* [27]. *Ngn2* and *Tbr2* are expressed in dorsal SVZ progenitors that become glutamatergic juxtaglomerular neurons [28], while *Sp8* is required for parvalbumin-expressing interneurons in the olfactory bulb [29]. In the SGZ, *Neurog2* and *Tbr2* are expressed in NPCs destined to become glutamatergic neurons in the hippocampus [27, 30, 31], while over-expression of *Ascl1* produces oligodendrocytes [32].

Neurotrophic growth factors have been studied extensively in the SVZ. Many, including, epidermal growth factor (EGF), transforming growth factor (TGF), and vascular endothelial growth factor (VEGF) can augment SVZ progenitor proliferation and migration of newly derived cells into structures beside the lateral ventricles; however these cells primarily differentiate into oligodendrocytes [33-36]. Fibroblast growth factor-2 (FGF-2) signalling promotes proliferation in both the SVZ and SGZ [37-39]. FGF-2 and TGF synthesis and secretion can be augmented by ATP, which can increase proliferation, and provide a potential explanation for the reduced neurogenesis in purinergic receptor knockout mice (P2Y1) [40, 41]. Other factors also play a role in neurogenesis, including neuregulin-1, which has been implicated in dentate gyrus neurogenesis in addition to having antidepressant effects [42] and Growth Hormone (GH) which augments EGF and FGF2-induced proliferation [43]. Growth factor signalling often leads to activation of Akt through phosphoinositide-3 kinase (PI-3K); one negative regulator of this pathway is the phosphatase and tumour suppressor PTEN, which has a role in regulating neurogenesis as demonstrated by increased proliferation and differentiation in mutant mice [44]. Furthermore, IGF-2 also regulates proliferation in the dentate gyrus in an Akt-dependent manner [45].

The gp130-associated cytokines, ciliary neurotrophic factor (CNTF) and leukemia inhibitory factor (LIF), activate Janus kinase (JAK/signal transducer of transcription 3 (STAT3)), mitogen activated protein (MAP) kinase and PI-3K/Akt pathways following ligand binding. These cytokines have been shown to regulate NSC proliferation and differentiation [46-49]. Specifically in the dentate gyrus, the activation of STAT3 from CNTF appears to be essential for the formation and maintenance of the NSCs [50]. The role of the JAK/STAT pathway will be discussed in more detail later. The MAPK pathway is important for neurogenesis as demonstrated by conditional knockdown of extracellular signal-related kinase 5 (ERK5) which limits neuronal differentiation and neurogenesis resulting in impaired contextual fear extinction and remote fear memory [51, 52].

Other molecules shown to have a role in controlling neuronal differentiation include Presenilin-1 (PS1), which is the catalytic core of the aspartyl protease gamma-secretase. Reduction of PS1 enhances differentiation, primarily through its transducers the EGF receptor and β-

catenin [53]. Interferon-γ, which signals via STAT1, and interferon-β which does not, both inhibit cultured adult NPC proliferation, but only interferon-γ promotes neuronal differentiation [54, 55].

3.2. Migration and integration

Migration from the SVZ along the RMS involves long distances and multiple pathways [56] For example, it is dependent on Shh signalling, as evident by a decrease of neuroblasts in the olfactory bulb following Hedgehog signalling interruption [11]. Shh is a chemoattractant cue extrinsic to the neuroblast that guides migration to the olfactory bulb. Neurotrophic growth factor signalling is also important for migration, in particular insulin-like growth factor (IGF-1) null mice show an abundance of neuroblasts in the SVZ that have failed to migrate to the olfactory bulb [57]. Guidance cues from EphB2/ephrin-B2 pathways also enable formation of the chain migration from the SVZ to the olfactory bulb [58]. Recently, endocannabinoid signalling has been shown to regulate migration and neurogenesis in both the SVZ and dentate gyrus [59, 60]. Other molecules involved in this migration include polysialated neural cell adhesion molecule (PSA-NCAM) [61-63], Slit-Robo [64] and integrins [65, 66]. Many of these factors signal via the Rho kinase pathway, which is a downstream regulator of NPC migration [67]. In addition adult NPCs express a range of chemokine receptors and chemokines are expressed in different brain regions, with the highest levels in the olfactory bulb, suggesting an as yet largely unexplored role for chemokines in regulating basal adult NPC migration [68].

The migration distance for new neurons from the SGZ is relatively short as they travel into the granular layer above the SGZ, where guidance molecules may control this movement. NMDA receptor signalling is required for the proper migration of newborn granular cells in the dentate gyrus [69]. This is achieved through the activation of Disrupted-in-schizophrenia (DISC1), as neurons without DISC1 migrate further into granular layer and into the molecular layer [69, 70]. DISC1 also controls the dendritic maturation of newborn granule cells through GABA depolarization of NKCC1 and activation of the Akt-mTOR pathway [70, 71].

New neurons must integrate into existing circuitry or they will not survive. The vast majority of new neurons do not survive past 4 weeks. Interestingly, NMDA receptors expressed in neuroblasts along the RMS are crucial to the integration of these neurons in existing olfactory bulb circuitry [72]. Glutamate is released from astrocyte-like cells that surround the neuroblasts. NMDA receptor activation in newly-born dentate gyrus granule cells also increases survival. Initial GABA depolarization plays a role in the maturation of neurons in the dentate gyrus and olfactory bulb [73, 74]. This depolarization and subsequent Ca^{2+} influx are required for dendrite initiation and elongation [75]. This process involves coordinated expression of the GABA receptor subunit alpha2 that controls the maturation of the new neurons [76]. In addition, agrin signalling is necessary for integration and survival of newborn neurons in the olfactory bulb, as demonstrated by a loss of agrin leading to improper synapse formation while an overexpression of agrin results in an increase in dendritic spines [77].

Neurotrophin signalling has important role in the survival and integration of new neurons. Brain-derived growth factor (BDNF) binding to the TrkB receptor tyrosine kinases increases

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the number and survival of NSCs in the SVZ and olfactory bulb [78-80]. Similarly, knockdown of TrkB receptors and disruption of BDNF signalling in dentate gyrus progenitors leads to shorter dendrites and reduced spine formation, culminating in a lack of survival [81]. Fibroblast growth factor (FGF-2) has a role in neurogenesis and memory consolidation in this context [39].

Intrinsic factors are also necessary for the maturation and survival of newly born neurons. In the dentate gyrus, *Prox1* [18], *NeuroD* [82, 83] and Kruppel-like factor 9 [84] play important roles in survival. In the SVZ, *Pax6* and *Dlx-2* influence neuronal fate, leading to the production of dopaminergic periglomerular cells in the olfactory bulb [85-87]. New neurons in the dentate gyrus rely on cyclic response element binding protein (CREB) signalling for maturation and integration into the network. Interestingly, CREB activates miR-132 which regulates dendrite maturation in newborn dentate gyrus granular neurons [88]. The collapsin response mediator protein-5 (CRMP5) is expressed in both the SVZ and dentate gyrus and CRMP5$^{-/-}$ mice show an increase in proliferation and neurogenesis in addition to displaying an increase in apoptosis of granular cells in both the olfactory bulb and dentate gyrus [89].

4. Signalling cascades regulating NPC fate following neural damage

Neurogenesis and gliogenesis are known to be initiated following brain damage, such as ischemia, seizures, traumatic injury and neurodegenerative diseases [90-92]. However, these new neurons and glia usually do not effectively replenish those that were lost. Many of the normal signalling cascades are altered following injury. Below is a discussion of the major changes in these cascades that influence neuronal fate of the NSCs generated in the SVZ and SGZ following injury or disease.

4.1. Brain injury

A traumatic lesion to the brain cortex results in an increase in proliferation of NSCs in the SVZ, although varied locations and degrees of injury have resulted in an incongruity of results across the literature [93-98]. Nonetheless, it is generally agreed that the increase in proliferation results in an increase in neurogenesis at the SVZ [99]. Expression of growth factors such as BDNF, FGF2, GDNF, IGF-1 and VEGF are increased following ischemia and exogenous application further augments NSC proliferation and survival [100-105]. Shh expression is also upregulated in the SVZ following ischemia, potentially playing a role in the increase of proliferation, while Wnt expression does not change [106, 107]. Phosphorylated CREB is upregulated following ischemia and induces hippocampal neurogenesis [108].

Following proliferation these cells must migrate and integrate to damaged cortical tissue. The majority of research on ectopic migration from the SVZ has been performed following an ischemic insult and has demonstrated that cells do reach the injured striatum [90, 109-114]. It appears that the cells no longer migrate in a chain formation and carry on individually, interestingly, at the expense of the RMS population [109, 115]. This change in migration is the direct result of chemoattractive cues expressed from the injury site.

Chemokines and their receptors can attract neuroblasts from the RMS, for example it has been shown that Stromal cell-derived factor-1 (CXCL12) and its receptor CXCR4 are upregulated at the injury site [116, 117]. Expression of several chemokines and their receptors is upregulated on adult NPCs by inflammatory cytokines, such as interferon-γ and TNF-α [68].

Migration is also altered following an epileptic seizure: the NSCs migrate along the RMS more quickly, while in the dentate gyrus there is faster integration and maturation [118, 119]. There are morphological changes to the hippocampal region including mossy fibre sprouting, dispersion of the granular cell layer, and ectopically migrated dentate granule cells in the hilus (reviewed in [120]).

When cells do migrate to the correct location they must differentiate into neurons to recover function of neurons lost. Unfortunately, this does not appear to be consistent. Recent work on ischemia has demonstrated that new neurons from the SVZ are found in the cortex near the lesioned area, while injury of the somatosensory cortex showed the generation of astrocytes and microglia/macrophages without any new neurons [98, 121]. Other work has found the production of astrocytes and oligodendrocytes near the injury site as a result of expression of repressors of neuronal fate [122, 123]. For example, the BMP antagonist, chordin, and the transcription factor Olig2 both induce glial expression in neuroblasts at the injury site [124, 125]. However, following ischemia, pro-neuronal transcription factors are expressed in primate progenitors in the SGZ, including *Emx2*, *Pax6* and *Ngn2* [126]. Recently it has been shown that following thirty and sixty days after stroke, *Ascl1/Mash1* expressing cells in the ischemic striatum gave rise to GABAergic neurons and mature oligodendrocytes [127]. Even when a NSC differentiates into a neuron, the survival of these neurons is very low. Recent work has demonstrated that the Ras-related GTPase, Rit, is an important component in the survival of young granular cells in the dentate gyrus following a brain injury. $Rit^{-/-}$ mice show a marked increase in new neuron death following injury [128]. Recently, the small non-coding RNA molecule, miR-124a, was shown to be altered following stroke. Interestingly, it can mediate stroke induced neurogenesis via the Notch signalling pathway [129]. Inhibition of the Notch pathway increases neurogenesis after spinal cord injury in zebrafish resulting in higher proliferation and more motor neurons [130]. Lentiviral expression of Wnt3 increased neurogenesis following focal ischemia and improved functional recovery [131].

4.2. Neurodegenerative diseases

Reports on neurogenesis in neurodegenerative diseases are highly dependent on the disease model used. Variations in transgenic mice and other drug induced models are the most probable cause for the conflicting results. In many models of Alzheimer's disease, Parkinson's disease and Huntington's disease there is impaired neurogenesis (reviewed in [132]). Alzheimer's disease (AD) is characterized by degeneration of basal forebrain cholinergic neurons in the cortex and hippocampus from the deposition of neurofibrillary tangles and amyloid-β plaques [133]. The neuropathologic hallmark of AD is the amyloid-β plaques; however small oligomeric amyloid-β appears to be the noxious component. Neurogenesis can be both increased and decreased in AD, depending on the transgenic model used (reviewed in [132]). Early in the disease, oligomeric amyloid-β may transiently promote the

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generation of immature neurons from NPCs. However, reduced concentrations of multiple neurotrophic factors and higher levels of FGF2 seem to induce a developmental arrest of newly generated neurons. Further, there is a down-regulation of *Olig2* and over-expression of *Ascl1* caused by amyloid-β that switches the cell fate to death [134, 135]. Generally, there is a decrease in proliferation and survival of NSCs in the dentate gyrus and SVZ with AD. A better understanding on the effects of amyloid-β on NSC proliferation and maturation is needed to improve this decrease in neurogenesis.

Parkinson's disease (PD) is the outcome of the loss of dopaminergic neurons in the substantia nigra of the midbrain (reviewed in [136]). In transgenic mouse models, there is a decrease in newly generated neurons in both the dentate gyrus and olfactory bulb [137, 138]. Alterations in neurogenesis have been linked to a decrease in *Notch1* and *Hes5* expression [138]. Lack of proliferation could be the explanation for a lack of migration of NSCs to the damaged regions in PD and AD [139]. Along these lines, manipulations that increase proliferation also demonstrate migration, for example intraventricular injection of clustering ephrin-A1-Fc increased proliferation in the SVZ, followed by migration to the striatum and differentiation into dopaminergic neurons in a rodent model of Parkinson's disease [140]. Furthermore, exogenous application of EGF and FGF2 showed similar results [141]. Exciting research in salamanders has shown regeneration of dopamine neurons following ablation involving neurogenesis in quiescent cells. This activation is due to the loss of dopamine, demonstrating a control of dopamine signalling maintaining homeostasis [142]. Replacement of dopaminergic neurons relies on NSC differentiation into the proper neuronal fate. Recent studies have elucidated the transcription factors necessary to produce dopaminergic neurons. The combination of *Ascl1/Mash1*, *Nurr1* and *Lmx1a* result in the generation of functional dopaminergic neurons from mouse and human fibroblasts [143]. Other studies have shown that *Foxa2* in combination with *Nurr1* can also induce the production of nigral (A9)-type midbrain neurons from NPCs [144].

Other neurodegenerative diseases such as Huntington's disease have shown a decrease in neurogenesis. NPC proliferation is decreased in Huntington's disease in both the SGZ and SVZ, with some reports of reduced numbers of newly born neurons (reviewed in [132]). In a rat model of Huntington's disease, SGZ progenitor cell proliferation is decreased due to an increase in *Sox2*-positive quiescent stem cells and a decrease in CREB signalling [145].

Overall, further investigation is needed to clarify the changes in signalling pathways following neurodegenerative disease. One pathway that has been extensively studied both in basal neurogenesis and after injury is the suppressor of cytokine signalling (SOCS) family of proteins. The following section will discuss research involving the SOCS proteins and related pathways.

5. SOCS molecules and cytokine signalling pathways

As discussed in the previous section, a diversity of signalling cascades are involved in regulating neuronal cell proliferation, differentiation and survival. However, JAK-STAT signal-

ling seems to be one of the central pathways in the regulation of adult neurogenesis. Since its discovery twenty years ago, this pathway has been studied extensively due to its key roles in modulating many different physiological processes through responses to various regulatory molecules [146].

5.1. JAK/STAT signalling

The JAK-STAT pathway can be activated by a range of cytokines, growth factors and hormones. In the regulation of adult neurogenesis, activation of this pathway is carried out by a group of neuroregulatory cytokines. Members of this cytokine group include CNTF, LIF and cardiotrophin 1 (CT-1), all of which belong to the interleukin 6 family of cytokines. These cytokines initiate JAK-STAT activation by binding and signalling through the LIF receptor-β (LIFRβ)/ glycoprotein 130 (gp130) receptor complex. The receptor complex bound by CNTF differs slightly in that it has a third extracellular receptor component, the CNTF receptor-α (structurally related to gp130), that is held to the membrane via a glycosylphosphoinositol [147].

Cytokine binding results in the dimerization of LIFRβ and gp130 receptors to form a complex [148]. This initiates autophosphorylation and activation of JAK proteins which are associated with the intracellular domains of the LIFRβ and gp130 receptors [149]. Members of the JAK protein family include JAK1, JAK2, JAK3 and TYK2. Cytokines signalling through the LIFRβ/gp130 pathway have been found to activate at least JAK1, JAK2 and TYK2 [150]. In terms of the CNS, only JAK1 and JAK2 expression has been found at significant levels [151]. JAK2 is highly expressed in the developing brain compared to JAK1, thus, a role for it in the regulation of neurogenesis in the developing brain has been suggested [151].

After activation, JAKs phosphorylate tyrosine residues in the intracellular domains of LIFRβ and gp130. These phosphorylated residues become binding sites for SH2 domain containing proteins such as STAT. STAT proteins are a family of transcription factors comprised of STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b and STAT6 [152]. Upon binding to the activated receptor complex, STAT proteins are phosphorylated by JAKs resulting in their dimerization. Dimerized STAT proteins are now able to translocate into the nucleus and induce gene expression of target neural genes such as glial fibrillary acidic protein (GFAP), peripherin and vasoactive intestinal peptide [46]. Other SH2 domain containing proteins can also bind the activated LIFRβ/gp130 receptor complex to activate the Ras/MAPK and PI-3K/Akt signalling pathways [49].

The LIFRβ/gp130 pathway is essential for the regulation of astrogliogenesis in the developing and adult brain. In cultured cortical precursors, CNTF, LIF and CT-1 all promote astrocyte formation through LIFRβ/gp130 activation [153-155]. Integral to this pathway is signalling via STAT3, as highlighted by the observation that STAT3 activation in neural stem cells induces glial differentiation, while its inhibition promotes a neuronal fate [156, 157]. Also, in neuroepithelial cells, STAT3 activation promotes astrogliogenisis via LIF induced bone morphogenetic protein 2 expression [158]. In addition to regulating astrogliogenesis, STAT3 induction by CNTF was found to be essential in the maintenance of the SGZ

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neurogenic niche [50]. Further, it has an important role in the positive regulation of reactive astrocytes in the injured CNS [159].

An important aspect to cytokine signalling via a pathway such as JAK-STAT is the need for its downregulation following activation. Thus far, JAK-STAT signalling is known to be negatively regulated by protein inhibitors of activated STATs (PIAS), the SH2-containing protein tyrosine phosphatases (SHPs) and suppressors of cytokine signalling (SOCS) proteins [160]. In this section, SOCS proteins will be the focus of discussion as the negative regulation of the JAK-STAT signalling pathway by SOCS has several effects on the regulation of neurogenesis and NPC fate.

5.2. The suppressors of cytokine signalling

The SOCS family consists of eight members, namely, SOCS1-7 and cytokine-inducible Src homology 2 (SH2) protein (CIS). They are characterised by a central SH2 domain, a C-terminal SOCS box and a variable N-terminal domain. In addition to these, SOCS1 and SOCS3 also contain a small kinase inhibitory domain. CIS was the first member of this protein family to be cloned. It is also unique to the rest of the SOCS family as a result of its SH2 domain which differs in a few amino acids from most all other known SH2 domains [161].

SOCS expression is induced following activation of the JAK-STAT pathway. This initiates a classic negative feedback loop whereby the SOCS proteins activated by JAK-STAT signalling now go on to inhibit it. SOCS proteins achieve downregulation of signalling by binding to tyrosine phosphorylated proteins via their SH2 domain. The exact mechanism by which signalling inhibition is achieved varies depending on the SOCS protein in question. For example, SOCS1 and SOCS3 both work to block the kinase activity of activated JAK proteins. In the case of SOCS1, this is achieved by directly binding and blocking access to the activated JAK. In the case of SOCS3, this is achieved by its binding to the activated gp130 receptor such that STAT proteins can no longer dock onto the phosphorylated tyrosine residues and be activated by JAK. One mechanism of action for SOCS2 is by blocking STAT access to the activated receptor [162].

SOCS proteins are also able to regulate activity of target proteins, including other SOCS proteins, through interaction with their SOCS box [163, 164]. Interestingly, SOCS2, SOCS6 and SOCS7 have the potential to interact with all members of the SOCS protein family including themselves [164]. In terms of SOCS2, when expressed at high levels, it is able to inhibit the action of SOCS1 and SOCS3 by targeting them for proteasomal degradation [164]. This has also been proposed as a mechanism for the dual action of SOCS2 on GH signalling as observed in the overgrowth phenotypes of SOCS2 knockout and overexpressing mice described below [165].

Signalling via the JAK-STAT pathway has an important role in neural precursor proliferation and differentiation [153, 166-168]. Following the discovery that SOCS proteins regulate the JAK-STAT pathway, the next obvious step was to examine them for possible roles in the nervous system. In doing so, analysis of the SOCS family gene expression in the developing mouse forebrain brought SOCS2 into the spotlight [168]. The genes SOCS1 – SOCS3 and CIS

were found to be expressed at all ages (E10 to P25) with a common peak in expression between E14 and P8. However, the level of SOCS2 expression was much higher in comparison. The spatial pattern of SOCS2 expression also distinguished it from the other SOCS genes, with moderate to high levels of expression in neurogenic regions and in newborn neurons. In the adult, SOCS2 was maintained in the CA3 region of the hippocampus and at a moderate level in the dentate gyrus, compared to other SOCS genes whose expression was not localized, if expressed at all under basal conditions. SOCS2 expression was also present in the cerebral cortex and other regions such as the olfactory bulb, forebrain and cerebellum. Interestingly, SOCS2 was first upregulated at the time of neuronal differentiation, which is between the developmental stages E10 and E12, suggesting a role for SOCS2 in neural precursor differentiation [168].

6. SOCS2 in the brain

This interesting spatiotemporal expression of SOCS2 instigated further research into its possible role in neuronal development. The generation of the SOCS2 knockout ($SOCS2^{-/-}$) and SOCS2 overexpressing transgenic (SOCS2Tg) mice has been instrumental in the functional characterisation of SOCS2 [169, 170]. $SOCS2^{-/-}$ mice display an overgrowth phenotype where adult mice are up to 40% heavier than their wild-type counterparts, mainly attributed to an increase in organ size and bone length [170]. This phenotype suggested an involvement of SOCS2 in the negative regulation of GH, a regulator of postnatal growth. To address this hypothesis, SOCS2Tg mice were generated [169]. Interestingly, SOCS2Tg mice also display an enhanced growth phenotype, indicating a potential dual action of SOCS2 where at high levels it may enhance rather than inhibit growth hormone signalling [169].

In-vitro, neural stem cells from $SOCS2^{-/-}$ mice show a marked reduction in the number of neurons generated [171], as opposed to SOCS2Tg mice which show an increase in neuron number [172-174]. Additionally, PC12 cells and neural cells from SOCS2Tg mice demonstrate increased neurite outgrowth in tissue culture [171, 174-176]. GH is an inhibitor of neural differentiation and its negative regulation by SOCS2 is evident by the reduction in neuronal differentiation in neural stem cell cultures of $SOCS2^{-/-}$ mice [171, 174]. The importance of GH/SOCS2 signalling in neuronal differentiation can be illustrated by their involvement in the regulation of the Ngn1 basic helix-loop-helix transcription factor [171]. Ngn1 has an important role in promotion of neurogenesis by at the same time inhibiting glial differentiation [177]. Importantly, Ngn1 is subject to inhibition by GH and this inhibition is overcome by SOCS2 overexpression [171]. Thus, a model has been proposed where GH and SOCS2 regulate neural stem cell differentiation through the modulation of Ngn1 expression [178].

GH binds and signals through the GH receptor (GHR) which belongs to the class I superfamily of cytokine receptors. Like the LIFRβ/gp130 complex, signal transduction is carried out through the JAK-STAT pathway. GH binding activates GHR resulting in JAK activation. JAK2 is the major contributor to GH signalling and it phosphorylates tyrosine residues on the GHR that become binding sites primarily for STAT5a or STAT5b. Activated STAT5 then

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induces SOCS gene expression [179]. JAK2 may also activate STAT1 and STAT3, however this can be cell type specific [180, 181]. One mechanism by which SOCS2 may block STAT5 activation is via its binding to phosphorylated tyrosine residues at the STAT5 binding site on the GHR [182].

SOCS2 can also regulate signalling via the EGF receptor (EGFR) [175, 176]. The main physiological target for EGFR is EGF. EGFR primarily activates and signals through the Ras/MAPK pathway [183]. In terms of the neuronal effects of EGF, it has been shown to enhance neurite outgrowth and survival of different populations of cultured neurons [175, 183]. Relevant to this review, it also has an important role in neurogenesis. As described above, in the adult SVZ and dentate gyrus, EGF regulates neural precursor cell proliferation [37]. The importance of this role is evident when, in response to brain injury, there is an expansion of neural stem cell numbers in the SVZ as a result of an increased responsiveness to EGF due to EGFR upregulation [184]. Important for SOCS2 interaction, EGF also activates STAT5, a process involving the Src tyrosine kinase [185-187]. Overexpression of SOCS2 in PC12 cells inhibited this EGF induced STAT5 phosphorylation [176]. The EGFR was also constitutively phosphorylated at the Src binding site, Tyr^{845}, in SOCS2 overexpressing PC12 cells. It was therefore proposed that SOCS2 competitively bound to Tyr^{845} and blocked its dephosphorylation by the phosphatase SHP2 to allow prolonged Src activation and enhancement of neurite outgrowth [176].

However, while SOCS2 regulated SVZ-derived neurogenesis in a GH dependent manner during development, in the adult SVZ it appears to regulate neurogenesis via regulation of erythropoietin signalling [188]. Further, the mechanism by which SOCS2 regulates adult hippocampal neurogenesis is different and does not appear to involve GH or erythropoietin, although Epo transiently enhanced SGZ NPC proliferation [189, 190]. Hippocampal neurogenesis was studied under control and voluntary exercise conditions (to enhance basal hippocampal neurogenesis) in wildtype, SOCS2Tg and $GHR^{-/-}$ mice. Mice of all 3 genotypes had similar basal levels of neurogenesis and equivalently increased neurogenesis in response to exercise at early timepoints (8 days) aimed at measuring extent of NPC proliferation. However, at later timepoints (35 days) aimed at examining newborn neuron survival, there was a 50% increase in the survival of adult hippocampal neurons in SOCS2Tg mice, under basal conditions and following voluntary exercise. Additionally, SOCS2Tg mice performed better than wildtype animals in the Morris Water Maze which probes hippocampal-dependent cognition [190]. This was an exciting result, as it identified SOCS2 as a potential therapeutic target that could enhance the survival of newly born neurons following brain injury. However, given that GHR-/- mice showed no differences in adult hippocampal neurogenesis compared to wildtype, the mechanism by which SOCS2 promotes survival in this case remains to be determined. One possible explanation for this increase in neuronal survival in SOCS2Tg mice may be that the enhanced neurite outgrowth observed in SOCS2Tg neurons may aid functional integration into existing circuitry and the consequent maturation and survival of neurons.

7. Roles of other SOCS proteins in the CNS

Other SOCS proteins also have roles in the modulation of signalling in the adult CNS. Other than SOCS2, SOCS3 is the best functionally characterised SOCS protein thus far. SOCS3 plays a role in the regulation of neural stem cell fate. Its overexpression in neural stem cells has been shown to inhibit astrogliogenesis and promote neurogenesis through the inhibition of STAT3 transcriptional activity [156]. More recently, SOCS6 involvement in neuronal differentiation was also established. Exogenous IGF1 was found to enhance neurite outgrowth and dendritic branching of neural stem cells through the induction of SOCS6 expression. The same phenotype was produced independently of IGF-1 by SOCS6 overexpression alone. Similar to SOCS2, SOCS6 is activated through the JAK2/STAT5 pathway, however, in this case it is activated through signalling via the IGF receptor. Activated STAT5 induces SOCS6 expression, which goes on to inhibit STAT5 mediated signalling following the classic negative feedback loop [191]. SOCS7 also plays a major role in the brain with SOCS7 null mice exhibiting severe hydrocephalus in early adulthood [192]. While the mechanism by which this occurs has not been elucidated, given the close relationship of ependymal cells and the ventricular space to NPCs in the SVZ, it is tempting to speculate that SOCS7 may also regulate adult NPC biology.

8. SOCS proteins and CNS injury

SOCS2, SOCS3 and SOCS6 all seem to have potential for use as therapeutic targets involving regulation of NPCs following CNS injury. As described earlier, SOCS2 overexpression increases the survival of newly born neurons in the adult brain under basal, physiological conditions. It would therefore be very interesting to look at the effects of SOCS2 overexpression under injury conditions in order to determine whether this phenotype would aid in functional recovery. Similarly, neurogenesis in an SOCS6 overexpressing system under basal and injury conditions should be examined. SOCS3 does not appear to affect neurogenesis *per se* but instead negatively regulates the proliferative and self-renewal effects of LIF on neural precursor cells [193].

SOCS3 has been studied the most extensively under various neural injury conditions, usually in concert with effects on neuroinflammation and astrocytes [194-196]. SOCS3 expression is induced or upregulated in various brain regions including hippocampus and lateral ventricles in response to CNTF administration [197], ischemic stroke [198, 199] and seizure, which also showed transient downregulation of hippocampal SOCS2 expression but no upregulation of SOCS1 [200]. Conversely, after transient forebrain ischemia, SOCS2 expression was upregulated in the hippocampus, not only in astrocytes but also a subset of nestin positive NPCs [201].

Expression of SOCS molecules following CNS damage has functional consequences. It was proposed that a major contributor to the poor axonal regeneration after injury was a compromised responsiveness to injury-induced growth factors and cytokines [202]. For example,

http://dx.doi.org/10.5772/53268

it was suggested that the transient neuroprotective effect of CNTF on injured neurons was due to CNTF induced negative regulation of cytokine signalling by upregulation of SOCS proteins. Use of a cyclic AMP analogue as an inhibitor of SOCS expression enhanced CNTF induced signalling [203], identifying a new route through which the outcome of neurotrauma treatments may be improved. Whether such an approach will also regulate and potentiate effects of cytokines on NPCs remains to be determined. Further, SOCS3 deletion resulted in an enhancement of axonal regeneration in retinal ganglion cells post optic nerve injury in a mouse model, by lifting its inhibitory effects on JAK-STAT signalling [202]. Similarly, PTEN deletion enhanced axon regrowth post injury [204]. PTEN is a negative regulator of signalling via the mammalian target of rapamycin (mTOR) which can be activated through a number of means, one of which being the PI-3K/Akt pathway [205]. Interestingly, much more robust axonal regrowth is achieved upon a simultaneous deletion of PTEN and SOCS3 through a synergistic activation of mTOR and STAT3 signalling pathways [206]. SOCS3 also inhibits the beneficial effects of LIF-mediated oligodendrocyte survival following demyelination, with enhanced STAT3 activation and survival of oligodendrocytes from SOCS3 null mice [207].

Thus, it is apparent that there are many aspects to signalling in the processes of adult neurogenesis. The JAK-STAT signalling pathway is one important player, although it is apparent that SOCS proteins can regulate pathways other than JAK/STAT in a cell type dependent manner. The regulation of JAK-STAT signalling by SOCS proteins has enhanced our understanding of the mechanisms of adult neuro- and astrogliogenesis under basal and injury conditions and has opened avenues into the search for potential therapeutic targets for CNS repair.

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