The Role of PSA-NCAM in Adult Neurogenesis

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Introduction

A fundamental feature of neural circuits is the continuous activity-dependent plasticity of synaptic connections. This lifelong self-reorganization process most likely involves a spectrum of modifications including the molecular remodeling of synapses, leading to their strengthening/silencing, the formation of new synapses, and the destabilization of previously established contacts [1–3]. A fascinating, newly recognized form of adult plasticity consists of the recruitment of newly generated neurons into functional circuits. In the mammalian brain, this process of "rejuvenation" of existing circuits occurs in two discrete regions, the subventricular zone of the lateral ventricle (SVZ) [4] and the subgranular zone of dentate gyrus (SGZ) in the hippocampus [5]. The exact physiological relevance of postnatal or adult neurogenesis is not yet clear. Neurogenesis in the dentate gyrus was shown to be changed by enriched environments, exercise, hippocampus-dependent learning tasks, stress, and pathological conditions [6–9]. Consequently, it has been proposed that integration of new neurons into functional circuits might be involved in learning and memory processes [10]. Neurogenesis in the SVZ and recruitment of new neurons into olfactory circuits was suggested to be important for olfactory sensory discrimination [11].

Neurogenesis in the adult brain recapitulates the complete process of neuronal development, including proliferation, neuronal fate specification, differentiation,

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migration, synaptic integration and survival of new neurons. Neural stem/progenitor cells located within the SVZ give rise to neuroblasts that migrate, first, tangentially via the rostral migratory stream (RMS), and then radially into the olfactory bulb. These new neurons differentiate into two types of interneuron: granule cells and periglomerular cells [11,12]. Stem cells in the SGZ of the dentate gyrus, generate neuroblasts that migrate into the inner granule cell layer and differentiate into new granule cells [5]. A critical feature of adult neurogenesis is that stem cell proliferation and cell migration are spatially restricted to a specific permissive environment where intercellular interactions play a critical role.

In adults, neural stem cells and their progeny are localized in specific niches [13–15]. By definition, the stem cell niche is an anatomical and functional unit that provides a specific microenvironment where stem cells replenish themselves through self-renewal and give rise to different progenies through asymmetric divisions. The cellular composition of the niche in the two germinal regions has been extensively studied and characterized [12,16–18]. In both structures, stem cells have been identified as glial fibrillary acidic protein (GFAP+) and nestin+ positive astrocytes (type B cells in the SVZ and radially oriented astrocytes in the SGZ). These cells show self-renewal through slow symmetric division and give rise to transit-amplifying cells (type C cells in the SVZ and type D1 cells in the SGZ) that, in turn, differentiate into doublecortin-positive committed neuroblasts (type A cells in the SVZ and D2/D3 cells in the SGZ) [13]. A particularly interesting feature of the neurogenic niche is the intimate association of neural precursor cells (NPCs) with microcapillaries in both the SVZ and the SGZ. Endothelial cells and the specialized basal lamina seem to provide attachment for NPCs and generate signals for the self-renewal and priming of stem cells for the production of neurons [13,19].

Remarkable progress has been made in identifying key molecules mediating interactions between stem cells, immature neurons and the local environment [20]. Among these, isoforms of the neural cell adhesion molecule (NCAM) carrying the large carbohydrate polymer, polysialic acid (PSA), are of particular interest. NCAM is a member of the immunoglobulin superfamily that is involved in cell surface recognition, and can promote cell adhesion through a homophylic Ca^{2+}-independent binding mechanism [21]. NCAM is traditionally viewed as mediator of cell–cell interactions establishing a physical anchorage of cells to their environment. However, the attachment of the PSA chain to the NCAM protein core provides unique properties to the molecule. PSA has a large hydrated volume and high negative charge density, and therefore, is well placed to attenuate adhesion forces, and to negatively regulate overall cell surface interactions [22,23]. Here, we review the expression pattern and role of PSA-NCAM in adult neurogenesis.

PSA-NCAM Expression in Adult Neurogenic Sites

NCAM and PSA-NCAM expression is a characteristic feature of the postnatal neurogenic niches [12,24,25]. The available evidence indicates that in the SVZ, PSA-NCAM is not expressed by type B stem cells or other astrocytes, though

these cells are NCAM positive [26]. Similarly, type C transit amplifying cells are negative for PSA-NCAM. On the other hand, type A, committed neuronal precursor cells, are strongly stained for this adhesion molecule [12,27]. The situation is similar in the SGZ niche, where radial astrocytes (primary progenitor or stem cells) as well as horizontal astrocytes do not appear to express PSA-NCAM [18,28]. The primary progenitor cell in the SGZ gives rise to D1 cells, which divides to generate D2 cells. This later extends processes and becomes a D3 cell, which eventually matures into a new granule neuron. It is of interest that, in contrast to type C cells in the SVZ, D1 proliferating transit amplifying cells as well as D2 and D3 cells express PSA-NCAM [18]. However, D1 cells differ in many respects from SVZ type C cells. D1 cells appear to divide only once, and to express doublecortin which is not expressed by C cells [18]. Therefore, D1 cells may be more like SVZ young neuroblasts (type A cells), which express PSA-NCAM and doublecortin. This contention received strong support from a recent study demonstrating that most of the proliferating cells in the SGZ niche express the neuronal marker Hu [28]. Taken together, PSA-NCAM expression in the postnatal neurogenic niche seems to correlate to the developmental stage when newborn neurons start to extend processes, detach from the proliferative niche and migrate. Interestingly, proliferative cells in the SGZ, including GFAP positive radial astrocytic stem cells express N-cadherin/catenin that is progressively downregulated in neuroblasts that withdraw from the niche [28]. Thus, the balance between PSA and N-cadherin/-catenin expressions may regulate anchoring and dynamic cellular arrangements in the niche [28].

Migratory newborn neuroblasts remain highly positive for PSA-NCAM in the olfactory system, as well as in the dentate gyrus. However, after having reached their final location, newborn neurons progressively downregulate PSA-NCAM during dendritic growth and synaptic integration [25].

Putative Functions of PSA-NCAM in Adult Neurogenesis

Neuronal Precursor Migration

The functional significance of PSA on NCAM in adult neurogenic zones is incompletely understood. Genetic deletion of the NCAM molecule ($NCAM^{-/-}$) results in about 30% decrease in the size of the OB, while the overall brain size is reduced by about 10% [29,30]. These defects can be duplicated by the injection of Endo-N, an enzyme that specifically cleaves the PSA moiety associated with NCAM, suggesting that the observed phenotypical changes in the $NCAM^{-/-}$ animal are primarily related to the absence of the PSA chain itself [31]. Parallel to the reduction of OB size, an increased number of neuronal precursors are observed in the SVZ-RMS of $NCAM^{-/-}$ animals compared to wild type (WT) littermates [31,32]. It has been suggested that this accumulation of neuroblasts in the SVZ-RMS is the result of impaired chain migration of these cells toward the OB [31,33]. To our knowledge, no defects in the migration of newly generated hippocampal neurons have been

reported in the absence of PSA, most likely, because of the short distance covered by these cells. Importantly, several lines of evidences demonstrate that in the SVZ, migrating capabilities of the NCAM molecule reside on PSA tails: (i) migrating cells expressing NCAM exhibited high PSA contents [12,34,35]; (ii) functional blocking of PSA residues (by enzymatic removal or by neutralizing antibodies) without alteration of the protein core was sufficient to disrupt migration [31,34,36,37]; and, (iii) simultaneous genetic deletion of the two enzymes responsible of PSA synthesis (polysialyltransferases ST8SiaII and ST8SiaIV) led to gross abnormalities in both radial and tangential neuronal migration during development [38].

The mechanism by which PSA-NCAM might influence neuroblast migration remains unknown. It has been proposed that PSA at the cell surface is required for weak adhesive interactions that would allow cell motility [31]. However, evidence suggests that PSA-NCAM may not be required for cell motility. Instead, PSA-NCAM seems to be critical for the efficiency of migration. For example, newly generated OB precursors express high levels of PSA-NCAM and migrate to the OB using a very effective strategy known as chain migration [25,39]. Albeit less efficiently, neuroblasts devoid of PSA are still able to migrate [40]. However, they are no longer capable of forming chains, resulting in an accumulation of the migrating neurons in the SVZ [31,33,40]. Moreover, NCAM deficient cells were shown to accurately migrate when transplanted into a wild type environment, whereas wild type cells into the mutant SVZ exhibited an NCAM knockout behavior suggesting that PSA effects on SVZ-migrating neuroblasts might be modulated by the environment [33]. In order to explain these observations, it was postulated that neuroblasts use other cells in the chains as a substrate for migration and, consequently, it is the presence/absence of chains more than the PSA complement which determines whether a transplanted cell would properly migrate or not. Interestingly, migrating neuroblasts derived from NCAM knockout animals actually formed chains when cultured in high matrigel concentrations as substrate [40], indicating again that environmental cues might override the absence of PSA.

One attractive hypothesis reconciling all these observations is that PSA would be involved in regulating directed migration towards guidance cues. A recent work focusing on oligodendrocyte progenitor cells (OPCs) migration gave further support to this hypothesis [41]. Using a direct-viewing chemotaxis chamber, Zhang and colleagues provide new insights into the functional consequences of PSA removal in motile neural cells. They showed that basic locomotion (chemokinesis) of OPCs was unaffected by the absence of PSA. In contrast, directional migration (chemotaxis) towards concentration gradients of Platelet-Derived Growth Factor (PDGF) was severely impaired. Interestingly, this effect was dose-dependent, as OPCs migrated towards high concentrations of PDGF independently of PSA. These findings support the contention that PSA-NCAM is part of the regulatory network required for the adequate sensing of environmental cues conferring, thus, the competence to be directionally guided by the tiny concentrations of these factors found in the extracellular milieu. Although this hypothesis is consistent with the observation that a large number of immature neurons in the RMS of $NCAM^{-/-}$ animals show altered orientation [42], it has not been confirmed in vivo yet.

How PSA-NCAM enhances, at the molecular level, the sensitivity to attractive/repellent cues remains unknown. Work in different experimental models has demonstrated that PSA increases the responses to BDNF [43], glutamate [44,45], CNTF [46] and PDGF [41]. In addition, PSA appears to be required for FGFR activation [47]. Thus, PSA might endow NCAM with the ability to interact and/or activate a number of receptors on the cell membrane. Indeed, it has been postulated that PSA, by disrupting NCAM-NCAM homophilic interactions, might promote a switch in NCAM functions from adhesion to a signaling state [48]. Alternatively, reduced adhesion per se in the presence of PSA could modulate membrane signaling.

Survival of Newly Generated Neurons

The role of PSA-NCAM in survival of newly generated neurons has been addressed in an in vitro model of neurogenesis [49]. It has been demonstrated that removal of the polysialic tail of NCAM by Endo-N dramatically decreases the number of newly generated neurons. Similar results were obtained when PSA was blocked by a specific antibody and in cultures prepared from the NCAM$^{-/-}$ mice [49]. Using pulse-chase labeling of neuronal progenitors with the proliferation marker BrdU, it was possible to differentiate between two distinct, nonetheless closely related, events of neurogenesis, namely the mitotic activity per se and the early survival of newly generated neurons [49]. The evidence indicates that the lack of PSA-NCAM or NCAM does not influence mitotic activity, but rather it increases early cell death of newly generated immature neurons. These observations are consistent with previous data demonstrating that interfering with PSA-NCAM affects the survival of neurons in dissociated [43] and organotypic cultures [46]. Most importantly, it has been recently shown that apoptosis is increased nearly threefold in the SVZ and RMS of NCAM knockout animals versus wild types [42]. The enhanced rate of apoptotic cell death was cell specific, since it occurred in the population of migrating neuroblasts (PSA+NCAM+) but not in GFAP positive astrocytes (PSA-NCAM+), supporting the hypothesis that PSA-NCAM and not NCAM is important for cell survival. This hypothesis receives further support from in vitro experiments demonstrating that enzymatic removal or antibody blocking of PSA produce a significant increase in TUNEL labeling [42]. These results are also in agreement with recent data indicating that loss of PSA induces massive neuronal apoptosis in the developing brain [38]. Whether PSA is also a prosurvival factor in hippocampal neurogenesis has not been examined in vivo. Nonetheless, indirect evidence suggests that PSA can prevent glutamate-induced cell death of hippocampal neurons in vitro arguing for this hypothesis [44].

How might PSA-NCAM have influenced the survival of newly generated neurons? One possibility is that BDNF signaling through Trk B receptors was impaired in the absence of PSA-NCAM [43,50]. Indeed, the survival promoting effects of BDNF were significantly less in Endo-N treated and NCAM$^{-/-}$ cultures than in control preparations [42]. Another, very interesting possibility is that PSA-NCAM

influences the low affinity neurotrophin receptor p75 signaling. The first evidence for this is related to the fact that SVZ derived neurons in culture express p75, TrkB, TrkC but not TrkA, the high affinity receptor for NGF [51]. In vitro, NGF significantly increased apoptosis in cells lacking PSA. Given that TrkA is not expressed by SVZ-derived neurons, this effect is mediated by p75. In agreement with these results, pharmacological blockade of p75, but not Trk receptors, prevented neuronal cell death induced by the removal of PSA. It has also been demonstrated that the inhibition of two well-established pro-apoptotic cascades downstream of p75, ceramide and c-Jun N-terminal kinase [52–56], completely prevented neuronal cell death induced by the absence of PSA in control as well as NGF treated cultures. Together, these data raised the possibility that the removal of PSA from NCAM induced an enhanced activation of p75 signaling pathways. In agreement with this idea, it was found that both in vivo and in vitro, immature neurons lacking PSA-NCAM express significantly higher levels of p75 than control cells. However, definitive evidence for this hypothesis would require further experiments involving the use of p75 knockout animals and function blocking antibodies. The fact that PSA removal did not affect TrkB or TrkC expression illustrates the specificity of this effect.

Neuronal Precursor Differentiation

Highly polysialated isoforms of NCAM are present in neurons at the time of neuritogenesis. This could limit the level of NCAM homophilic interactions and, consequently, neurite outgrowth. In agreement with this expression profile, major defects in fasciculation and lamination of mossy fibers in the hippocampus has been described in the NCAM deficient animal [57]. Since similar deficits are also observed in the ST8SiaII/ST8SiaIV double knockout, it appears that PSA contribute to proper axonal growth of hippocampal granule cells [58].

More recent data suggest that the absence of PSA from the surface of neuroblasts may induce differentiation of newly generated neurons. According to a recent report, application of Endo-N into the rostral migratory zone results in a large number of multiple processes bearing cells [59]. This premature differentiation of neuroblasts in the absence of PSA has also been detected in the NCAM knockout animals [48] and is consistent with in vitro results showing an accelerated neurite outgrowth from neuroblastoma cells after removing PSA [60,61]. Intriguingly, Petradis et al. found that differentiation required activation of MAP kinase through p59fyn and hypothesized that, in the absence of PSA, enhanced NCAM homophylic interactions might account for this effect. However, results obtained in the NCAM$^{-/-}$ RMS argue against this possibility and suggest that additional pathways might be activated in the absence of PSA. In vitro studies provide one potential explanation to these observations. Indeed, it has been shown that PSA removal results in the rapid upregulation of p75 receptor [42]. Since p75 signaling contributes to early dendritic growth of new olfactory neurons [51], these data open the intriguing

possibility that progressive decrease in PSA contents might contribute to the arrest of migration and the initiation of neurite growth.

At later stages, neurite development seems to depend specifically on BDNF-TrkB [51]. In contrast, p75 stimulation leads to neuronal death [48]. These dual effects of p75 have been long identified [62] and are likely to be related to the complement of Trk receptors expressed at each maturational stage.

Concluding Remarks

Recent evidence suggests that newly generated neurons might endow the postnatal brain with new levels of plasticity [11]. Interestingly, PSA-NCAM appears to be tightly involved in regulating migration, survival and neurite maturation of new neurons [29,31,33,51]. The mechanism by which PSA-NCAM affects these processes is not yet clear. Influencing p75 neurotrophin receptor expression and signaling might play a role in these processes. It is intriguing that p75 receptors have been implicated in cell death as well as in neurite outgrowth [48,51]. It is possible that by limiting p75 expression, PSA-NCAM protects newborn neurons from being dependent on trophic support, restrains neurite outgrowth and promotes migration before integration into functional circuits. The progressive downregulation of PSA-NCAM and the increase in p75 expression after neurons reached their appropriate place would contribute to the adequate maturation and synaptic integration of new neurons (Fig. 1).

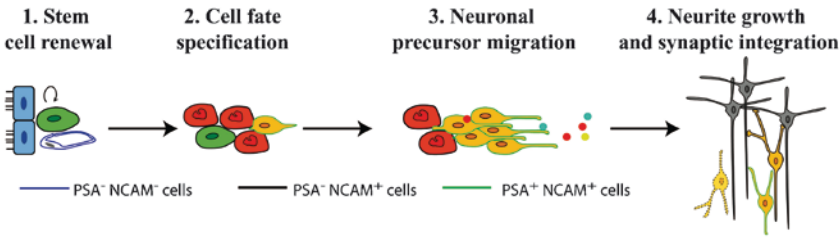

Fig. 1 Proposed model of PSA functions in adult neurogenesis. Schematic representation of PSA-NCAM expression in the sequential steps of adult neurogenesis. (a). Neural stem cells (*green cells*) require a complex local microenvironment (neuro-vascular niche) for self renewal. The niche, represented here by blood vessels (in white) and ependymal cells (*in blue*), contains NCAM but is essentially devoid of PSA. NCAM does not seem to be involved neither in stem cell maintenance nor in niche physiology. (b) When stem cells divide asymmetrically, they give rise to transient-amplifying (*red*) cells that will differentiate into committed neuroblasts (*in yellow*). Similar to stem cells, transient-amplifying cells express nonsialylated NCAM that might participate in cell fate choice. (**c**) After specification, neuroblasts detach from the niche and migrate to their final location. PSA-NCAM is strongly expressed in migratory neuroblast where it might be essential for the adequate sensing of tiny concentrations of environmental cues (*colored circles*) required for efficient migration. (d) In the olfactory bulb, progressive downregulation of PSA results in a parallel increase of p75 that initially promotes neurite outgrowth and then the apoptotic elimination of misplaced/nonconnected neurons (*dashed cell*)

Numerous questions remain. For example, does PSA-NCAM play a role in the synaptic integration of new neurons? How is the polysialylation state of NCAM regulated during this process? Do the activation of new neurons and the physiological network activity regulate PSA-NCAM expression? If yes, how? Could PSA engineering promote the generation and integration of new neurons? Answering these questions represents the next challenge for future research. More importantly, with the recent association of PSA-NCAM with a number of psychiatric diseases [63–65], this information will be invaluable in the development of therapeutic treatment for these disorders.

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