The interesting interplay between interneurons and adult hippocampal neurogenesis

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Abstract

Adult neurogenesis is a unique form of plasticity found in the hippocampus, a brain region key to learning and memory formation. While many external stimuli are known to modulate the generation of new neurons in the hippocampus, little is known about the local circuitry mechanisms that regulate the process of adult neurogenesis. The neurogenic niche in the hippocampus is highly complex and consists of a heterogeneous population of cells including interneurons. Because interneurons are already highly integrated into the hippocampal circuitry, they are in a prime position to influence the proliferation, survival, and maturation of adult-generated cells in the dentate gyrus. Here we review the current state of our understanding on the interplay between interneurons and adult hippocampal neurogenesis. We focus on activity- and signaling-dependent mechanisms, as well as research on human diseases that could provide better insight into how interneurons in general might add to our comprehension of the regulation and function of adult hippocampal neurogenesis.

Keywords

hippocampus; dentate gyrus; subgranular zone; interneuron; GABA; reelin; NPAS3; apoE; SDF-1

INTRODUCTION

Adult neurogenesis is a form of structural and functional plasticity seen in only a few regions in the mammalian brain, such as the hippocampus [1]. The hippocampus is integral to learning and memory formation [e.g. 2,3,4], and evidence suggests that adult hippocampal neurogenesis is important in learning, memory, and other hippocampal functions [e.g. 5]. While many factors such as stress [6], age [7], environmental enrichment [8], voluntary exercise [9] and exposure to drugs of abuse [10,11,12,13] affect the process of adult hippocampal neurogenesis, the local circuitry mechanisms mediating these changes remain elusive. Identification of these mechanisms is important if we are to harness the novel neuroplasticity of adult hippocampal neurogenesis to help repair the injured, diseased, or aged brain [e.g. 14,15,16].

The dentate gyrus (DG) of the hippocampus contains a neurogenic niche, the subgranular zone (SGZ), which is inhabited by a heterogeneous population of cells and cellular elements (Fig 1A, 1B). The niche is a nursery of sorts, hosting those cells in the process of adult hippocampal neurogenesis (Fig 1A): Type-1 neural stem cells (NSCs), actively-dividing progenitors (Type-2, Type-3), and immature and mature DG granule neurons [17,18,19], all of which are surrounded by vasculature [20]. Several publications have examined the

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relationship of adult-generated and embryonic-generated excitatory glutamatergic granule cell (GC) neurons with the vasculature [20,21,22], and have clearly demonstrated a complex but intriguing crosstalk between these elements of the niche.

However, the DG and SGZ niche also host many other cells whose relationship with NSCs, progenitor cells, and adult-generated neurons is much less studied. These other niche elements include excitatory hilar mossy cells, many classes of interneurons (which are generally inhibitory), and glial cells [23,24]. Interneurons are particularly interesting to consider for their regulation of adult hippocampal neurogenesis based on their proximity to adult neural stem cells and their progenitors in the SGZ (Fig 1B, 1C) [23]. Many hippocampal interneurons reside within the DG and have dendritic and axonal projections limited by the boundaries of the dentate gyrus (e.g. Fig 1). However, the projections of hippocampal interneurons are highly complex [23]. In fact, there is evidence that the axons of interneurons in the CA1 region of the hippocampus traverse the hippocampal fissure and also innervate the DG [25,26]. This raises the interesting possibility that activity of "downstream" hippocampal regions like CA3 or CA1 could feedback onto and regulate the process of adult neurogenesis in the "upstream" DG (Fig 1B) [e.g. 26,27]. Even with this complex integration of interneurons into the hippocampal circuitry and proposed interneuron regulation of general synaptic activity in the hippocampus (both reviewed in [28]), interneurons have received surprisingly little attention in regards to how they influence the neurogenic niche and the generation of new neurons in the adult brain.

For this review, we mined the existing literature linking interneurons to adult hippocampal neurogenesis. Our search reveals that most publications fall into one of two main branches. The first branch of research is concentrated on activity-dependent interneuronal regulation of adult hippocampal neurogenesis. We consider this branch to include work on how GABA (γ-aminobutyric acid) and other neurotransmitters that are released from interneurons influence adult hippocampus neurogenesis. The second branch of research focuses on cell signaling-based interneuron regulation of adult hippocampal neurogenesis. We consider this branch to include signaling molecules such as reelin, apolipoprotein E (apoE), stromal cell-derived factor-1 (SDF-1, also called CXCL12) and its receptor C-X-C chemokine receptor 4 (CXCR4), and basic helix-loop-helix (bHLH)-PAS transcription factor, neuronal PAS domain protein 3 (NPAS3). There are some molecules that are represented in both branches, such as SDF-1/CXCR4. However, for the sake of this review we consider direct neurotransmitter effects in the activity-dependent branch and signaling molecules under the signaling-based branch.

We found many publications that could fall into these two branches, and discussion of these studies form the bulk of this review. However, it is useful to say from the outset that in contrast to these publications, we found only a handful of papers that address another question of obvious interest: are new interneurons themselves generated in the adult hippocampus? It appears possible in other brain regions, as adult-generated GABAergic interneurons are evident in both the striatum and neocortex [29]. Likewise, evidence suggests that adult-generated GABAergic interneurons may also exist in the hippocampus [30,31,32,33], although additional work is needed. If production of new hippocampal interneurons during adulthood proves true, it adds yet another layer to the complexity of brain plasticity and the regulation of both synaptic activity and adult neurogenesis.

Given that it remains controversial as to whether new hippocampal interneurons are formed during adulthood [e.g. 1,34], here we restrict our review to the two complementary branches of research that are less controversial: interneuron activity-dependent regulation of adult hippocampal neurogenesis, and interneuron cell signaling-dependent regulation of adult hippocampal neurogenesis.

INTERNEURON ACTIVITY-DEPENDENT REGULATION OF ADULT NEUROGENESIS IN THE SGZ

Prior to discussing what is known about activity-dependent mechanisms relevant to interneurons that may contribute to the process of adult hippocampal neurogenesis, it is useful to stress the heterogeneity of DG interneurons. The subclasses of interneurons that reside within the hippocampus are remarkably diverse, and there are various factors to take into consideration when classifying interneurons: location, morphology, target fields, and expression of proteins like parvalbumin, calretinin (Fig 1C), and calbindin [23,35]. For example, interneurons whose soma or neurites are in close proximity to the SGZ and the neurogenic niche include the molecular layer perforant path interneuron (MOPP), the hilar commissural-associational pathway related interneuron (HICAP), the hilar perforant path-associated interneuron (HIPP), the s. lacunosum/s. moleculare (L-M) interneuron, and basket cells (Fig 1B) [23,36]. Even within a given interneuron class there is striking diversity; for example, there are at least five classes of hippocampal basket cells alone [37], and only one type, the DG pyramidal basket cell is highlighted in Fig 1B. This diversity aside, most hippocampal interneurons share a common characteristic: they are GABAergic, producing and releasing this largely inhibitory neurotransmitter [35]. Thus, the major portion of this first section on activity-dependent regulation of neurogenesis as it relates to interneurons, will focus on GABA, with only a small portion at the end to highlight non-GABAergic research.

GABA

A few groups have undertaken the task of exploring the role of GABA in mediating both developmental as well as adult neurogenesis. During embryonic and early postnatal development, newly-generated neurons follow a distinct sequence of events through which they form their synaptic connections within the developing neurocircuitry (reviewed in [38]). Initially the neurons are "silent", meaning that they have no spontaneous or evoked postsynaptic currents to any of the commonly applied agents (e.g. GABA, NMDA, AMPA, glycine). However, upon the formation of GABAergic synapses (within 12 days of retroviral labeling in the postnatal mouse brain [39]), they become sensitive to depolarization by GABA, followed by the development of glutamatergic inputs, and lastly a switch to hyperpolarization by GABA, a sign of neuronal maturity. Adult-generated neurons in the DG SGZ go through an almost identical progression of steps initiating synaptic connectivity with the surrounding and preexisting hippocampal circuitry [40]. This stepwise maturation and integration closely synchronizes with the progressive stages of the process of adult neurogenesis, beginning with Type-1 neural stem cells which give rise to transiently amplifying progenitor cells (Type-2), followed by immature neurons and eventual maturation to fully integrated DG granule cells (reviewed in [41]).

Type-1 cells in the SGZ of the hippocampus are the putative neural stem cells (NSCs), which are thought to be the "source" cells of the process of adult neurogenesis [19,42]. They are often identified by their unique radial glial-like morphology and expression of markers such as Nestin, Sox2, and BLBP [34]. While Type-1 cells divide infrequently [43], there is some indication that perhaps proliferation of Type-1 cells is hippocampal activity-dependent. For example, Type-1 cell number increases after kainate-induced seizures in mice [44]. Interestingly, laboratory animals given drugs to induce seizures also have fewer DG interneurons [45]. However, whether Type-1 cells and hippocampal interneurons are sensitive to the same seizure-related stimulus or if a loss of interneuron activity or signaling increases Type-1 cell division has yet to be investigated (Fig 2). It is also still unclear whether Type-1 cells specifically express functional GABA receptors, which would make them able to respond to extrasynaptic GABA in the DG [46,47,48,49]. Only one study

published by Wang et al. [47] was able to show a Type-1 cell response to GABA$_A$ receptor agonist muscimol and the inhibition of a GABA-mediated response by the GABA$_A$ receptor antagonist bicuculline. It is intriguing to consider whether GABAergic interneurons, which innervate the SGZ, GCL, and molecular layer of the DG [23], regulate the rare or slow proliferation of these radial-glial like Type-1 cells. There is minimally anatomical support for such a relationship; Type-1 cells retain their cell bodies in the SGZ and extend their processes into the outer GCL and inner molecular layers [50], all regions with significant interneuron innervation (Fig 1B) [23].

Significantly more data have been published regarding the impact of GABA on the maturation of Type-2 cells, the transiently amplifying progenitors that arise from the Type-1 putative neural stem cells (Fig 1A). Based on expression of particular antigens, the Type-2 cell population can be divided into "younger" Type-2a progenitors expressing Nestin and "older" Type-2b progenitors expressing Nestin and the immature neuronal marker doublecortin (DCX; Fig 1A), indicating a transition into the neuronal lineage [51,52]. The heterogeneity of Type-2 cells is also supported by analysis of their electrophysiological properties. One subset of Type-2 cells is referred to as "silent", responding to tonic but not phasic GABA, while the other subset is referred to as "GABA-only", depolarized by phasic GABA but not yet responding to glutamatergic stimuli [46,49]. Retroviral labeling of adult-generated cells with GFP also supports this heterogeneity, where GFP-labeled cells show responses to tonic GABA as early as 3 days-post-infection (dpi) and phasic GABA at 7dpi [40,49]. While it is tempting to consider Type-2a Nestin+ cells "silent" and the Type-2b Nestin+/DCX+ cells responsive to "GABA-only", this has not yet been shown. In fact, the specific GABAergic electrophysiological properties of Type-2a and -2b cells have yet to be directly studied.

There is some evidence that proliferation of these progenitor cells may be influenced by tonic GABA in the adult hippocampus [53]. In this study, Duveau et al. show that there is decreased proliferation of cells in the dentate gyrus of mice constitutively lacking the GABA$_A$ receptor subunit α4, a subunit responsible for regulating tonic GABA inputs [53,54]. Likewise, adult-generated cell migration may be negatively affected in the GABA$_A$ receptor subunit α4 KO animals [53]. However, whether these data are a result of entire animal KO of the receptor subunit or specific deletion in the adult generated cells still needs to be investigated (Fig 2). This is an ideal question for application of the novel cell-specific deletion or manipulation of genes that has become more widely used in recent years [55,56].

As adult-generated cells differentiate into mature DG GCLs, they not only respond to tonic GABA but also receive phasic GABAergic inputs. This phasic input is important because it depolarizes the maturing cells and elevates their intracellular Ca^{2+} ([Ca^{2+}]$_i$) levels via activation of voltage-gated calcium channels [57]. This increase in [Ca^{2+}]$_i$ has been shown to stimulate the expression of NeuroD [46,57], a transcription factor necessary for the survival and differentiation of adult-generated cells in the SGZ [58,59]. In this activity-dependent manner, GABAergic interneurons in the existing hippocampal circuitry have the power to regulate the differentiation of adult-generated DG cells (Fig 2). However, it is important to note that NeuroD is expressed in cells that retain proliferative capacity [58]. Although GABA released from interneurons can stimulate differentiation of Type-2 cells, the effect of GABA on proliferation of these cells, as with the Type-1 cells, is yet to be explored.

The process of adult neurogenesis continues its progression with the transition of Type-2 cells to Type-3 cells and immature neurons (Fig 1A) [18]. While still mitotically active, Type-3 cells lose Nestin expression (becoming Nestin-) and retain expression of immature neuronal markers such as DCX and NeuroD, confirming their neuronal lineage and earning

them the status of neuroblast [51]. The terminology in the literature is mixed on this point, with neuroblasts being considered either immature neurons or the precursors to immature neurons. However, most studies agree on the definition of an immature neuron: an SGZ cell that is DCX+/NeuroD+ and perhaps NeuN+ or Prox1+ (markers of mature granule neurons) that has begun to extend its processes into the outer 2/3 of the molecular layer [60]. Because dendritic propagation and maturation is not dependent on exit from the cell cycle [61], dendritic arborization and thus synaptogenesis follows a heterogeneous timeline. Some information is published on the timeline of the formation of dendrites, spines, synapses, and axon guidance [39,62,63], but much about these processes remains unknown. For example, it is not clear if or how arborization and synaptogenesis are synchronized with each other or across cells. This uncertainty aside, it is still interesting that GABA appears to regulate the maturation of adult-generated DG neuron processes (reviewed in [64]). For example, the immature DG neurons of mice given a GABA$_A$ receptor antagonist have shorter dendrites and decreased spine density [65]. In contrast, the immature DG neurons of mice given a GABA$_A$ receptor agonist have longer dendrites [49]. Of course, systemic administration of a compound (particularly GABA compounds, which can have robust behavioral effects) does not prove that hippocampal GABAergic interneurons are responsible for dendritic regulation. This could, for example, be the result of a change in circuitry or behavior that influences SGZ neurogenesis (Fig 2). Likewise, while the pool of hippocampal GABA is largely interneuronal [35,66], it has been suggested that ambient GABA may be released from other sources such astrocytes [67,68,69]. However, the concept of GABAergic interneurons regulating adult neurogenesis is intriguing, and has some support in the fact that stimulation of a certain type of interneuron, the hippocampal basket cell, enhances tonic currents in adult-generated DG cells [49]. Additional studies with local application of GABA compounds or other more sophisticated ways to locally manipulate or stimulate GABAergic interneurons coupled with tracking adult hippocampal neurogenesis are warranted.

The influence of other neurotransmitters

The potential regulation of SGZ neurogenesis by GABA and perhaps GABAergic interneurons is most concentrated on the "early" stages on neurogenesis. However, "later" stages of neurogenesis, when immature neurons are making synapses in CA3, are also influenced by other neurotransmitters. For example, it is during the initial synaptogenic period when adult-generated cells are approximately 14-18 days old, that the first excitatory glutamatergic inputs are received [39,40,49]. This last synaptogenic step is followed by a switch from depolarizing to hyperpolarizing GABA [49] and the completion of adult-generated cell integration into the existing hippocampal circuitry. When fully integrated in the DG circuitry, the adult-generated neurons are able to glutamatergically regulate interneuron activity [70]. Thus, a dynamic pattern of influence emerges: GABAergic interneurons potentially influence the complex, multi-step process of SGZ neurogenesis, and the resulting adult-generated neurons can then in turn regulate the activity of GABAergic interneurons.

As we have stressed above and as is nicely reviewed elsewhere [23,28], most DG interneurons are GABAergic, and most DG GABA neurotransmission comes from DG or hippocampal interneurons. However, there are cholinergic interneurons in the DG as well, and it is worth considering how these ChAT+ interneurons (named after the enzyme responsible for synthesizing acetylcholine (ACh)) with their broadly-branching dendritic trees [71,72] might influence the process of neurogenesis. However, since the vast majority of the cholinergic input into the hippocampus and DG comes from the forebrain [72,73,74], it remains challenging to determine whether DG cholinergic interneurons have any direct impact on SGZ neurogenesis. Interestingly, lesion of forebrain cholinergic neurons impairs

SGZ neurogenesis, leading to decreased proliferation and survival of adult-generated cells [75,76]. While such studies show that SGZ neurogenesis is sensitive to cholinergic signaling – potentially through Ach-stimulated release of GABA from hippocampal interneurons [77] – it is still unclear what role the resident cholinergic interneurons, optimally located within the DG, may play in the regulation of the process of adult SGZ neurogenesis.

While GABA and ACh are secreted by interneurons [35], and have the potential to directly modulate adult neurogenesis in the hippocampus (reviewed above and in [27]), there are an enormous number of factors that could indirectly regulate interneuron function and interneuron regulation of neurogenesis. For example, the neurotransmitter serotonin can excite CA1 hippocampal interneurons that project to the DG [26]. Disruption of serotonin signaling has a profound effect on SGZ neurogenesis [78,79,80,81,82]. These correlative data with serotonin are reminders that regulation of interneuron activity in the hippocampus, indirectly via other neurotransmitters apart from GABA, is another important mechanism by which interneurons regulate SGZ neurogenesis.

As reviewed above, various neurotransmitters have been implicated in regulating hippocampal interneuron activity both directly (GABA, perhaps ACh) and indirectly (serotonin) to modulate adult neurogenesis in the SGZ. However, interneurons secrete various proteins and participate in numerous signaling pathways that may also have the ability to regulate adult neurogenesis [48,83,84]. Therefore, the second half of this review will focus on signaling proteins and mechanisms, which involve hippocampal interneurons and regulate adult neurogenesis in the DG.

INTERNEURON SIGNALING-DEPENDENT REGULATION OF ADULT NEUROGENESIS IN THE SGZ

While much attention has been given to GABAergic regulation of adult hippocampal neurogenesis, it is also important to address proteins and signaling pathways involving interneurons that may play a role in regulating the generation of new DG granule cells in the adult hippocampus. These factors include reelin, apoE, SDF-1, and NPAS3, and are discussed below.

REELIN

Reelin is a very large extracellular matrix glycoprotein expressed by Cajal-Retzius cells during development. Reelin plays an integral role in neuronal migration and the development of the brain (reviewed in [85]), and its disruption results in a robust developmental phenotype. Mutant mice lacking functional reelin, termed *reeler* mice, have an inversion of cortical layers and a highly disorganized hippocampus in which a significant portion of DG radial-glial cells have prematurely differentiated into astrocytes [86,87,88,89]. Interestingly, these same radial-glial cells, whose number is decreased in the *reeler* mice, are the putative Type-1 NSCs in the SGZ (Fig 2). Likely because of this, *reeler* mice show decreased neurogenesis in the adult hippocampus and in other regions of adult neurogenesis as well [39,90]. Although loss of reelin has been implicated in disrupting adult hippocampal neurogenesis in *reeler* mice, the phenotype is likely a secondary effect of the developmental defects and not a result of the loss of function of the reelin protein solely in the adult hippocampus. Unfortunately, because *reeler* mice have such a prominent developmental phenotype, it is difficult to glean the precise function of the protein in the adult brain just from examination of these mutant mice.

Fortunately, other experimental approaches have been employed to explore the role of reelin in the adult brain and several of these studies have relevance for SGZ neurogenesis. For example, immunohistochemical studies have revealed that during adulthood reelin is

expressed by a subset of GABAergic hippocampal interneurons including basket cells in the hilus of the DG [91]. Behavioral and electrophysiological studies strongly suggest that reelin signaling is important for synaptic plasticity and hippocampal-based learning and memory [92,93]. Recently, a study published by the Soriano group has taken an interesting tactic in genetically overexpressing reelin in the adult mouse forebrain [94]. They find increased reelin expression increases adult neurogenesis and regulates neuronal migration and synaptic density (Fig 2). While the study does not explore the specific mechanism by which reelin regulates adult neurogenesis, the authors propose that reelin may alter the cell cycle properties of the transiently amplifying progenitors (probably Type-2 cells) and increase the survival of DCX+ immature neurons (Fig 2). This is supported by the increased number of DCX+ labeled immature neurons in older mice that overexpress reelin, which is in sharp contrast to wildtype mice where adult neurogenesis decreases with age [7].

Another useful approach to dissecting the role of reelin in regards to adult neurogenesis is to focus on the signaling molecules that comprise the reelin signaling cascade. For example, the signaling molecule Disabled 1 (Dab1) is an integral part of the intracellular portion of the reelin signaling pathway, and is found in both hippocampal radial-glial cells and neural progenitors [87,95]. However much remains unknown in regards to reelin signaling and adult hippocampal neurogenesis. For example, it is undetermined whether neural progenitors and immature neurons show reelin-induced phosphorylation of Dab1 (Fig 1B). It has also not yet been shown whether the hippocampal adult-generated cells even express the reelin receptors Apoer2 and Vldlr (Fig 1B). If they do, this would suggest that adult hippocampal neurogenesis can be directly responsive to the reelin produced by DG interneurons [96].

If adult-generated cells and neurons are able to directly respond to reelin signaling – and more careful anatomical work is needed before we can say that with certainty – there are numerous questions that one could ask. For example, since *reeler* mice have such a profound migrational effect during development, it would be interesting to explore how reelin affects the migration of adult-generated hippocampal neurons. The majority of adult-generated granule neurons remain in the inner third of the hippocampal DG granule cell layer as they mature [40,97]. It is possible that reelin controls this very restricted migration; particularly in light of work showing that adult-generated GCs in transgenic animals overexpressing reelin have aberrant migration, with adult-generated neurons spread throughout the GCL [94]. Additionally, seizure-induced loss of reelin-producing interneurons correlates with the seizure-induced ectopic migration of DG granule neurons [95,98]. These studies indicate that a very precise level or location of reelin expression may be required to maintain an organized DG GCL. Based on these published data, the field would obviously benefit from the generation of reelin conditional and inducible knockout mouse lines and viruses that would allow cell-specific production or disruption of reelin signaling related genes. Such tools would allow the exploration of the mechanisms underlying how interneurons may modulate not only proliferation and survival of adult-generated hippocampal neurons, but also their migration through reelin signaling.

APOE

ApoE is a protein that has critical functions in lipid transport [e.g. 99,100]. ApoE in the brain is produced mainly by astrocytes [101] and it has the ability to bind to reelin receptors [99]. Although hippocampal interneurons likely do not produce apoE in a healthy brain [102,103], in the mouse, interneurons appear to be highly susceptible to age-related effects of the human apoE4 isoform [104], the major risk factor for late-onset Alzheimer's disease (AD) (reviewed in [105]). More specifically, the number of hilar GABAergic interneurons significantly decreases with age in the human apoE4 knock-in mice when compared to wildtype mice [104,106]. It is because of these detrimental effects of apoE4 on the interneurons – and the subsequent loss of GABAergic inputs onto adult progenitor cells in

the SGZ – that there is a significant decrease in adult neurogenesis in the apoE4 knock-in mouse hippocampus [106] (Fig 2). This promising link between decreased adult neurogenesis and AD is addressed later in this review.

SDF-1 and CXCR4

One of the most intriguing links between interneurons and adult hippocampal neurogenesis comes from studies on SDF-1, a chemokine expressed in postnatal DG interneurons [107]. More specifically, SDF-1 is found in the vesicles of basket cell terminals and colocalizes with GABA-containing synaptic vesicles [48,107]. The receptor for SDF-1, CXCR4, is expressed by cells in the early and later stages of adult hippocampal neurogenesis, namely the Type-2 cells and immature neurons, but not mature DG GCs [48,107]. Thus, the SDF-1/ CXCR4 ligand/receptor coupling offers a presumably direct route for interneurons to influence adult hippocampal neurogenesis (Fig 2). Interestingly, concomitant release of SDF-1 with GABA from the DG interneurons enhances GABAergic inputs on Nestin+ Type-2 progenitors and DCX+ immature neurons [48]. This is in keeping with work showing that GABAergic activity plays an important role in regulating adult neurogenesis [e.g. 27]. It is also of note that i.c.v. administration of a CXCR4 antagonist decreases adult-generated mature granule cell number in the rat [108]. Functionally, the CXCR4 antagonist also has the ability to impair long-term memory formation in animals housed in an enriched environment, a stimulus known to increase adult neurogenesis [8,108]. Of course, additional work is needed, for example, to examine how SDF-1 from endothelial cells might also fit into this regulation scheme [48]; whether inducible deletion of CXCR4 from adult-generated SGZ cells blocks the GABAergic regulation; and whether a similar SDF-1/CXCR4 coupling regulates neurogenesis in other regions of postnatal neurogenesis. However, the recent publications with SDF-1 signaling noted above, shed much needed light on how DG interneurons might signal to regulate neurogenesis and relevant hippocampal function as well.

NPAS3

The bHLH-PAS transcription factor NPAS3 is expressed by GABAergic interneurons in the adult hippocampus [84]. Mice deficient for NPAS3 show decreased hippocampal levels of both the fibroblast growth factor receptor 1 (FGFR1) [109], a growth factor receptor implicated in affecting adult neurogenesis [110,111], and reelin [84], without grossly influencing interneuron number [84]. Interestingly, they also show impaired SGZ neurogenesis [109]. However, whether this impairment is a result of disrupted FGF or reelin signaling or from some other phenotype (such as small body size in general) has yet to be conclusively determined (Fig 2).

HUMAN DISEASE, INTERNEURONS, AND ADULT NEUROGENESIS

Some very interesting clues about the interplay between hippocampal interneurons and neurogenesis have emerged from research on human disease and disorders. Here we briefly review what key diseases – AD, schizophrenia, seizure disorders, and psychiatric disorders like depression and addiction and animal models of these disorders – can reveal about the relationship between interneurons and neurogenesis. Also, while ageing is not a disorder *per se*, the process of ageing is relevant to the onset of many of these disorders, and therefore is also discussed.

Alzheimer's disease and schizophrenia

Alzheimer's disease, a neurodegenerative disorder, and schizophrenia, a neuropsychiatric disorder, are quite distinct in their neuropathology [e.g. 112,113]. However, both AD and schizophrenia are marked by abnormal hippocampal structure and disrupted hippocampal

neurogenesis [e.g. 14,114,115,116,117], and both disorders are also correlatively associated with the interneuronal protein reelin [e.g. 118]. Both Alzheimer's disease animal models and schizophrenia patients display decreased numbers and function of hippocampal interneurons [104,119,120]. In addition, reelin binds apoE4, one of the major risk factors for late-onset Alzheimer's disease [e.g. 121]. Highly relevant for this section on research from human disease is a recent paper that studied mice genetically modified to express apoE4 [106]. ApoE4 mice have decreased interneuron number and impaired hippocampal neurogenesis (an interesting combination of enhanced proliferation but impaired survival and dendritic arborization) (Fig 2). Most notably for this review, apoE4 reduces GABAergic signaling onto adult-generated neurons and disrupts neurogenesis, a defect that can be reversed by potentiation of GABAergic signaling [106]. Reelin signaling can also modulate the phosphorylation state of the microtubule stabilizing protein tau, which when hyperphosphorylated initiates the formation of neurofibrillary tangles, a major pathological constituent of the disease [122]. It appears that the elimination of the Tau protein from apoE4 knock-in mice rescues the demise of GABAergic interneurons in the hippocampus as well as the deficits in hippocampal-dependent learning and memory [104]. Post mortem human tissue analysis reveals decreased reelin levels in the hippocampi of schizophrenic patients [123], and mice heterozygous for reelin show similar results in sensorimotor gating tests as those seen in schizophrenics [120,124]. It is also important to mention that NPAS3, like reelin, has been related as a genetic link to schizophrenia, as it is mutated in a family with schizophrenia [125]. Taken together, these studies underscore the utility of the interneuron/neurogenesis hypothesis when considering the trajectory and potential treatment strategies for disorders like Alzheimer's disease and schizophrenia. Also, when considered with other work cited above [e.g. 46,49,65], many of these studies add to the growing evidence that GABAergic interneurons may regulate hippocampal neurogenesis and that this regulation is functionally important.

Seizure disorders

Epilepsy is a seizure disorder, and neuropathological examination of the brains of epileptic humans reveals dispersion of the granule cell layer of the DG and abnormal sprouting of axonal fibers in humans [126,127,128]. Animal models of seizure disorders show a similar dispersion of the DG GCL, and notably aberrant adult neurogenesis post-seizure [128,129], in keeping with the disrupted neurogenesis seen in the epileptic human brain [e.g. 130,131,132,133]. In addition to these changes in neurogenesis, there is a small change in number, distribution, and connectivity of some hippocampal interneurons in the human epileptic brain [e.g. 130,134,135]. There is evidence that the aberrant dispersion of cells in the human GCL in patients with temporal lobe epilepsy shares an inverse relationship with reelin expression, likewise, reelin expressing interneurons are sensitive to seizures [95,128]. These data further confirm that the scientific community may find clues to which mechanisms regulate adult neurogenesis in the hippocampus by further exploring epilepsy and seizure animal models. For example, it would be useful to identify whether reelin signaling is more important for maintaining dentate structure or neuronal number.

Stress-related disorders and depression

Stress was among the first stimuli shown to decrease proliferation in the adult hippocampal SGZ [6], and since that time has become appreciated as one of the most potent regulators of neurogenesis [e.g. 136]. Stress hormones, like corticosterone, are likely responsible for stress-induced disruption of SGZ neurogenesis [e.g. 137,138,139,140]. In addition, adult-generated hippocampal cells and neurons appear to be directly responsive to stress hormones since, for example, corticosterone receptors are evident on cells in discrete stages of adult neurogenesis [e.g. 141]. However, research has shown that stress can also influence interneuron structure and function, which in turn might influence adult neurogenesis. For

example, hippocampal parvalbumin interneurons may be sensitive to chronic stress, as tree shrews undergoing long-term psychosocial stress show decreased parvalbumin-immunoreactivity in the hippocampus [142]. However, whether this loss of immunoreactivity is due to loss of GABAergic interneurons or a loss of parvalbumin expression is still unclear. Furthermore, while many publications show that stress can result in altered hippocampal interneurons population number and/or diversity balance [e.g. 142,143,144], this may be stress- and species-specific [e.g. 145]. Regardless, a direct effect of stress on hippocampal interneurons is certainly feasible since hippocampal interneurons express receptors that allow them to respond to stress hormones [e.g. 146,147]. Therefore, if GABAergic interneuron function is negatively affected by most stressors, it could help clarify how stress decreases adult neurogenesis in the hippocampus (Fig 2).

There is also functional relevance for this line of thinking about stress effects on adult neurogenesis. For example, chronic mild stress (CMS) paradigms are generally used to generate models of depression in laboratory animals (reviewed in [148]). CMS models show a disruption of the GABAergic system in the brain [149], replicating human data showing that depressed individuals have decreased GABAergic function (reviewed in [150]). While decreased adult neurogenesis is not currently implicated as a cause for depression, adult neurogenesis may be required for antidepressant function [e.g. 15,151,152]. Interestingly, Sahay and Hen have proposed that the non-heterogeneous distribution of different classes of interneurons across that septo-temporal axis of the hippocampus maybe be partially responsible for the varied effects of antidepressants on adult neurogenesis in the dorsal and ventral hippocampus (reviewed in [153]).

Addiction

It is well known that many drugs of abuse, such as opiates and psychostimulants, have a profound effect on adult neurogenesis in the hippocampus [e.g. 13,154]. However, the mechanism of how drugs of abuse influence SGZ neurogenesis is unknown. While researchers are exploring the likely possibility that drugs of abuse act via circuit-level changes and perhaps direct effects on progenitor cells, it is also possible that drugs of abuse directly or indirectly influence interneuron function, which in turn alters SGZ neurogenesis. There is evidence for some direct action of drugs of abuse on hippocampal interneurons. For example, interneurons express receptors for a major ingredient in tobacco, nicotine (the nicotinic ACh receptor [155,156,157]), the active ingredient in marijuana, delta-9-tetrahydrocannabinol (Δ9-THC) (the cannabinoid receptor 1 [157,158]), and for morphine, heroin, and other opiates (the mu opioid receptor [159,160]). Activation of the cannabinoid receptor 1 and mu opioid receptor on hippocampal interneurons decreases GABAergic activity (as reviewed in [161,162]), which could then lead to decreased GABAergic influence on SGZ neurogenesis. While the effects of drugs of abuse on the GABAergic activity of interneurons residing near and innervating the neurogenic niche could be involved in the changes seen in adult neurogenesis after drug exposure and the progression of addiction, additional research in this realm is warranted. Since stress is a predisposing factor in relapse to drug-taking [e.g. 154,163] and hippocampal interneurons express receptors for both drugs of abuse and stress hormones [146,147], one useful future line of research might focus on how stress-induced changes in interneuron function alter both neurogenesis and relapse to drug-taking or drug-seeking.

Age

While ageing is not a disorder or a disease, there are several disorders whose occurrence increases with age, such as Alzheimer's disease and depression [e.g. 164,165]. Therefore it is useful to note findings from ageing research that have relevance to understanding the interplay between interneurons and hippocampal neurogenesis. For example, there is a

correlation between the age-induced decline in interneurons immunoreactive for GAD67 (glutamic acid decarboxylase; the enzyme that catalyzes the production of GABA) and the decline in adult neurogenesis. Specifically, there are 41% fewer GAD+ interneurons in middle aged rats (15 months) and 50% fewer in aged rats (23 months) compared to adult rats (7 months) [166]. Likewise, adult hippocampal neurogenesis, as measured by the number of DG GC cells immunoreactive for the mitotic marker BrdU given 4-6 weeks earlier, significantly decreases in the middle-aged (12 months) and aged (27 months) rat. Adult hippocampal neurogenesis drops to about 10-30% of adult (6 month) rat levels, and interestingly, there is no significant difference between middle-aged and aged animals [7]. These data bring up an attractive correlation: in middle-age there is a significant deficit in both GABA-producing interneurons and adult hippocampal neurogenesis in the DG. Of course, a decrease in GAD67 expressing interneurons is not the only change that occurs in the neurogenic niche with age. For example, neurotrophic factors such as VEGF also decrease with age [167,168], and this decrease and other age-dependent changes in the niche could contribute to age-induced decrease in adult hippocampal neurogenesis. Regardless, an age-dependent decrease in adult hippocampal neurogenesis (as a result of any mechanism) is particularly intriguing in light of the association with neurodegenerative diseases such as Alzheimer's disease.

CONCLUSION

Correlative evidence shows that interneurons play a substantial activity-dependent role in modulating adult neurogenesis in the mammalian hippocampus. GABAergic activity has the ability to promote adult-generated cell maturation and differentiation in the GCL. Various signaling elements, such as apoE or SDF-1 and its receptor CXCR4, regulate interneuron GABAergic activity and thus adult-neurogenesis in an activity-dependent manner. On the other hand, the interneuron-mediated reelin pathway exerts a primarily signaling-dependent effect on the generation of new granule cells in the hippocampus. While we have made strides in understanding this interplay between interneurons and neurogenesis, many questions remain unanswered (Fig 2). For example, the direct effect of GABAergic activity on proliferation of various neuronal progenitors still needs to be addressed, and more work is needed to verify that this is indeed a direct effect of GABAergic interneurons and not a more widespread circuit level influence. We also need a better understanding of what receptors and signaling components are evident on which stages of adult-generated neurons in order to really appreciate how signals from interneurons might influence the dynamic process of adult hippocampal neurogenesis. This would also allow us to inducibly manipulate these signaling cascades by, for example, conditionally knocking out key receptors for reelin on cells once they reach a particular stage of adult hippocampal neurogenesis as has been done for other molecular regulators of adult hippocampal neurogenesis [e.g. 50,169]. We also need greater understanding of how interneuron influence might vary among species, strains, and even anatomically along the septotemporal axis of the hippocampus [170,171,172]. The latter is particularly critical given the distinct function of the hippocampus along the septotemporal axis [153,173]. Finally, while here we have focused on how interneurons might regulate adult hippocampal neurogenesis (Fig 2), it is important to remember that once the adult-generated cells themselves are differentiated, they in turn could regulate interneuron signaling and perhaps number. Given this complexity of interactions, the dynamic nature of adult hippocampal neurogenesis, and the diversity of hippocampal interneurons, the question of the interplay between interneurons and neurogenesis would certainly benefit from the insight that computer modeling of neurogenesis and its regulation might provide [e.g. 174,175,176]. It would also be beneficial for the field if more computer simulations of neurogenesis began to take into account the likely robust influence of hippocampal interneurons on the process of neurogenesis.

While the field is beginning to grasp potential outlets with which to pursue identification of the local circuitry and related molecular mechanisms regulating adult hippocampal neurogenesis, we are still in search of an answer. Clearly, many human diseases and disorders show interplay between hippocampal interneurons and adult neurogenesis. Therefore in addition to the lines of research proposed above, we propose that better scrutiny of human diseases and animal models of these diseases will be intellectually profitable in allowing us to better understand the mechanisms by which interneurons can influence neural stem cell and progenitor proliferation, survival, and maturation and their putative impact on hippocampal function.

Acknowledgments

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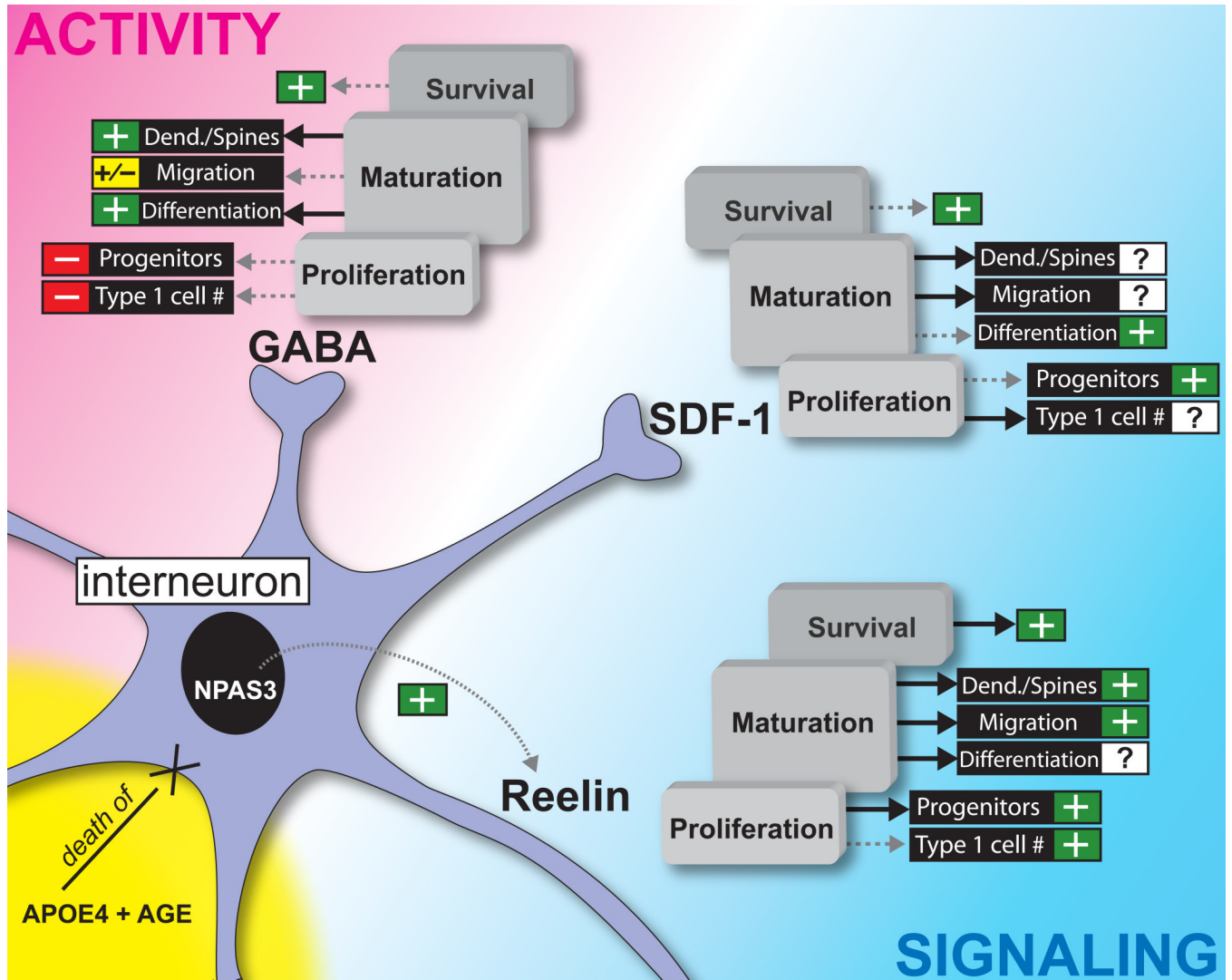153. Sahay A, Hen R. Adult hippocampal neurogenesis in depression. Nature Neuroscience. 2007; 10:1110–1115.

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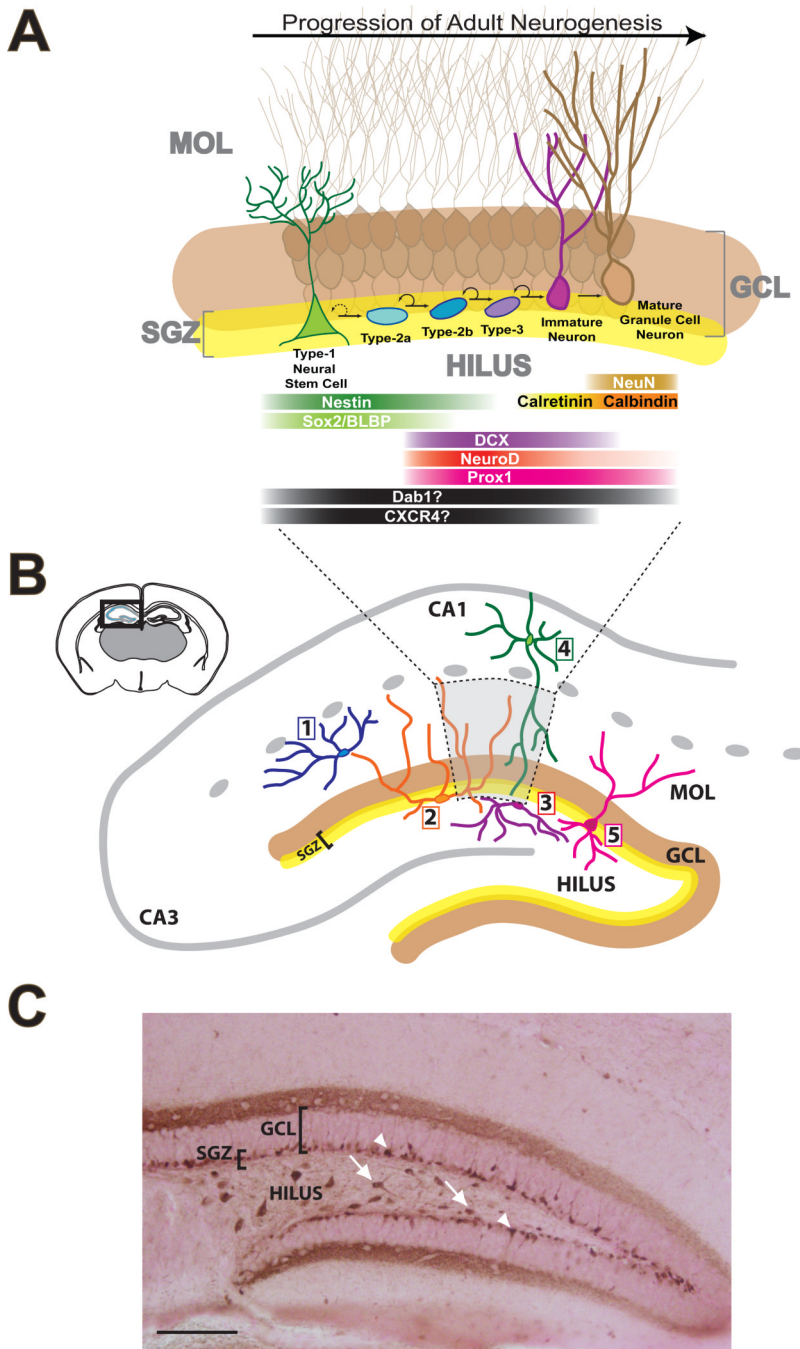
Figure 1. An overview of hippocampal neurogenesis and dentate gyrus (DG) interneurons
(A) Simplified schematic of the stages of adult neurogenesis [modeled after: 16] depicting the presumed generation of adult generated hippocampal neurons in the subgranular zone (SGZ, yellow area). The remaining regions of the dentate gyrus labeled include the molecular layer (MOL), granule cell layer (GCL, brown), and hilus. In the SGZ, Type-1 cells (green) give rise to proliferating cells (blue and darker purple) to immature (magenta) and mature (brown) dentate gyrus granule cells which extend their dendritic process up into MOL and their axons to the hippocampal CA3 region (not shown). The SGZ is often defined as a zone that includes the innermost portion of the GCL bordering the hilus and

approximately two cell body thicknesses into the hilus [97,172,177,178,179]. Depicted below the schematic of the cellular progression of adult neurogenesis in the SGZ and GCL are various proteins expressed in cells at each stage of neurogenesis [e.g. 17,34,180]. As noted in the text, Nestin and Sox2/BLBP are expressed in Type-1 cells; DCX, NeuroD, and Prox1 are expressed in progenitors; and Calretinin, Calbindin, NeuN are expressed in immature and mature granule cell neurons. Relevant to this review on interneurons, there is some evidence that Dab1 and CXCR4 are expressed in adult-generated cells and neurons [48,87,95,107]. However, as this evidence is not firm or confirmed for a particular stage of neurogenesis, expression of these proteins is indicated by a question mark. As described in the text, it will be important to determine the expression of Apoer2 and Vldlr and other interneuron- and reelin-relevant proteins during the process of adult neurogenesis. The dotted lines below **(A)** indicate that the stages of neurogenesis depicted occur within the dentate gyrus proper, which is showed in lower magnification in **(B)**. **(B)** Upper left and smaller schematic in **(B)** depict a coronal section through a mouse brain with the hippocampus outlined [modeled after: 14]. Larger schematic in **(B)** depicts the enlarged DG and the regions of the DG of interest when discussing adult hippocampal neurogenesis. It also shows the hippocampal CA1 and CA3 regions for reference. The larger schematic in **(B)** also highlights five different types of hippocampal interneurons with close proximity to and likely innervation of the SGZ and neurogenic niche. Note the large cell bodies of the MOPP interneurons (molecular layer perforant path cell, #1, blue); the HICAP interneurons (hilar commissural-associational pathway related cell, #2, orange); the HIPP interneurons (hilar perforant path-associated cell, #3, purple); the L-M interneurons (s. lacunosum/s. moleculare cells, #4, green); and a typical DG basket cell (also called pyramidal basket cell, #5, pink) [23,25,26,37]. The grey region outlined with the dotted line identifies the sample area of the neurogenic niche depicted in **(A)**. When the adult-generated cells and neurons shown in **(A)** are considered in conjunction with the 5 types of hippocampal interneurons shown in **(B)**, we hope it is apparent that there is significant opportunity for hippocampal interneurons to influence adult hippocampal neurogenesis. Interneurons, for example, are poised to release GABA near the cell bodies and dendrites of cells in many stages of adult hippocampal neurogenesis. **(C)** Photomicrograph of the DG of a wildtype mouse stained for calretinin via colorimetric immunohistochemistry. Calretinin+ cell bodies in the SGZ represent maturing granule cells (indicated by arrowheads) [181]. Calretinin+ cell bodies in the hilus represent interneurons and mossy cells (indicated by arrows). Calretinin+ terminals in the inner MOL [e.g. 182,183] represent fibers from a few different regions: associated and commissural hilar mossy cell projections (reviewed in [184]), afferents from the supramammillary nucleus of the hypothalamus [134,185,186], and an undetermined contribution from maturing adult-generated cells in the SGZ/GCL [181]. Scale bar=~200μm.

Figure 2. A summary of the key interneuronal players, both activity-(neurotransmitter dependent) and signaling-dependent, which play a role in the regulation of adult hippocampal neurogenesis

Solid lines indicated findings that are supported by one or more publication. Dotted gray lines indicate findings that are suggested in the published literature, but that warrant more in-depth research. Question marks indicate areas in the field that have not yet been explored. +/- indicates either a positive influence (+) or negative (-) influence, respectively, of the specified neurotransmitter/protein on a given stage of neurogenesis (proliferation, maturation, survival). The "Dend./Spines" subcategory refers to an effect on either dendritogenesis or spine formation, or both. **GABA:** GABA released from interneurons has distinct effects on SGZ/GCL cells in the stages of proliferation, maturation, and survival. For example, evidence shows a correlation among the increase in neuronal activity in seizures, the decrease in interneuron number, and the increase in the number of Type-1 cells in the hippocampal SGZ [44,45]. This suggests that GABA may be inhibiting Type-1 number, but more work is needed to clarify this. Likewise, recent evidence suggests that constitutive deletion of select $GABA_A$ receptor subunits increases SGZ cell proliferation [53]. This indicates that GABA may exert a negative effect on the proliferation of SGZ progenitors. This same publication showed a $GABA_A$ receptor subunit-dependent alteration

in cell migration towards the outer GCL, with constitutive deletion of one subunit decreasing the migration away from the SGZ and deletion of another subunit increasing the migration away from the SGZ [53]. A series of studies has shown that phasic GABA inputs raise intracellular Ca^{2+} levels, which initiate NeuroD expression, a transcription factor necessary for the differentiation and survival of adult-generated cells in the SGZ [46,57,58,59]. This indicates that GABA has a positive influence on differentiation and survival, although more work is needed to clarify the effect on survival specifically. These results coincide with other studies exploring the activation/inactivation of GABARs, concluding that GABA positively influences dendritogenesis [49,53,65]. **Reelin:** Reelin released from interneurons appears to positively influence cells across all stages of hippocampal neurogenesis. For example, decreased developmental levels of reelin expression result in fewer Type-1 cells in adulthood [86,87,88,89]. However, the effect of reelin overexpression on Type-1 cell number remains unknown. Overexpression of reelin increases proliferation of progenitors and also plays a role in neuronal migration and dendritic spine hypertrophy [94]. While there is no direct evidence that reelin influences differentiation of adult-generated cells, there is a significant effect of reelin overexpression on the survival of adult-generated cells with age [94]. Inducible interneuron-specific ablation of reelin in adulthood is needed to complement the current research on reelin overexpression. **SDF-1:** Less is known about the role of SDF-1 signaling in hippocampal neurogenesis, but some messages have emerged. For example, it has not yet been investigated how Type-1 cell number and adult-generated cell migration and dendritogenesis are affected by SDF-1. However, it is proposed that SDF-1 may increase adult neurogenesis; administration of an antagonist against the SDF-1 receptor, CXCR4, results in a decrease in adult-generated GCs in the DG [108]. Likewise, concomitant release of SDF-1 with GABA from DG interneurons enhances GABAergic inputs on progenitors and immature neurons, and therefore has the potential to increase intracellular Ca2+ levels positively affecting differentiation and adult-generated cell survival in the SGZ through NeuroD expression [46,48,57,58,59]. **NPAS3:** While there is no direct link showing that the transcription factor NPAS3 regulates reelin expression, NPAS3 KO mice show decreased levels of reelin and decreased neurogenesis [84,109]. This is additional correlative evidence that reelin in general promotes adult hippocampal neurogenesis. **APOE4/AGE:** While more work is needed on the role of the Alzheimer's risk factor apoE4 in regulating the interneuron/neurogenesis relationship, it is notable that expression of apoE4 significantly decreases interneuron number with age. Thus, apoE4 and age may work in concert to decrease interneuron number, which would influence adult neurogenesis by disrupting the various interneuron influences on adult neurogenesis that are depicted in this figure [104,105,106].