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Epigenetic aging in adult neurogenesis

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Abstract

Neural stem cells (NSCs) in the hippocampus generate new neurons throughout life, which functionally contribute to cognitive flexibility and mood regulation. Yet adult hippocampal neurogenesis substantially declines with age and age-related impairments in NSC activity underlie this reduction. Particularly, increased NSC quiescence and consequently reduced NSC proliferation are considered to be major drivers of the low neurogenesis levels in the aged brain. Epigenetic regulators control the gene expression programs underlying NSC quiescence, proliferation and differentiation and are hence critical to the regulation of adult neurogenesis. Epigenetic alterations have also emerged as central hallmarks of aging, and recent studies suggest the deterioration of the NSC-specific epigenetic landscape as a driver of the age-dependent decline in adult neurogenesis. In this review, we summarize the recently accumulating evidence for a role of epigenetic dysregulation in NSC aging and propose perspectives for future research directions.

KEYWORDS
aging, chromatin, DNA methylation, epigenetic, hippocampus, histone, Lamin B1, neural stem cells, neurogenesis

1 | INTRODUCTION

The hippocampus harbors a neurogenic niche in which a neural stem cell (NSC) pool is maintained throughout life (Bond et al., 2015; Denoth-Lippuner & Jessberger, 2021; Kempermann, 2015). Hippocampal NSCs generate excitatory granule cells, which are integrated into the hippocampal circuitry and contribute to cognitive processes, such as pattern separation and spatial navigation, but also to mood regulation and stress resilience (Anacker & Hen, 2017; Gonçalves et al., 2016). The contribution of adult-born neurons to hippocampal function seems to be particularly impactful during their maturation phase, when they possess a transient period of increased excitability and elevated synaptic plasticity (Toni & Schinder, 2016). However, the numbers of new-born neurons in the hippocampus sharply declines with age, and this has been attributed predominantly to their reduced production by NSCs (Kempermann et al., 1998; Kuhn et al., 1996; Kuhn et al., 2018). Manipulating NSCs to enhance neurogenesis in the aged hippocampus can promote brain function and counteract age-related cognitive impairments (Berdugo-Vega et al., 2020; Seib et al., 2013). Due to this promising therapeutic potential, much research in recent years has been directed at understanding the sources of the age-dependent decline in adult neurogenesis, and both alterations in cell-extrinsic signals as well as age-related changes in NSC-intrinsic molecular programs have been identified as potential drivers (Bedrosian et al., 2020; Bin Imtiaz et al., 2021; Kalamakis et al., 2019; Leeman et al., 2018; Navarro Negredo et al., 2020; Villeda et al., 2011). Importantly, research in the past decade has identified impairments in epigenetic regulation as a cell-intrinsic factor of aging in most, if not all, tissues and organism examined so far (Booth & Brunet, 2016; Pal & Tyler, 2016; Seale et al., 2022). Yet, the role of epigenetic regulation in NSC aging has only recently begun to be explored.

Epigenetic mechanisms have long been acknowledged to be critically important for stem cell differentiation, where they guide the establishment and maintenance of celltype-specific gene expression

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programs (Mohn & Schübeler, 2009; Smith & Meissner, 2013). Along these lines, multiple studies have demonstrated that epigenetic regulators, including those controlling DNA methylation and post-translational histone modifications, also regulate NSC function during hippocampal neurogenesis (Covic et al., 2010; Ma et al., 2010; Sun et al., 2011; Yao et al., 2016). However, it is now apparent that epigenetic regulators also control cellular function beyond development, and that the loss of cell type-specific epigenetic patterns is a major driver of cellular dysfunction during aging (Booth & Brunet, 2016; Pal & Tyler, 2016). NSCs possess characteristic epigenomes, which are dynamically altered during the switch from NSC quiescence to proliferation and vice versa (Kremer et al., 2022; Martynoga et al., 2013; Maybury-Lewis et al., 2021), or during neuronal differentiation (Noack et al., 2022; Zocher, et al., 2021). Due to the critical role of epigenetic regulation in controlling cell state-dependent gene expression programs, the long-term maintenance of the NSC epigenome during aging must be a prerequisite for preserving their capability to proliferate, self-renew and generate new neurons.

Here, we review recent studies that suggest a role of epigenetic alterations in NSCs for the age-dependent decline in hippocampal neurogenesis. First, we briefly summarize the current knowledge regarding cellular alterations in adult neurogenesis during aging. We then discuss transcriptomic and epigenetic changes that have been suggested to underlie those alterations. Finally, we propose open questions and future directions on the topic, with the aim to facilitate research toward understanding the role of epigenetic mechanisms in NSC aging.

2 | AGE-DEPENDENT CHANGES IN ADULT NEUROGENESIS

Aging is associated with progressive alterations of NSC behavior, and thereby affects the composition of the hippocampal neural precursor cell pool and its progenies. In the following section, we will give a brief overview of the current knowledge regarding age-dependent cellular alterations during neurogenesis in the hippocampus.

2.1 | Increased NSC quiescence

The total numbers of NSCs in the hippocampus decreases during the lifespan (Gontier et al., 2018; Harris et al., 2021; Ibrayeva et al., 2021; Martín-Suárez et al., 2019), while the fraction of quiescent NSCs increases (Berg et al., 2019; Encinas et al., 2011; Harris et al., 2021; Ibrayeva et al., 2021). Moreover, NSCs progress into a deeper quiescence state during aging, which is characterized by prolonged time periods between cell divisions and an increased tendency of proliferating NSCs to return to quiescence (Harris et al., 2021; Ibrayeva et al., 2021). Consequently, reduced numbers of proliferating cells, including transiently amplifying progenitors, and a pronounced decrease in the numbers of new-born neurons can be found in the aged hippocampus (Ben Abdallah et al., 2010; Kempermann, 2015; Kuhn et al., 1996). Adult hippocampal neurogenesis declines exponentially early in life, with a more than 80% decrease from 1 to 6 months after birth in rodents, and is preserved at very low levels in the aged brain (Ben Abdallah et al., 2010). Moreover, lineage tracing experiments have revealed that NSCs change their cell division mode during the lifespan, with NSCs in 6-months-old mice exhibiting an increased fate choice toward self-renewing, symmetric divisions and a reduced fate toward neuronal differentiation compared to 2-months-old mice—a change that is maintained during brain aging (Ibrayeva et al., 2021; Harris et al., 2021). NSC aging is also associated with morphological changes toward a reactive astrocyte-like morphology, which has been related to their reduced activation in response to external cues (Martín-Suárez et al., 2019). The progressive increase in NSC quiescence during the lifetime has been suggested to prevent NSC depletion and enable the maintenance of a NSC pool in the aged brain (Bottes et al., 2021; Ibrayeva et al., 2021).

2.2 | Altered NSC pool composition

Recent studies hinted at the existence of NSC subpopulations in the hippocampus which differ based on morphology, proliferative activity, division mode and response to extrinsic cues (Bottes et al., 2021; Gebara et al., 2016; Jhaveri et al., 2010) and that those subpopulations might be differentially affected by age (Harris et al., 2021; Ibrayeva et al., 2021; Schouten et al., 2020). For instance, long-term in vivo imaging and lineage tracing experiments revealed that Ascl1-expressing NSCs proliferate more rapidly following activation and get depleted thereafter (Bottes et al., 2021), leading to an exhaustion of this subpopulation early in life (Ibrayeva et al., 2021). In contrast, NSCs that are characterized by the expression of Nestin or Gli1 were found to be long-term self-renewing NSCs, which reduce their division frequency over time and are therefore preserved in the aged brain (Bottes et al., 2021; Ibrayeva et al., 2021). Although single-cell RNA sequencing has revealed subtle gene expression differences between these NSC subpopulations (Bottes et al., 2021), direct evidence for whether they represent functionally distinct NSC types or different developmental cell stages along one lineage requires further experimentation. An improvement of depth of single-cell RNA sequencing in combination with lineage tracing methods will help to unravel these questions in the near future. Another study showed that NSC subpopulations can be distinguished based on the expression of the glucocorticoid receptor (Gr) and that the relative abundance of Gr-positive and Gr-negative NSCs changes during aging (Schouten et al., 2020). Consistent with the function of glucocorticoids in mediating quiescence, Gr-negative NSCs were highly proliferative in the young mouse hippocampus but depleted by 6 months of age, while Gr-positive NSCs reduced numbers linearly during life and were maintained in the aged brain. Interestingly, this study related the differences in NSC glucocorticoid signaling and proliferation to epigenetic mechanisms, specifically DNA methylation. While the existence of functionally distinct NSCs subpopulations is still under debate, these reports indicate that the composition of the hippocampal NSC pool changes during aging.

2.3 | Delayed maturation of the NSC progeny

In addition to the effects of aging on NSCs, the dynamics of new-born neuron maturation are altered during the lifespan, which influences immature neuron numbers in the aged hippocampus. In the young rodent brain, new-born neurons mature over a period of 4–6 weeks (Toni & Schinder, 2016). Starting at middle-age, however, adult-born neurons exhibit a pronounced delay in their morphological development, including dendritic outgrowth and spine formation, resulting in markedly slowed functional integration (Trinchero et al., 2017). This prolonged maturation period has been suggested to increase the time window for experience-dependent functional needs of the immature neurons. In addition, the survival rate of adult-born neurons has been reported to increase during aging although total numbers of surviving cells are reduced (Kuipers et al., 2015), indicating that possible compensatory mechanisms may exist to balance the reduced production of adult-born neurons in the aged brain. It would be intriguing to investigate whether these age-related changes in adult-born neurons derive from cell-intrinsic or -extrinsic changes.

3 | TRANSCRIPTOMIC CHANGES ASSOCIATED WITH NSC AGING

Transcriptomic changes are considered to reflect changes in NSC states during aging. A number of recent studies have applied single-cell RNA sequencing to identify transcriptomic changes underlying the age-related alterations in NSC function (Artegiani et al., 2017; Harris et al., 2021; Ibrayeva et al., 2021). These studies have suggested that aged NSCs clustered in a deeper quiescence state than young NSCs when their distributions along a pseudo-time axis from quiescent to activated NSC states were analyzed (Harris et al., 2021; Ibrayeva et al., 2021). Hence, the age-dependent increase in NSC quiescence identified with lineage tracing experiments is reflected on the transcriptomic level.

While single-cell RNA sequencing has proven to be robust in revealing age-related differences in NSC state distributions, it has been less powerful in identifying differentially expressed genes between young and aged NSCs, likely due to the limited genomic coverage of most single-cell RNA sequencing techniques (Harris et al., 2021; Kalamakis et al., 2019). Using an improved Smart-Seq4 single-cell RNA sequencing protocol that achieved higher gene coverage, Ibrayeva and colleagues identified around 1000 genes that were differentially expressed between quiescent NSCs from young (2-month-old) and middle-aged (4.5-month-old) mice (Ibrayeva et al., 2021). Interestingly, the genes downregulated in middle-aged NSCs were enriched in biological processes related to the regulation of transcription and epigenetic mechanisms, hinting at impairments in epigenetic regulation in NSCs during aging. In another study that applied bulk RNA sequencing, almost 2000 genes were found to be differentially expressed between NSCs that were isolated from the hippocampus of young and aged mice and expanded in vitro (Bin Imtiaz et al., 2021). The fact that age-related changes in NSCs are retained under in vitro conditions suggests that they are regulated, at least partially, by cell-intrinsic, epigenetic mechanisms. Intriguingly, two recent reports have identified lamin B1 as one of the epigenetic factors underlying NSC aging (Bedrosian et al., 2020; Bin Imtiaz et al., 2021), and the age-related reduction of lamin B1 protein was also maintained in vitro (Bin Imtiaz et al., 2021). Since lamin proteins are key factors for the maintenance of heterochromatin and lineage-specific epigenetic regulation, these findings suggest age-related changes in lamin-associated epigenetic regulation as one of the drivers of NSC aging (refer to Section 4.1 for details). Further analysis and functional validation of the gene pathways identified in these studies as well as the identification of their up-stream regulators will likely help to understand mechanisms underlying increased NSC quiescence during aging.

Adult neurogenesis also declines with age in the sub-ventricular zone (SVZ), where the age-related reduction follows a similar temporal pattern as in the hippocampus (Kalamakis et al., 2019; Luo et al., 2006). Increased NSC quiescence has also been identified as a factor underlying NSC aging in the SVZ (Kalamakis et al., 2019), suggesting that despite differences in transcription profiles and activity-dependent regulation between the NSCs of these two niches (Adusumilli et al., 2021), there are common cellular changes during aging. Using bulk RNA sequencing of NSCs purified from the SVZ of young (3-month-old) and aged (20-month-old) mice, Leeman and colleagues found that quiescent NSCs exhibit a higher number and stronger transcriptional changes with age compared to activated, proliferating NSCs (Leeman et al., 2018). In contrast, an age-related increase in cryptic transcription, which refers to transcriptional initiation from non-promoter regions within gene bodies, was found in proliferating NSCs purified from the SVZ but not in quiescent NSCs (McCauley et al., 2021). This latter study detected more than 250 genes exhibiting cryptic gene expression in aged proliferating NSCs, but the identity of those genes was not reported—hence, it remains unclear whether those genes were related to NSC proliferation. McCauley et al. further showed that, in aged mesenchymal stem cells, cryptic transcription was associated with loss of DNA methylation and altered chromatin states, and suggested that these age-related epigenetic changes enable spurious genomic access for RNA polymerase to chromatin regions that are normally closed. Whether similar epigenetic changes underlie cryptic gene expression in aged NSCs was not demonstrated.

Recent studies have successfully applied bulk RNA sequencing of purified NSCs to identify cell-intrinsic and extrinsic regulators of NSC aging. For instance, Leeman and colleagues found reduced expression of genes associated with lysosome function in aged quiescent NSCs, which resulted in impaired lysosome activity and an accumulation of insoluble protein aggregates, hampering NSC proliferation in the aged SVZ (Leeman et al., 2018). Another study identified the interferon signaling pathway as a mediator of age-related NSC quiescence in the SVZ, with "response to interferon-beta" signaling being the strongest enriched biological process among age-related differentially expressed genes in NSCs (Kalamakis et al., 2019). Manipulation of the interferon-beta pathway revealed that elevated niche-derived IFNa/

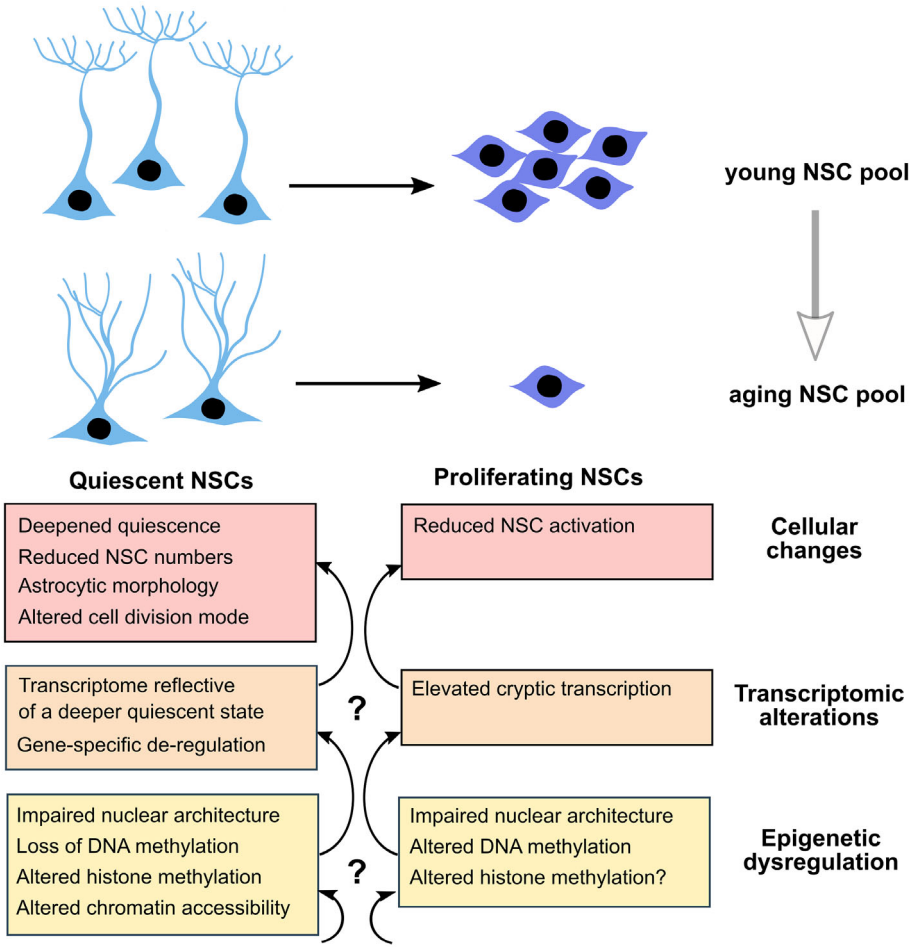

FIGURE 1 Summary scheme of age-related changes in quiescent and proliferating NSCs at the cellular, transcriptomic and epigenetic level. Age-related epigenetic changes have emerged as an important driver of NSC aging, although the exact mechanisms downstream of epigenetic aging and the functional link between the different epigenetic layers still needs to be determined.

IFNb is a predominant mediator of NSC quiescence in aging. Using mathematical modeling of single-cell expression data, Kalamakis and colleagues further found that downregulation of non-canonical Wnt signaling and upregulation of canonical Wnt signaling in NSCs contributes to age-related NSC quiescence, with a strong upregulation of the non-canonical Wnt signaling antagonist *Sfrp5* in aged NSCs. Inhibiting *Sfrp5* in the aged SVZ activated NSC proliferation and reduced total NSC numbers, thereby counteracting NSC aging (Kalamakis et al., 2019). Whether the age-related pathways identified by these studies are shared between the NSCs of both neurogenic niches and also occur in the hippocampus requires further investigation.

Together, these studies identified gene-specific transcriptomic changes in quiescent NSCs during aging, and suggested a loss of gene regulation with aging in NSCs that involves epigenetic mechanisms (Figure 1).

4 | EPIGENETIC CHANGES UNDERLYING NSC AGING

Epigenetic regulators are required for the long-term maintenance of celltype-specific gene expression programs, and represent likely upstream regulators of the NSC-specific transcriptional alterations during aging described in the previous section. Epigenetic mechanisms are known to control the gene expression programs that govern cell stage transitions during adult neurogenesis, such as the switch between NSC proliferation and quiescence, or the upregulation of neuronal gene expression during differentiation (Gontier et al., 2018; Santiago et al., 2019; Yao et al., 2016; Zocher, Overall, Berdugo-Vega, et al., 2021). Epigenetic regulation takes place on multiple, interconnected layers in the nucleus: from the organization of chromatin structure and gene locations in three-dimensional space (nuclear architecture) over two-dimensional control of chromatin accessibility by histone modifications or transcription factors to DNA methylation (Aboelnour & Bonev, 2021). Since epigenetic regulators in the brain are sensitive to environmental signals (Schouten et al., 2020; Zocher, Overall, Lesche, et al., 2021), they are suggested to function as integrators of cell-extrinsic cues into cell-intrinsic transcriptional networks—although the current evidence for their role in activity-dependent adult neurogenesis is sparse. In the following section, we describe the epigenetic modifications for which a role in NSC aging has been suggested. We briefly summarize the known function of those epigenetic marks in the regulation of adult hippocampal neurogenesis and discuss the existing evidence for their contribution to NSC aging (Figure 2).

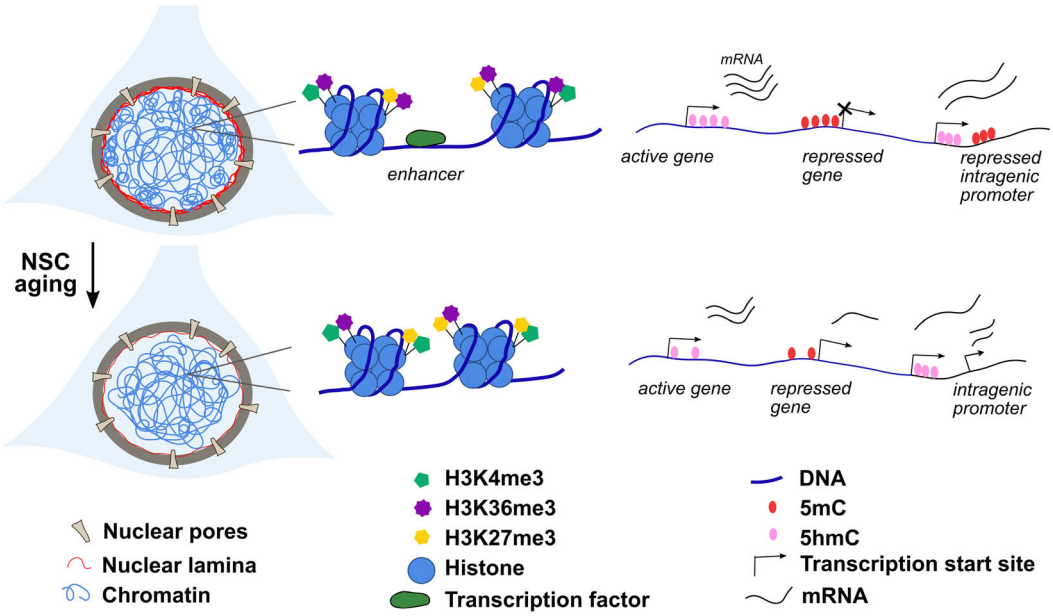

FIGURE 2 Epigenetic aging in NSCs. Aging is associated with impairments of the NSC-specific nuclear architecture, which involves a loss of lamin B1 that likely leads to the re-organization of chromatin in the nucleus. The reduced expression of other epigenetic regulators in aged NSCs, including histone lysine demethylases, DNA methyltransferases/demethylases and pioneer transcription factors, leads to progressive changes in histone modifications, DNA methylation and chromatin accessibility at regulatory elements of genes required for NSC activation. This loss of epigenetic regulation leads to reduced expression of NSC-specific genes and aberrant activation of genes that are repressed in young NSCs, which contributes to impairments of NSC function during aging.

4.1 | Nuclear architecture

The nuclear architecture represents the non-random, three-dimensional organization of chromatin in the nucleus and contributes to cell type-specific epigenetic regulation (Aboelnour & Bonev, 2021; Misteli, 2020). The nuclear envelope and its associated proteins are instructive for the nuclear architecture, not only by determining shape and organization of the nucleus but also through their direct roles in gene regulation. Accumulating evidence also suggests a critical importance of nuclear structural proteins in the control of NSC behavior (Kinkel & Prince, 2010; Mestres et al., 2022). Intriguingly, two recent studies have identified reduced levels of the nuclear lamina protein lamin B1 as one factor underlying the age-related reduction in adult hippocampal neurogenesis (Bedrosian et al., 2020; Bin Imtiaz et al., 2021).

Lamins are important structural components of the nuclear envelope which bind heterochromatin at the inner nuclear membrane and interact with epigenetic modifiers to control gene expression (Mestres et al., 2022). Neural cells show cell type-specific lamin B1 expression patterns, with NSCs and neuroblasts expressing high levels of lamin B1 which decrease during neuronal maturation (Bedrosian et al., 2020; Bin Imtiaz et al., 2021). However, there is an age-dependent reduction in lamin B1 expression in hippocampal NSCs, which can already be observed at an age of 5.5 months and hence parallels the temporal profile of the age-related decrease in NSC proliferation (Bedrosian et al., 2020; Harris et al., 2021). Recent studies further showed that lamin B1 expression is essential for NSC maintenance, with genetic deletion triggering differentiation and a long-term depletion of the NSC pool (Bedrosian et al., 2020). Conversely, lamin B1 overexpression repressed NSC differentiation in vivo (Bedrosian et al., 2020) and retarded quiescence entry of NPCs in vitro, consistent with its higher expression in proliferating NSCs compared to quiescent NSCs (Bin Imtiaz et al., 2021). Rescuing the age-related reduction of lamin B1 in NSCs induced proliferation and consequently enhanced levels of adult neurogenesis in the aged hippocampus (Bin Imtiaz et al., 2021), suggesting that targeting lamin-directed nuclear architecture can restore NSC function in aged brains.

The decline of lamin B1 expression in the hippocampus during aging was restricted to the neurogenic lineage and absent from astrocytes, microglia and interneurons (Cole et al., 2022). Although a recent study reported an age-related reduction in lamin B1 expression also in GFAP-positive astrocytes in the dentate gyrus, the study did not distinguish between NSCs and astrocytes to exclude that this signal was derived from NSCs (Matias et al., 2022). An age-related loss of lamin B1 was also found in Drosophila fat body cells (Chen et al., 2014), and in the human hippocampus (Matias et al., 2022), among other tissues. Whether loss of lamin B1 expression also underlies age-related stem cell dysfunction in other stem cell niches has not been tested yet. Nevertheless, these previous studies suggest a cell type-specific but evolutionary conserved role of lamin B1 in cellular aging.

The age-related lamin B1 reduction in NSCs likely influences their chromatin organization and epigenetic landscape, although the exact mechanisms remain to be investigated. The nuclear lamina interacts with the genome at so called lamina-associated domains (LADs), which contains predominantly heterochromatic and transcriptionally

inactive genomic regions (Peric-Hupkes et al., 2010). In other cell types, lamin B1 deletion caused a detachment of LADs from the nuclear membrane, a redistribution of chromatin toward the nuclear centre and a global increase in activating histone marks (Chang et al., 2022). Whether an age-related LAD redistribution contributes to NSCs aging is unknown. Yet many of the genes upregulated upon lamin B1 deletion in NSCs overlapped LADs (Bedrosian et al., 2020), making it likely that age-related loss of lamin B1 in NSCs leads to LAD redistribution and chromatin reorganization. How lamin-directed nuclear architecture changes during NSC quiescence and aging represents an exciting future field of study.

The induction of cellular quiescence has been reported to be associated with chromatin compaction and global transcriptional repression in different cell types (Boonsanay et al., 2016; Evertts et al., 2013; Swygert et al., 2019). For instance, the quiescent state in *Saccharomyces cerevisiae* is associated with major changes to the nuclear architecture, characterized by an increased frequency of long-distance interactions and decreased centromere clustering (Swygert et al., 2019). This increased chromatin condensation upon quiescence entry was related to global transcriptional repression in quiescent cells (Swygert et al., 2019). Global transcriptional repression has also been found in quiescent NSCs in the hippocampus compared to proliferating NSCs (Harris et al., 2021), and a predominant reduction in chromatin accessibility in aged NSCs has recently been reported (Maybury-Lewis et al., 2021). Yet, the epigenetic changes underlying NSC quiescence are not well understood. In muscle stem cells and fibroblasts, chromatin compaction upon quiescence entry has been shown to depend on the deposition of repressive histone marks and was required to maintain cell quiescence (Boonsanay et al., 2016; Evertts et al., 2013). Moreover, quiescence-induced chromatin compaction in yeast was mediated by the protein complex condensin, which is critical to the control of the nuclear architecture (Swygert et al., 2019). Components of the condensin complex have been reported to also control NSC chromatin structure and function (Nishide & Hirano, 2014). Future studies should address whether age-dependent increases in global chromatin compaction and transcriptional repression contribute to deepened NSC quiescence.

Together these studies suggest that the maintenance of a NSC-specific nuclear architecture is crucial for preserving NSC function during aging, although the exact mechanisms are still unknown. Further nuclear envelope-associated proteins are known to control NSC function, including nucleoporins which are the main structural components of nuclear pores (Cho & Hetzer, 2020; Toda et al., 2017). These proteins interact with chromatin as well as with cell type-specific transcription factors and histone modifications to shape transcriptional programs and have also been suggested to contribute to the long-term maintenance of NSC identities during aging (Cho & Hetzer, 2020; Toda et al., 2017).

4.2 | Histone modifications

Post-translational modifications at histones regulate chromatin accessibility and transcription factor binding and hence control cell type-specific gene expression programs (Bonitto et al., 2021; Yao et al., 2016; Yao & Jin, 2014). The two most extensively studied modifications are the reversible acetylation or methylation of lysine residues at histones H3 and H4, which are catalyzed by the activity of histone acetylases and deacetylases or histone methyltransferases and demethylases, respectively. The individual histone marks differ based on their association with gene-regulatory elements, their spatial location in the nucleus and their relationship with transcription. A number of studies reported that histone-modifying enzymes are involved in controlling the balance between NSC proliferation and quiescence (Jiang & Hsieh, 2014; Ma et al., 2014; Rhodes et al., 2016), and a few recent studies also suggested their potential involvement in NSC aging.

Recent single-cell RNA sequencing data indicated that histone lysine demethylases, specifically *Kdm1b*, *Kdm2a*, *Kdm4a*, and *Kdm5d*, are expressed at lower levels in NSCs from the hippocampus of middle-aged mice compared to NSCs from young mice (Ibrayeva et al., 2021). A lower expression of several histone lysine demethylases has also been detected in aged NSCs in vitro (Bin Imtiaz et al., 2021). These results suggest altered histone methylation as a potential factor underlying increased NSC quiescence in aging. In support of that, expression of *Kdm1a* in NSCs, which together with *Kdm1b* demethylates H3K4me1/me2, has been shown to be required for NSC proliferation (Sun et al., 2010). Moreover, Maybury-Lewis and colleagues suggested that shared patterns of H3K4me3 on promoters of differentially expressed genes in proliferating and quiescent NSCs enable rapid gene switches between activated and quiescent cell stages in the young SVZ (Maybury-Lewis et al., 2021). Another study found that in vitro NPCs isolated from the aged SVZ cluster distinctly from young NPCs based on H3K4me3 intensity (Benayoun et al., 2019), further suggesting alterations in histone modifications as a contributor to the altered balance of proliferation and quiescence in aged NSCs. Since H3K4me1/2/3 have been predominantly associated with active promoters (Du et al., 2015) as well as with intragenic start sites of cryptic transcription (McCauley et al., 2021), an age-related loss of histone lysine demethylases in NSCs could result in spurious transcriptional activation and loss of regulation, but this needs to be experimentally addressed.

Multiple studies have demonstrated that histone deacetylases control NSC function (Jiang & Hsieh, 2014; Ma et al., 2014), but whether changes in histone acetylation contribute to deepened NSC quiescence during aging has not yet been investigated. In other cell types it has been shown that a reduction of histone acetylation mediates cellular quiescence (Bonitto et al., 2021). For instance, histone acetylation marks which are associated with active promoters have been reported to decrease upon quiescence entry in yeast, and this decrease was mediated by histone deacetylase complex Rpd3 and required for the initiation and maintenance of quiescence (McKnight et al., 2015). This could suggest that deepened NSC quiescence during aging might potentially involve the increased activity of histone deacetylases. In support of that, histone deacetylase *Sirt1* has been reported to mediate NSC quiescence, with *Sirt1* deletion promoting NSC proliferation (Ma et al., 2014). On the other hand, deletion of

histone deacetylase *Hdac3* reduced NSC proliferation (Jiang & Hsieh, 2014). However, in addition to its deacetylase activity, Hdac3 also has non-canonical functions in tethering LAD-overlapping heterochromatin to the nuclear lamina (Poleshko et al., 2017; Rao et al., 2019), and therefore potentially interacts with lamin B1 to promote NSC proliferation. Taken together, these previous studies suggest a likely involvement of alterations in histone acetylation and methylation and their regulating enzymes in NSC aging, but more comprehensive investigations are warranted.

4.3 | DNA methylation

DNA methylation controls the establishment of cell type-specific gene expression patterns during neurogenesis and contributes to the maintenance of NSC identities (Santiago et al., 2019; Wu et al., 2010; Zocher, Overall, Berdugo-Vega, et al., 2021). The differentiation of hippocampal NSCs is associated with dynamic DNA methylation changes which involve both hypomethylation and hypermethylation of specific genes (Zocher, Overall, Berdugo-Vega, et al., 2021). DNA methylation controls gene expression by regulating the binding of transcription factors to regulatory regions or by interacting with other epigenetic layers (Noack et al., 2022; Schübeler, 2015). Cellular DNA methylation patterns are determined by the coordinated activity of DNA methyltransferases, which catalyze the attachment of methyl groups to cytosines, and Tet enzymes, which remove methyl groups from DNA (Jeltsch & Jurkowska, 2014). The enzymes of the DNA methylation machinery control different cell stages during adult neurogenesis, including NSC maintenance, proliferation, cell fate determination, neuronal survival, and neuronal maturation (Gontier et al., 2018; Li et al., 2017; Noguchi et al., 2015; Zhang et al., 2013; Zocher, Overall, Berdugo-Vega, et al., 2021). Moreover, it is becoming increasingly clear that alterations of cellular DNA methylation patterns are hallmarks of aging, and represent accurate biomarkers of organismal age (Seale et al., 2022). Intriguingly, overexpression of enzymes of the DNA methylation machinery in the aged hippocampus promotes learning and memory in aged rodents (Gontier et al., 2018; Oliveira et al., 2012), suggesting a functional contribution of DNA methylation to brain function in old age. Moreover, cellular reprogramming of aged cells to a youthful functional state depends on the removal of DNA methylation marks in aged cells (Lu et al., 2020). Some recent studies suggest age-related alterations of the NSC methylome as a potential factor underlying the age-dependent reduction in adult neurogenesis.

Schouten and colleagues showed that aging is associated with a global loss of 5-methylcytosine in hippocampal NSCs (Schouten et al., 2020), which is consistent with the age-related hypomethylation observed in other stem cell systems (McCauley et al., 2021) and in the hippocampus (Zocher, Overall, Lesche, et al., 2021). Schouten et al. further investigated a potential link between the altered DNA methylation pattern of aged NSC, age-related increases in oscillatory plasma glucocorticoid levels and its consequences on NSC proliferation. Oscillatory treatments of NSC cultures with corticosterone decreased the expression of DNA methyltransferases, reduced global 5mC levels in NSCs and induced persistent hypomethylation and altered expression of genes involved in stem cell proliferation, such as Wnt signaling inhibitor Dkk3. Since oscillating corticosterone supplementation also affected NPC proliferation, the authors suggested the age-related DNA methylation alteration as a potential mechanism that determines NSC maintenance during aging. In other cell types, a global loss of 5-methylcytosine during aging has been associated with aberrant activation of intragenic promoters and gene expression noise (McCauley et al., 2021). While the precise function of the age-related DNA methylation alterations and the affected genes in NSCs still have to be determined, Schouten and colleagues provided evidence that the NSC methylome is affected by aging and can be dynamically altered in response to cell-extrinsic signals.

Proliferation and differentiation of NSCs are known to be controlled by active DNA demethylation (Gontier et al., 2018; Li et al., 2017; Zhang et al., 2013). Gontier et al. showed that the level of DNA demethylase *Tet2* decreases in the hippocampus during the mouse lifespan concomitantly with the reduction in numbers of proliferating cells (Gontier et al., 2018). The authors further found an age-related reduction of hydroxymethylation at neurogenesis-related genes in the hippocampus, which, due to the known function of hydroxymethylation in mediating gene activation, was likely associated with a reduced expression of those genes in the aged hippocampus. Overexpression of *Tet2* in the middle-aged hippocampus was sufficient to expand the NSC pool, increase adult neurogenesis and promote cognitive abilities of mice (Gontier et al., 2018). Although the study did not confirm that the treatment enhanced Tet2 expression and DNA hydroxymethylation in NSCs, it provided first evidence that targeting the DNA methylation machinery in the aged hippocampus can restore NSC proliferation and brain function. Since Tet enzymes are also critical for the function of mature neurons (Bayraktar & Kreutz, 2018; Li et al., 2021; Rudenko et al., 2013; Yu et al., 2015), and there is known pro-proliferative signaling from mature granule cells to hippocampal NSCs (Vicidomini et al., 2020), the role of Tet2 and age-related DNA demethylation as a cell-intrinsic driver of NSC quiescence during aging needs further investigation.

The limited number of NSCs in the hippocampus has so far hampered genome-wide DNA methylation profiling, and hence the specific genes and regulatory elements that change DNA methylation during NSC aging in the hippocampus are yet unknown. Lupo et al. performed genome-wide DNA methylation sequencing on NSC cultures that were derived from the SVZ of young and aged mice. They identified 79 hypomethylated genes and 162 hypermethylated genes in aged NSCs, and assessed the function of one such gene—*Dbx2*, which exhibited promoter hypomethylation and related transcriptional upregulation in aged NPCs (Lupo et al., 2018). *Dbx2* overexpression in young NPCs reduced proliferation, suggesting that age-related upregulation of *Dbx2* could contribute to increased NSC quiescence in aging. *Dbx2* is also upregulated in NSCs isolated from the aged hippocampus (Bin Imtiaz et al., 2021), and might hence be a common mechanism underlying NSC aging. Whether the loss of *Dbx2* promoter methylation caused transcriptional upregulation during aging, has, however, not been shown and would require site-specific manipulation of DNA methylation patterns in NSCs.

4.4 | Chromatin-modifying transcription factors

Pioneer transcription factors can bind heterochromatin regions and facilitate chromatin access to downstream transcription regulators to enable lineage-specific gene expression programs (Mayran & Drouin, 2018). Pioneer transcription factors can also recruit or block other epigenetic regulators, such as enzymes involved in the DNA and histone methylation machineries, and with that trigger long-lasting changes in the epigenetic landscape. A number of key transcription factors in NSCs act as pioneer transcription factors, including Ascl1 which has been shown to be critically involved in the age-related reduction of NSC proliferation (Harris et al., 2021). Mice with reduced Ascl1 expression in the hippocampus exhibit increased NSC quiescence and higher total numbers of NSCs, indicating reduced age-related depletion of the NSC pool (Harris et al., 2021). Ascl1 overexpression has been shown to cause wide-spread increases in chromatin accessibility at neurogenic genes (Wapinski et al., 2017). Since Ascl1 levels decrease in the NSC pool with aging (Harris et al., 2021), these data suggest a potential role of reduced chromatin accessibility at Ascl1 genomic targets as a mediator of age-related NSC quiescence. Sox2 is another key transcription factor involved in NSC proliferation that has been shown to influence the NSC epigenetic landscape (Cimadamore et al., 2013). Bertolini et al. showed that Sox2 promotes long-range chromatin interactions in NSCs to activate gene expression and promote NSC maintenance (Bertolini et al., 2019). Sox2 has also been shown to regulate gene expression through its interaction with other epigenetic regulators, including nucleoporins (Toda et al., 2017) and histone acetylases (Cimadamore et al., 2013). Together these reports suggest that the NSC transcription factor network closely interacts with epigenetic regulation to control NSC maintenance and that impairments in this interaction likely contribute to NSC aging.

The reduced expression of those chromatin-modifying transcription factors during aging could alter chromatin accessibility in NSCs. Although changes in chromatin accessibility have not yet been assessed during aging in hippocampal NSCs, Maybury-Lewis et al. found that induction of quiescence promoted chromatin compaction in NSCs which had been isolated from the SVZ and maintained in vitro (Maybury-Lewis et al., 2021). Using ATAC-sequencing they found that quiescent and proliferating NSCs differed in their chromatin accessibility particularly at active enhancers related to genes with known role in proliferation and neuronal commitment, with the majority of those sites being closed in quiescent NSCs compared to activated NSCs. Quiescent NSCs further exhibited a pronounced loss of open chromatin sites during aging, while proliferating NSCs showed only minor age-related changes in chromatin accessibility. Particularly, the genomic sites that lost accessibility in aged quiescent NSCs were enriched at distal regulatory regions related to genes involved in NSC metabolism and control of transcription. Interestingly, most of the chromatin regions that were closed in quiescent NSCs but not in proliferating NSCs from the young SVZ gained accessibility after re-entry of NSCs into proliferation, raising the possibility that quiescence-associated closed chromatin in aged NSCs might also be reversible.

5 | OPEN QUESTIONS AND FUTURE PERSPECTIVES

The studies summarized above suggested that age-related impairments in epigenetic regulation in NSCs critically contribute to their increased quiescence during aging. They further showed that epigenomes can be targeted in the aging brain to acutely increase hippocampal neurogenesis and promote learning and memory. Yet, research on the epigenetic control of NSC aging is still in its infancy and the majority of age-related epigenetic changes in NSCs and their precise mechanistic role are still unknown. In the following section, we highlight five open questions which we hope will help to direct future research in the field.

1. *What are the genome-wide, multi-layer epigenetic changes in NSCs across the lifespan and what is their functional contribution to NSC behavior?* The low numbers of NSCs in the hippocampus and their further reduction during aging represented major obstacles for epigenetic analyses, such that no genome-wide profiles of any epigenetic mark exist to date for age-related changes of hippocampal NSCs ex vivo. However, the impressive progress in sequencing technology for epigenetic research in recent years now allows the profiling of DNA methylomes, histone modifications, chromatin accessibility and transcription factor binding from the small population of NSCs in adult brains, and even enables the combined profiling of multiple epigenetic marks in single cells (Armand et al., 2021; Bartosovic et al., 2021; Kremer et al., 2022). Profiling of the different epigenetic layers (from DNA methylation to nuclear architecture) in purified NSCs at different ages across the lifespan would help to understand epigenetic aging in NSCs, as well as its temporal relationship with life-time changes in NSC proliferation. Do epigenetic changes precede age-dependent increases in NSC quiescence? How do different layers of epigenetic regulation interact to control NSC behavior? Moreover, such screening experiments should be combined with the targeted manipulation of epigenetic information in NSCs to obtain further insight into the mechanistic role of epigenetic changes in NSC aging.
2. *Does epigenetic regulation link hallmarks of NSC aging?* Other cell-intrinsic mechanisms underlying age-related declines in NSC function have been described, including impaired NSC proteostasis (Leeman et al., 2018; Vonk et al., 2020), altered NSC metabolism (Audesse & Webb, 2020; Beckervordersandforth et al., 2017; Stoll et al., 2011) and increased NSC senescence (Fatt et al., 2021; Molofsky et al., 2006), and there is suggestion that those pathways are under epigenetic regulation (Crouch et al., 2022; Lapierre et al., 2015; Wong et al., 2017). In addition to directly regulating genes involved in NSC proliferation/quiescence, age-related epigenetic alterations could therefore influence NSC function by inducing or interacting with other cell-intrinsic hallmarks of NSC aging. For instance, aged NSCs lose chromatin accessibility at regulatory regions of metabolic genes (Maybury-Lewis et al., 2021), suggesting that epigenetic dysregulation during aging could alter NSC metabolic states. Moreover, reduction of lamin B1 protein is

widely used as a senescence marker (Fatt et al., 2021; Freund et al., 2012) and could contribute to the observed age-dependent accumulation of hippocampal NSCs with senescence-like characteristics (Fatt et al., 2021). Yet, the concept of senescence during NSC aging is still under debate and requires further studies. The interaction between the different hallmarks of NSC aging and whether epigenetic regulation has a central role in driving those pathways is an exciting open research question in the field.

3. *What are the upstream factors that drive age-related epigenetic changes in NSCs?* Despite the well-established role of epigenetic aging in both dividing and non-dividing cells, the factors that lead to epigenetic alterations during aging are unclear. On the one hand, other cell-intrinsic factors have been proposed to underlie epigenetic aging, such as age-related DNA damage response pathways or a replication-dependent accumulation of epigenetic changes in stem cells (Seale et al., 2022), but evidence for this is sparse. On the other hand, epigenetic patterns are known to be highly plastic toward cell-extrinsic signaling cues, and the availability of those signals in the NSC niche might change during aging, thereby impairing NSC epigenetic regulation. Cell-extrinsic signals that are also known to influence hippocampal neurogenesis during aging include alterations in secreted signaling molecules derived from neighboring cells, other brain areas or from the systemic environment, as well as altered cellular contacts due to age-related changes in the NSC niche composition or even altered input from granule cells (for reviews see Navarro Negredo et al., 2020; Vicidomini et al., 2020). Intriguingly, the function of many epigenetic regulators is known to be dependent on metabolites to act as their substrates or cofactors, and both systemic metabolite levels as well as NSC metabolism are known to be affected by age (Brunet & Rando, 2017; Wong et al., 2017). There is even evidence that the expression of enzymes of the DNA methylation machinery in the aged hippocampus is regulated by signals coming from the blood (Gontier et al., 2018). Identifying the upstream factors that mediate age-related epigenetic changes is a promising field of study and could help to develop intervention strategies to rejuvenate epigenetic patterns in aged NSCs to promote adult neurogenesis.
4. *Do epigenetic differences contribute to functional heterogeneity of NSCs and determine their intrinsic responsiveness to external signals?* Comparing epigenetic patterns between different NSC lineages or at a single-cell level could help providing evidence for the existence of the proposed NSC subpopulations in the hippocampus (Bottes et al., 2021; Gebara et al., 2016; Jhaveri et al., 2010; Schouten et al., 2020) and identifying molecular signatures underlying their functional heterogeneity. In fact, a very recent study suggested that quiescent NSCs in the SVZ can be clearly distinguished from SVZ astrocytes based on DNA methylation patterns, while such a separation had been difficult based on gene expression patterns (Kremer et al., 2022), highlighting the remarkable cell type specificity of DNA methylation. It would be fascinating to investigate whether subtype-specific NSC epigenomes determine their intrinsic responsiveness to the activation by extrinsic cues and contribute to altered NSC subpopulation abundance during aging.
5. *What is the biological importance of NSC aging?* Lastly, the question remains whether the age-dependent reduction in adult neurogenesis represents an aging phenotype or rather a continuous, lifelong development. The phase of the strongest decline in NSC neurogenic activity falls within the first 6 months of life in rodents and with that clearly precedes organismal aging, although neurogenesis continues to decline at a protracted rate after middle-age. Some of the underlying epigenetic changes in NSCs (Bedrosian et al., 2020; Gontier et al., 2018) and the age-dependent re-organization of the hippocampal NSC niche (Cole et al., 2022) follow a similar lifespan trajectory as the decline in neurogenesis, reaching an "aged" phenotype by middle-age. It will be important in future research to detangle the relationship between organismal age and molecular regulators of NSC aging. Moreover, the contribution of the age-dependent reduction in adult neurogenesis to age-related cognitive decline should be investigated more carefully, given that hippocampal neurogenesis reaches low levels long before the onset of age-related cognitive decline (Radulescu et al., 2021). Finally, future studies should investigate more carefully whether stimulating NSC proliferation as a pro-cognitive intervention has lasting beneficial effects or rather leads to a long-term depletion and accelerated aging of the NSC pool

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CONFLICT OF INTEREST

The authors declare no competing or financial interests.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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