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Comparative analysis of neural stem cell markers and their anatomical distribution across species: a systematic review

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ABSTRACT

BACKGROUND Research on neural stem cells (NSCs) using rodents to represent NSC protein markers and their anatomical distribution in comparison to humans is still limited. To address this gap, this review aimed to identify the protein markers expressed by NSCs and compare their anatomical locations in rodents and humans.

METHODS A systematic review was performed in accordance with preferred reporting items for systematic reviews and meta-analysis guidelines. Comprehensive searches were performed in PubMed, ScienceDirect, and Nature databases for studies published between March 2023 and March 2024. Eligible studies, data extraction and synthesis focused on the type of NSC markers and the sites of detection.

RESULTS A total of 47 studies were analyzed. Frequently reported NSC markers included Nestin, glial fibrillary acidic protein (GFAP), sex determining region Y (SRY)-box transcription factor 2, SRY-box transcription factor 9, doublecortin, oligodendrocyte transcription factor 2 (Olig2), Ki-67, β-tubulin III, and S100β. In rodent, NSCs were consistently positive detected in the lateral ventricle, hippocampus, peri-infarct area, and cerebral cortex. In humans, similar patterns were observed with additional reports of NSC markers such as Ki-67, GFAP, Olig2, and Nestin may detected in peri-infarct, blood serum, and cerebrospinal fluid.

CONCLUSIONS NSC markers and anatomical distribution are similar between rodents and humans, emphasizing the validity of rodent models in neurogenesis research.

KEYWORDS biomarkers, brain, humans, neural stem cells, rodents

Stem cells (SCs) are undifferentiated cells that give rise to specialized cell types in multicellular organisms and lack the phenotypic characteristics of differentiated cells.[1] SCs have the capacity for self-renewal and proliferation, as well as the ability to differentiate into various specialized cell types.[2] This potency has been extensively studied, particularly in neurogenesis research. Among the different types of SCs, neural stem cells (NSCs) are particularly important, as they play a central role in the development of the central nervous system and contribute to neurogenesis in the adult brain.[1,3] Neurogenesis is the process by which NSCs generate new neurons and glial cells, thereby supporting brain plasticity, tissue repair, and functional recovery after injury.[4] Neurons, which are responsible for neural communication within the central and peripheral nervous systems, rely on support from astrocytes

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and oligodendrocytes, which are known as glial cells.[5,6]

These findings represent a significant breakthrough, as the discovery of NSCs challenges the old paradigm that neurons exist in fixed numbers and cannot be replaced once they die or are damaged.[7] Recent studies on adult NSCs (aNSCs) have revealed their potential to maintain tissue organization, promote neuronal regeneration, and improve cognitive function in post-ischemic stroke animal models.[4,8] Specifically, studies using adult rat cerebral ischemia models have shown that on days 3 and 10 after intravenous NSC transplantation, the expression levels of proteins such as doublecortin (DCX), glial fibrillary acidic protein (GFAP), and oligodendrocyte transcription factor 2 (Olig2) were increased in specific brain regions.[8,9] These results indicate that the anatomical localization of protein markers is equally important for interpreting NSC function and relevance, as these proteins are essential for supporting research and establishing meaningful analogies with human biology. Beyond their role in basic research, the identification of NSC protein markers also has diagnostic and therapeutic potential, as reliable markers and their anatomical locations may serve as indicators of neurogenic activity and provide targets for regenerative interventions in neurological diseases.[9] Despite these advances, the characterization of NSC markers and their anatomical locations across species, especially rodents and humans, remains incomplete. To address this issue, this systematic review aimed to identify NSC protein markers and compare their anatomical locations between rodents and humans to assess their translational relevance.

METHODS

Eligibility criteria

The articles were selected according to preferred reporting items for systematic reviews and meta-analysis guidelines.[10] The inclusion criteria were original research articles involving rodent or human subjects, studies identifying NSC markers, studies reporting the anatomical localization of these markers within the brain, articles published in English, and studies published between March 2023 and March 2024. The exclusion criteria included review articles, conference abstracts, *in vitro* studies without *in vivo* correlation, and articles lacking anatomical context.

Search strategy

Articles were searched using the PubMed, ScienceDirect, and Nature databases. The search keywords were combined using Boolean operators and included "neural stem cell" OR "protein marker." The inclusion and exclusion criteria were applied during the search.

Study selection

All retrieved records were imported into Mendeley (Elsevier, United Kingdom), and duplicates were removed. Titles and abstracts were screened independently by NH and IKL to identify potentially relevant studies. Full-text articles were then evaluated and analyzed according to the eligibility criteria.

Data collection and extraction

Information from the included studies was systematically extracted in accordance with the study objectives. Data extraction was performed independently by NH and IKL to ensure accuracy. The key data components included specific protein markers and their positive staining locations, which were categorized according to rodent species and developmental stage (prenatal and postnatal). For human studies, the extracted data included specific protein markers, subject age, sex, disease status, and analyzed specimens. In addition, NSC-related findings were identified and compared across different stages of the rodent neurogenesis timeline. Positive staining results were interpreted as reported in each study, such as brown staining observed in the cell membrane or nucleus in immunohistochemistry analysis or fluorescent signals detected in fluorescence-based analysis. The findings were then comparatively analyzed between rodents and humans to identify conserved and divergent patterns of NSC protein expression and anatomical localization. To ensure clarity and facilitate interpretation, all data were organized into comparative tables, enabling direct synthesis of similarities and differences between rodent and human studies.

Statistical analysis

In this systematic review, narrative and descriptive approaches were used to summarize the included study

Table 1. Summary of included studies on neural stem cell markers in rodents and humans

First author, year	Subject	Brain region	Marker(s)	Detection method	Research findings	Article quality after JBI assessment
Imai,[11] 2023	Mice	Whole brain	NeuN, GFAP, Olig2, and Nestin	IHC	NeuN$^+$ and STEM121$^+$ NS/PCs observed around injured sites indicating neuroprotective effects.	High
Heo,[14] 2024	Mice	Cerebral cortex	GFAP, Tuj1, and Nestin	IF	NGV unit formation showed astrocyte and neuron marker co-expression	High
Chang,[16] 2023	Rat	Hippocampus	Nestin, Ki-67, and β-tubulin III	IHC	Subchronic propofol exposure decreased Nestin$^+$ and Ki-67$^+$ NSCs, indicating neurogenesis suppression	High
Engert,[17] 2024	Rat	Thalamus	Nestin, DCX, SOX2, β-tubulin III, GFAP, and MBP	IHC	Adult medial geniculate body retained neurogenic potential; Nestin$^+$/DCX$^+$ cells indicated persistent NSC activity	High
Pastor-Alonso,[18] 2024	Mice	SGZ	Ki-67, DCX, and GFAP	IHC	Ki-67 and DCX expression identified proliferating type-2b NSCs and astrocytes in postnatal SGZ	High
Williamson,[21] 2023	Mice	SVZ/peri-infarct cortex	SOX2 and S100β	IHC	SVZ cytogenesis supported neural repair via activation of CXCR4$^+$ and SOX2$^+$ NSCs in infarcted regions	High
Attaluri,[24] 2023	Mice	Hypothalamic parenchyma and SVZ of lateral ventricle	GFAP	IHC	Extracellular vesicles reduced apoptosis and restored GFAP expression in AD brains	High
Tan,[26] 2023	Rat	*In vitro* (primary NSC)	Nestin, GFAP, β-tubulin III, and Ki-67	IHC	Leptin enhanced NSC proliferation and Nestin$^+$ expression in cultured primary cells	High
Mendonça,[27] 2024	Mice	Brain section	MAP2 and GFAP	IHC	MAP2 and GFAP corelated in neural maintenance for 6 months *in vivo*	High
Gao,[28] 2024	Mice	SVZ	GFAP and S100β	IHC	DDAH1 regulated GFAP$^+$ astrocyte and S100β$^+$ cell activation after ischemic stroke	High
Yeo,[29] 2023	Mice	SVZ	GFAP, S100β, Ki-67, and DCX	IF/IHC	Aging reduced NSC adhesion and proliferation; GFAP$^+$ astrocytes and Ki-67$^+$ progenitors declined in aged SVZ	High
Xu,[30] 2024	Mice	SGZ	Nestin, Tuj1, GFAP, and Olig2	IHC	Mysm1 regulated Id4-dependent proliferation and differentiation of NSCs in the SGZ with cell positive stainig in Tuj1$^+$, Nestin$^+$, GFAP$^+$, and Olig$^+$	High
Dietert,[32] 2023	Mice	SVZ	Nestin and LRP1	Migration assay	Nestin-driven LRP1 knockout reduced CXCR4 expression and impaired NSC migration post-stroke	High
Amodeo,[35] 2023	Mice	SVZ	GFAP, SOX2, and Nestin	IHC	p53 maintained NSC identity while GFAP and SOX2 co-expressed in SVZ astroglial cells	High
Ma,[36] 2024	Mice	Striatum	β-tubulin III, DCX, S100β, GFP, and GFAP	IHC	Mild hypothermia (35°C) promoted neuronal differentiation with ~45% of hNSCs expressing β-tubulin III and DCX	High
Zhang,[37] 2024	Mice	SGZ/ hippocampus	Nestin, Ki-67, and Tuj1	IHC	Circadian factors modulated Nestin$^+$ NSC proliferation and Tuj1$^+$ neuron differentiation	High

Table continued on next page

Table 1. (Continued)

First author, year	Subject	Brain region	Marker(s)	Detection method	Research findings	Article quality after JBI assessment
Chen,[38] 2023	Mice	Hippocampus	GFAP, Olig2, and IGF-1	IHC	GFAP, Olig2, and IGF-I of NSCs reduced Aβ deposition and improved spatial memory in 5XFAD mice	High
Zhang,[45] 2023	Mice	Cerebral cortex	SOX2, Ki-67, and MAP2	IHC	NSC-derived exosomes enhanced neurogenesis and reduced infarct volume post-stroke	High
Guan,[46] 2024	Mice	Cortex and cerebrum	MAP2, SA-β-Gal, SOX2, Ki-67, and Olig2	IHC/SA-β-Gal assay	Oxidized SOD1 accelerated cellular senescence and reduced SOX2$^+$ NSC population	High
Gonzalez,[48] 2023	Mouse/ rat	SEZ	CDK6 and CDK2	WB/IF	RingoA/Spy1 regulated CDK-mediated cell-cycle progression of NSCs	High
Amirbekyan,[51] 2023	Rat	Cerebrum	GFAP, Tuj1, and NeuN	IHC	Intranasally delivered L-myc immortalized hNSCs improved cortical recovery and neuronal survival after CCI injury	High
Zhang,[55] 2023	Mice	Embryonic brain	SOX2 and Nestin	IHC	BCAT1 regulated proliferation and migration of eNSCs which expressed protein SOX2 and Nestin	High
Liu,[56] 2023	Mouse and Human	Mouse section/ human fetal brain	GFAP and Olig2	IHC	Purified human NSCs expressed GFAP, Olig2, and EGFR, confirming lineage-specific differentiation potential	High
Tang,[57] 2023	Mice	SVZ	Ki-67, Nestin, and GFP	IHC	Marker for endogenous NSC in ipsilateral of stroke area was significantly increased compared to contralateral area	High
Imitola,[12] 2023	Mice	SVZ (lateral wall)	SOX2 and Nestin	IHC	STAT1 depletion increased Nestin$^+$ NSCs in the adult SVZ	Moderate
Fukuda,[13] 2024	Mice	SVZ	DCX, Nestin, and GFAP	IHC	HDAC8 inhibition suppressed Nestin$^+$ NSC proliferation and altered GFAP expression	Moderate
Zhang,[15] 2024	Mice	DG	GFAP, S100β, and Nestin	IHC	S100β$^+$ astrocytes and Nestin$^+$ NSCs indicated lysosomal protein turnover after fertilized cell injection	Moderate
Luan,[19] 2023	Mice	SGZ	Ki-67, SOX2, and DCX	IHC	CCN3/Nov signaling enhanced proliferation of immature neurons in the SGZ	Moderate
Hirano,[20] 2023	Mice	Peri-ischemic area	Nestin and Iba-1	IHC	Microglia negatively regulated NSC proliferation; Iba-1$^+$ cell area increased in peri-ischemic tissue	Moderate
Huang,[22] 2023	Rat	Substantia nigra	NSE and GFAP	IHC	GFAP and NSE expression marked glial activation following NSC transplantation	Moderate
Rieskamp,[23] 2023	Mice	DG	GFAP and GFP	IHC/ fluorescence	Excitatory AAT1 supported GFAP$^+$ astrocyte maintenance in DG region	Moderate
Yale,[25] 2023	Mice	Dorsal forebrain, DG, and hippocampus	GFAP, Ki-67, and Olig2	IHC	GFAP$^+$ and Ki-67$^+$ cells indicated active neurogenesis during embryonic development	Moderate
Duan,[31] 2024	Mice	Embryonic cortex	GFAP	IF	GFAP associated with astroglial differentiation	Moderate
Ban,[34] 2023	Mouse/ rats	SVZ and OB	SOX9 and GFAP	IHC	SOX9 regulated NSC proliferation and GFAP$^+$ astrocytes in the OB	Moderate

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Table 1. (Continued)

First author, year	Subject	Brain region	Marker(s)	Detection method	Research findings	Article quality after JBI assessment
Ayyubova,[39] 2023	Rat	SGZ-GCL	NeuN, Iba-1, and GFAP	IHC	Peripheral inflammation reduced $BrdU^+$ NSCs and altered $GFAP^+$ astrocyte structure in the SGZ	Moderate
Gabarró-Solanas,[43] 2023	Mice	SGZ	DCX and NeuN	IF	Intermittent fasting did not significantly alter NSC number or neurogenesis rate	Moderate
Barón-Mendoza,[44] 2024	Mice	Dorsal DG	DCX	IHC	Altered hippocampal neurogenesis and reduced DCX^+ immature neurons observed in autism-related variants	Moderate
Kyung,[47] 2023	Rat	Whole brain	Nestin and Ki-67	IHC	Repeated human cell injections increased $Nestin^+$/$Ki\text{-}67^+$ NSC populations in aged brains	Moderate
Han,[49] 2023	Mice	Hippocampus	MAP2	IHC	Dying transplanted NSCs mediated neuroprotection through bystander $MAP2^+$ neuron survival effects	Moderate
Zhou,[50] 2024	Rats	OB	MAP2, GFAP, and Ki-67	IHC	Olfactory stimulation enhanced $MAP2^+$ neuron maturation and GFAP astrocyte activation after SAH	Moderate
Mosini,[40] 2023	Rat	Cerebellum/ SVZ	GFAP	Gene expression/ IHC	Temporal patterns of Fos and Jun genes showed age-related variation in GFAP expression	Low
Liu,[41] 2023	Human	CSF	GFAP	ELISA	CSF GFAP was a predictive biomarker for neurodegeneration severity and clinical outcome	High
Genchi,[52] 2023	Human	Plasma/CSF	Tau, NfL, UCH-L1, and GFAP	Digital immunoassay	Intrathecal transplantation of hfNPCs was safe and reduced GFAP and NfL biomarkers, suggesting neuroprotection	High
Baig,[53] 2024	Human	SVZ	Olig2, SOX9, and GFAP	IHC/proteomic	Multipotent NSC-like cells in adult human SVZ expressing EGFR/VIM with glial and endothelial markers.	High
van Dam,[54] 2023	Human patients	Blood (CSF & serum)	GFAP and sNfL	ELISA	Elevated GFAP and sNfL correlated with cognitive impairment in MS patients	High
Leone,[33] 2023	Human	Serum and CSF	GFAP	ELISA	GFAP and neurofilament increased after ICV administration, indicating axonal response	Moderate
Lv,[42] 2023	Human patients	Whole brain and plasma of the blood	GFAP and sNfL	ELISA, immunoassay, and MRI	Intranasal allogeneic NSC therapy showed safety and reduced GFAP plasma levels	Moderate

Aβ=amyloid-beta; AAT1=amino acid transporter 1; AD=Alzheimer's disease; BCAT1=branched-chain amino transferase 1; BrdU=bromodeoxyuridine; CCI=controlled cortical impact; CCN3=cellular communication network protein 3; CDK=cyclin-dependent kinase; CSF=cerebrospinal fluid; CXCR4=C-X-C chemokine receptor type 4; DCX=doublecortin; DDAH1=dimethlarginine dimethylaminohydrolase 1; DG=dentate gyrus; EGFR=epidermal growth factor receptor; ELISA=enzyme-linked immunosorbent assay; eNSC=embryonic neural stem cell; GCL=granular cell layer; GFAP=glial fibrillary acidic protein; GFP=green fluorescent protein; HDAC8=histon deacetylase 8; hfNPC=human factor neural progenitor cell; hNSC=human neural stem cell; Iba-1=ionized calcium-binding adaptor molecule 1; ICV=intracerebroventricular; Id4=inhibitor of DNA binding 4; IF=immunofluorescence; IGF1=insulin-like growth factor-I; IHC=immunohistochemistry; JBI=Joanna Briggs Institute; LRP1=low-density lipoprotein receptor related protein 1; MAP2=microtubule-associated protein 2; MBP=myelin basic protein; MRI=magnetic resonance imaging; MS=multiple sclerosis; Mysm1=Myb-like, SWIRM, and MPN domain-containing protein 1; NeuN=neuron-specific nuclear; NfL=neurofilament light; NGV=neuro-glia-vascular; NOV=nephroblastoma overexpressed; NS/PC=neural stem/progenitor cell; NSC=neural stem cell; NSE=neuron-specific enolase; OB=olfactory bulb; Olig2=oligodendrocyte transcription factor 2; S100β=S100 calcium binding protein β; SA-β-Gal=senescence-associated β-galactosidase; SAH=subarachnoid hemorrhage; SEZ=subependymal zone; SGZ=subgranular zone; sNfL=serum neurofilament light chain; SOD1=superoxide dismutase 1; SOX=sex determining region Y-box transcription factor 2; STAT=signal transducer and activator of transcription; SVZ=subventricular zone; UCH-L1=ubiquitin carboxy-terminal hydrolase L1; VIM=vimentin; WB=western blot

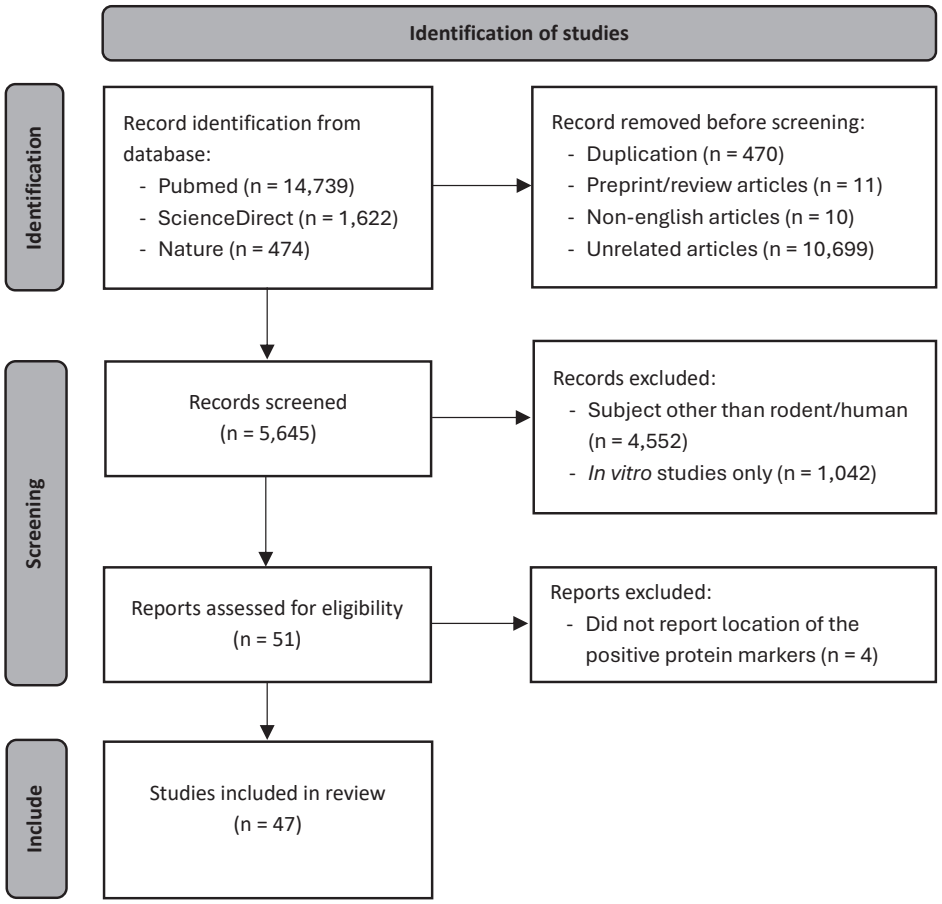


Figure 1. Flow diagram of the systematic review search according to the preferred reporting items for systematic reviews and meta-analyse (PRISMA) guideline

characteristics, specific data from each study, positive protein markers, and anatomical locations. Due to heterogeneity in methodology, sample characteristics, and outcome measures among the included studies, statistical analysis could not be performed.

Quality assessment

The methodological quality of the included studies was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Quasi-Experimental Studies, which consists of nine domains. Each domain was assessed as yes, no, unclear, or not applicable. The evaluation covered study design, sample representativeness, detection methods, and reporting clarity. Each study was classified as having a low, moderate, or high risk of bias based on the proportion of criteria fulfilled in the JBI critical appraisal checklist (Table 1).[11–57] Studies meeting 81–100% of applicable items were categorized as having a low risk of bias, those meeting 51–80% as having a moderate risk of bias, and those meeting less than 50% as having a high risk of bias, following the previously published criteria of Barghouthi et al.[58]

RESULTS

The literature search initially yielded 16,835 publications. After applying the inclusion and exclusion criteria, eventually we analyzed 47 articles in these systematic reviews (Figure 1); 41 focused on rodents, while 6 focused on human subjects. Specific protein markers and their anatomical locations of positive staining are shown in Table 2. In human studies, the extracted information included protein markers, participant characteristics, and specimen type (Table 3). In rodent studies, the extracted information was categorized according to developmental stage (prenatal and postnatal) to compare patterns of marker expression across studies (Table 4, Figure 2).

DISCUSSION

In this systematic review, 41 articles specifically focused on NSC protein markers and their anatomical locations in rodent brains were identified. Among these studies, multiple protein markers were

Table 2. Protein marker for NSC

Protein marker	Description	Location	Reference
Nestin	Expressed in NSCs/progenitor cells and given rise to both neuron and glia	SVZ	11–14
		SGZ of hippocampus	15–19
		Ischemic area post-stroke	20, 21
		Striatum and substantia nigra	22
GFAP	Expressed by NSC during differentiation into astrocytes	Hypothalamic parenchyma	24
		DG and hippocampus	15, 17, 24, 25
		Cerebral cortex	25, 26
		SVZ of lateral ventricle	14, 24, 27–35
		SGZ of hippocampus	13, 17, 18, 36–39
		Peri-infact cortex	21
		Cerebellum	40
Olig2	Oligodendrocyte marker	DG of hippocampus	25, 38
		Cerebrum	19, 41–46
		SVZ	12, 13, 35
		Cerebral cortex	41
DCX	Neuroblast cells marker protein which migrates for maturation	SGZ of hippocampus	15, 17–19, 43, 44
		Corpus callosum	33
		SVZ	13, 29
SOX2	Marker activated quiscence NSC	SVZ	12, 35
		SGZ of hippocampus	15, 17, 19
		Cerebral cortex	21, 45, 46
SOX9	Expression localized of NSC proliferation	SVZ and bulbus olfactorius	12
Ki-67	Identify the proliferation of NSC	SGZ of hippocampus	15, 16, 18, 19, 37
		SVZ	29
		Cerebral cortex	25, 26, 45–47
		SEZ	48
		Peri-infact cortex	21
β-tubulin III (Tuj1)	Expressed by neurons in the early developmental stages, indicates the pre-neural fate of the cells	Hippocampus	16, 36, 49
		SGZ of hippocampus	17, 30, 31
S100β protein	Marker of Bergmann glia in the cerebellum, maintaining proliferation potential of RG cell	DG	15, 28, 36
MAP2	Expressed by dendrit neuron while in differentiation stage	Hippocampus	49, 50
		Cerebral cortex	45, 46
NSE	Marker of neurons	Striatum and substantia nigra	22
NeuN	Marker of adult neuron	SGZ of hippocampus	11, 39, 43, 51

DCX=doublecortin; DG=dentate gyrus; GFAP=glial fibrillary acidic protein; MAP2=microtubule-associated protein 2; NeuN=neuron-specific nuclear; NSC=neural stem cell; NSE=neuron-specific enolase; Olig2=oligodendrocyte transcription factor 2; RG=radial glial; S100β=S100 calcium binding protein β; SEZ=subependymal zone; SGZ=subgranular zone; SOX=sex determining region Y-box transcription factor; SVZ=subventricular zone

consistently detected, and their distribution is summarized in Tables 2 and 4. The proteins identified in this review included those expressed from the embryonic stage to adulthood, and differences in protein marker expression are mapped in Figure 2. Briefly, embryonic NSC (eNSC) markers included GFAP, Nestin, microtubule-associated protein 2 (MAP2), Ki-67, β-tubulin III (Tuj1), and neuron-specific enolase (NSE). aNSC markers included GFAP, Nestin, S100 calcium binding protein β, Ki-67, DCX, sex determining region

Table 3. Protein marker identified in humans

Protein marker	Patient age (years), mean (SD)/range (min–max)	Sex	Patient's disease	Specimen analyzed	Reference
GFAP	60.85 (9.78)	Male and Female	*De novo* PD	CSF	41
	44–50	Female	Secondary progressive MS	Plasma/blood serum	52
	38–72	Male and Female	Normal MRI	Lateral ventricular walls of the human brain	53
GFAP, Ki-67, and β-tubulin III (Tuj1)	38–57	Male and Female	Progressive MS	Microsectioned of brain thickness 15–20 µm	33
GFAP and sNFL	48 (11)	Female	MS	Blood of venipuncture & CSF	54
Olig2 and β-tubulin III (Tuj1)	3–12	Male and Female	Moderate to severe spastic cerebral palsy	Blood serum	42

CSF=cerebrospinal fluid; GFAP=glial fibrillary acidic protein; MRI=magnetic resonance imaging; MS=multiple sclerosis; PD=Parkinson's disease; SD=standard deviation; sNfL=serum neurofilament light chain; Olig2=oligodendrocyte transcription factor 2

Table 4. NSC during the lifetime of the rats

Stages	Description	NSC formation and differentiation	Positive staining	Age	Reference
Prenatal					
Early embryonic/ expansion phase	Symmetric cell division in the embryonic neural tube	NEC/matrix cell (columnar shape)	MAP2 and GFAP	E10.5–E12.5	25
Neurogenic phase	Asymmetric cell division, NSC begin to generate RG and 1 neuron or RG and 1 IP in germinal VZ	RG; soma at the VZ, while radial fiber out of the neural tube to the pial surface	SOX2 and Nestin	E13.5	55
			MAP2, SOX2, Ki-67, and Nestin	E14–E17	22, 26, 31, 46
			β-tubulin III+ (Tuj1)	E16	25
Gliogenic phase	NSCs produce RGPs, which proliferate dominantly in a SVZ	- RG differentiate: ependymal cells (forming internal lining) - Neurons migrate along a radial filament to cortical layer II–V	Nestin, NSE, and GFAP	E17.5	22
Postnatal					
Neonatal/PND	Brain growth spurt and NSC differentiation	Type B cells as NSCs	GFAP, Nestin, and S100β	P0–P14	15, 17–19, 30, 41, 49
	NSC divide asymmetrically	Generating IPCs (type C cells)	Ki-67		15
Adult brain	Migration along the RMS	C cells produce A cells (neuroblast)	DCX and SOX2	P14–P20	43
	Maturation in OB	Mature cells	NeuN and Olig2	>P20	11, 39, 43, 51

DCX=doublecortin; E=embryonic day; GFAP=glial fibrillary acidic protein; IP=intermediate progenitor; IPC=intermediate progenitor cells; MAP2=microtubule-associated protein 2; NEC=neuroepithelial stem cells; NSC=neural stem cell; NSE=neuron-specific enolase; OB=olfactory bulb; Olig2=oligodendrocyte transcription factor 2; P=postnatal day; PND=postnatal day; RG=radial glial; RGP=radial glial progenitor cell; RMS=rostral migratory stream; S100β=S100 calcium binding protein β; SOX=sex determining region Y-box transcription factor; SVZ=subventricular zone; VZ=ventricular zone

Y-box transcription factor 2 (SOX2), neuron-specific nuclear (NeuN), and Olig2. Based on these data, GFAP and Nestin were consistently expressed from the embryonic to adult stages. Meanwhile, some markers, such as SOX2 and Ki-67, showed reduced expression during development but reappeared in adulthood. These patterns of expression across developmental stages are important for understanding the molecular dynamics of NSCs and validating rodent models in translational research. Therefore, the systematic

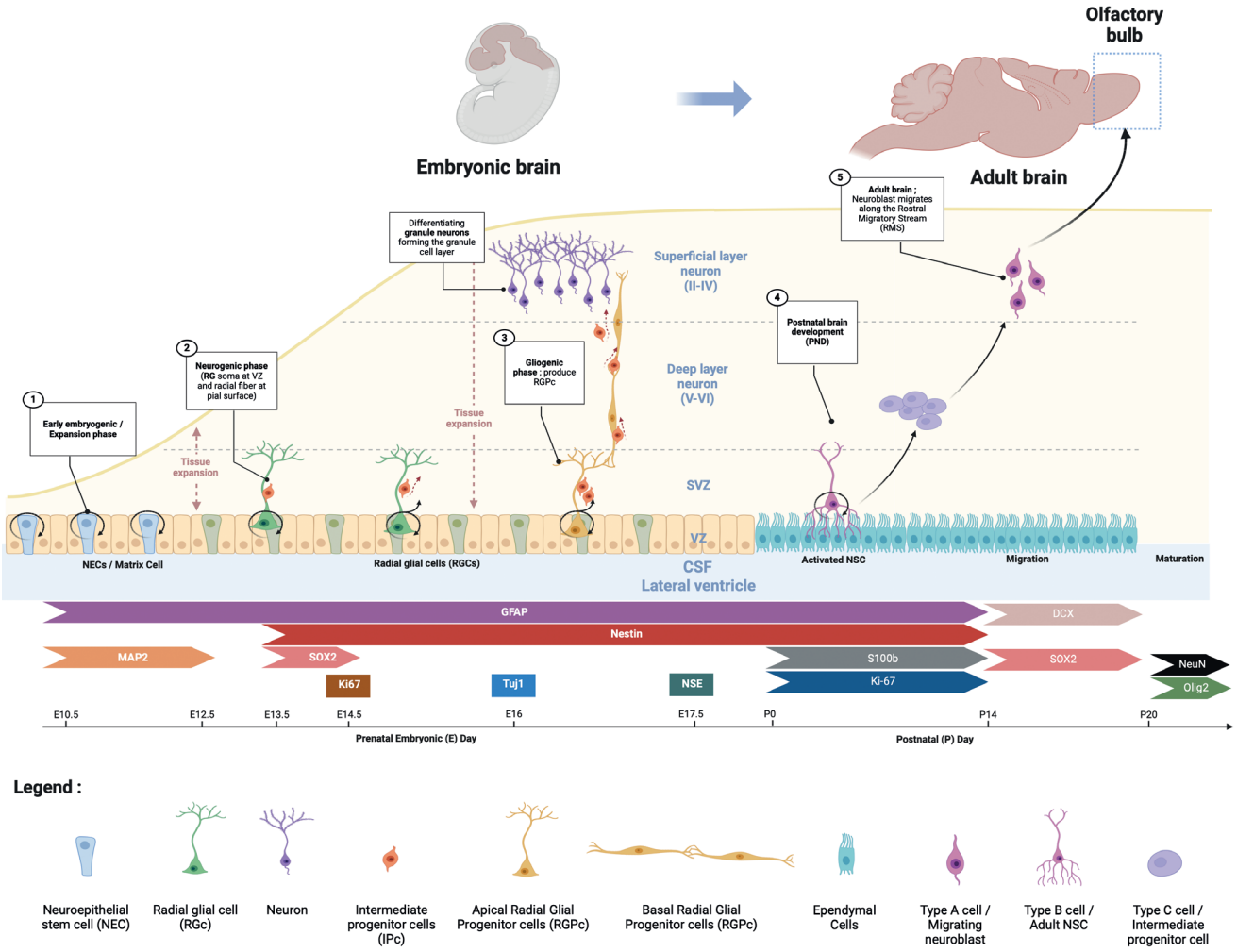


Figure 2. Stages of neurogenesis from embryonic until postnatal in the lateral ventricle of rodent brain with their protein expression (created with BioRender.com)

identification and mapping of these protein markers are important for facilitating translational research and supporting their potential application in diagnosis and therapy. Rodents, especially rats and mice, are the primary models for such identification and mapping, as their neurogenic niches and molecular markers show close parallels with those observed in humans.[6,59] Rodents are mammals classified under the order Rodentia and are characterized by prominent incisors. This group includes rats, mice, guinea pigs, hamsters, and squirrels.[59] Analysis of NSCs using rat models can provide valuable insights into their anatomical locations and the protein markers they express.[60]

Studies of eNSCs in rat and mouse models have revealed their critical role in early brain development (Table 4). During the prenatal stages of rat brain development, NSCs undergo distinct phases characterized by specific patterns of division, differentiation, and protein marker expression.[61] In the early embryonic expansion phase, symmetrical cell division occurs in the embryonic neural tube, producing neuroepithelial cells. These cells were detected by positive staining for MAP2 and GFAP, typically around embryonic days (E) 10.5 to E12.5.[25] Development then progresses to the neurogenic phase, during which NSCs shift to asymmetric cell division and generate radial glial (RG) cells and intermediate progenitors (IPs) within the ventricular zone (VZ) of the lateral ventricle.[55,61] These cells begin extending radial fibers to the pial surface and initiating neurogenesis. Positive markers expressed during this phase include SOX2 and Nestin as early activation markers, followed by MAP2, Ki-67, and β-tubulin III (Tuj1) as neural fate and proliferative markers. Early activation of eNSCs occurs through various pathways, including the Notch signaling pathway.[19] In mice, Notch

signaling involves cell-surface Notch receptors 1–4, which are non-covalently coupled transmembrane protein heterodimers. These receptors interact with nuclear mediators of Notch signaling bound by the silencing mediator for retinoid and thyroid hormone receptors and histone deacetylases, resulting in signal recombination that triggers SOX2 protein expression.[60] SOX2 is self-regulated and ultimately activates the Wnt signaling pathway, which can govern niche-induced neuronal fate and proliferation of type 3 cells (neuroblasts).[50,60] Based on its anatomical distribution, SOX2 has been positively detected in the VZ of embryos at E13.5.[55] After activation, NSCs enter the gliogenic phase at E17.5, during which they differentiate into radial glial progenitors and ependymal cells that form the ventricular lining in the subventricular zone (SVZ).[22] At this stage, neurons migrate along radial filaments toward cortical layers II–V and express Nestin, GFAP,[24] and NSE in the germinal zone of the SVZ.[5,22] During early development in rats and mice, the SVZ serves as a neurogenic niche containing a population of RG cells that divide to generate new neurons.[53]

Whereas eNSCs play a crucial role in early brain development, aNSCs are essential for maintaining neurogenesis and supporting brain plasticity throughout life.[62] In the adult brain, aNSCs are detected in several locations, including the SVZ, subependymal zone (SEZ), and dentate gyrus (DG).[11–13] NSCs in the SEZ contribute to the formation of transit-amplifying neural progenitor cells (NPCs), which proliferate and differentiate into interneurons in the olfactory bulb (OB), thereby contributing to olfactory circuits. Ki-67 has been detected in this region.[48] Neurogenesis in the SVZ occurs in several stages. In the first stage, NSCs (type 1 cells) form IPs (type 2a cells) by expressing Nestin and GFAP. Subsequently, transcription factors transform type 2a cells into type 2b cells, resulting in migratory neuroblasts (type 3 cells) that express Ki-67 and DCX.[60,63] Neuroblasts then migrate through the rostral migratory stream to the OB, where they mature and express the positive marker NeuN.[63] During this neurogenic process, several biomarkers are expressed, including GFAP,[14,29,32] Nestin,[11–14] Olig2,[11,46] and SOX9.[12] Imitola et al[12] analyzed NSCs using the protein markers Nestin and SOX2 and found significant positive results in the adult SVZ ($p<0.008$). MAP2 and SOX2 are typically identified during the early stages of NSC differentiation (Figure 2).[21,45,64] Under pathological conditions, such as ischemic stroke and brain trauma, NSC-mediated neuronal regeneration in the SVZ is activated.[21,37,65] This is supported by previous studies detecting positive Nestin expression in ischemic areas of the rat brain on days 3 or 7 post-stroke ($p<0.05$).[20]

Neurogenesis in aNSCs occurs not only in the SVZ but also in the DG of the hippocampus. This is consistent with previous research showing that aNSCs in the hippocampus of transgenic mice were localized in the subgranular zone (SGZ) and expressed 34% Ki-67-positive cells, indicating a proliferative stage, although this finding was not statistically significant ($p = 0.9165$).[43] In addition, the SGZ expressed GFAP and Nestin in rats subjected to interventions such as intermittent fasting[43] and intracerebral hemorrhage (ICH).[37] According to Zhang,[37] most ICH events occur in the basal ganglia, located distal to the hippocampus, which activates normally quiescent NSCs in this region, also referred to as the peri-infarct area.

The presence of NSCs in the adult human brain remains a major topic of debate among scientists.[53] During development, the formation of neurogenic niches in the human brain parallels that in rats, in which RG cells function as NSCs, self-renew, and generate progenitors that give rise to three main neural cell lineages: neurons, oligodendrocytes, and astrocytes.[56] Baig et al[53] isolated NSCs from human brain tissue with normal magnetic resonance imaging findings and found that the cell-type-specific protein marker GFAP was localized in the SVZ. Transcriptomic and biological analyses identified four main NSC populations, including adult RG1, adult RG2, oligodendrocyte progenitor NSCs, and neuronal progenitor NSCs, which were marked by GFAP, SOX9, and Olig2.[53] The results from this therapy demonstrated increased GFAP expression from 11% to 25% ($p = 0.05$) over 2 years,[33,52] an increase in Ki-67 from 3.3% to 6.1%, although this change was not statistically significant ($p>0.05$), and a slight but statistically significant increase in β-tubulin III from 9.2% to 9.4% ($p<0.05$).[33] In blood serum analysis, the presence of NSCs was indicated by positive GFAP, Olig2, and β-tubulin III (Tuj1), which contributed to clinical improvement in patients with cerebral palsy. This improvement was evidenced by an increase of more than 11 points in activities of daily living scores, an improvement of almost 7 points in standing ability, and an increase of more than 7 points in walking, running, and jumping ability.[42]

Another study used cerebrospinal fluid (CSF) to examine NSCs in patients with Parkinson's disease

(PD), focusing on the protein marker GFAP. This study revealed that GFAP concentrations in CSF samples from male subjects were higher than those in female subjects ($p = 0.025$).[41] In the adult brain, increased GFAP expression is associated with neurogenesis in response to pathological conditions.[56] This is supported by the findings of Liu et al,[41] who demonstrated that astrocyte activation increases in PD, as indicated by an increase in GFAP-positive areas.

The limitations of this study include the predominance of rodent studies over human studies and methodological heterogeneity across the included articles. Protein marker expression also varied according to developmental stage, and not all studies distinguished between eNSCs and aNSCs. These factors should be considered when interpreting the findings and their translational relevance.

Neurogenesis research is widely conducted using animal models, such as rats and mice, due to their potential to represent aspects of human biology. Studies of NSCs in rat models have shown that NSC activation initiates the production of specific proteins that serve as markers, which this review shows are similar to those found in humans. These markers are associated with cell proliferation and neural development and include GFAP, Ki-67, β-tubulin III (Tuj1), and Olig2. In rats, these markers were positively detected in the lateral ventricle, hippocampus, cerebral cortex, and peri-infarct area. In humans, they were detected in the peri-infarct area, lateral ventricle, CSF, and blood serum. This review highlights fundamental similarities in NSC characteristics and behavior across species, which are critical for bridging the translational gap between rat models and humans. The similarities in protein marker expression and anatomical localization between rats and humans provide a strong basis for future investigations into their therapeutic potential for neurodegenerative diseases and brain injuries, thereby reinforcing the validity of rodents as models in translational neuroscience.

Conflict of Interest

This study affirm no conflict of interest in this study.

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