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Transgenic mouse models for studying adult neurogenesis

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Abstract

The mammalian hippocampus shows a remarkable capacity for continued neurogenesis throughout life. Newborn neurons, generated by the radial neural stem cells (NSCs), are important for learning and memory as well as mood control. During aging, the number and responses of NSCs to neurogenic stimuli diminish, leading to decreased neurogenesis and age-associated cognitive decline and psychiatric disorders. Thus, adult hippocampal neurogenesis has garnered significant interest because targeting it could be a novel potential therapeutic strategy for these disorders. However, if we are to use neurogenesis to halt or reverse hippocampal-related pathology, we need to understand better the core molecular machinery that governs NSC and their progeny. In this review, we summarize a wide variety of mouse models used in adult neurogenesis field, present their advantages and disadvantages based on specificity and efficiency of labeling of different cell types, and review their contribution to our understanding of the biology and the heterogeneity of different cell types found in adult neurogenic niches.

Keywords

adult neurogenesis; mouse models; neural stem cells; neuroprogenitors; lineage tracing

In the adult mammalian brain, two regions, the subgranular zone of the dentate gyrus of hippocampus (SGZ) and the subventricular zone (SVZ), harbor stem/progenitor cells that give rise to newborn neurons and astrocytes throughout life (Altman, 1962; Eriksson et al., 1998; Ming and Song, 2011; Morshead et al., 1994; Palmer et al., 1997; Spalding et al., 2013). The neuroprogenitor cells from the SVZ give rise to GABAergic interneurons of the olfactory bulb, responsible for odor discrimination and mating behavior (Doetsch et al.,

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Conflict of interest

Fatih Semerci and Mirjana Maletić-Savatić declare no conflicts of interest.

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1997, 1999; Gheusi et al., 2000; Mak et al., 2007; Mouret et al., 2009; Sakamoto et al., 2014). The neuroprogenitor cells from the SGZ give rise to glutamatergic granule cells, associated with hippocampal-dependent spatial learning and memory (Clelland et al., 2009; Deng et al., 2009; Farioli-Vecchioli et al., 2008; Imayoshi et al., 2008; Kitamura et al., 2009; Saxe et al., 2006; Shors et al., 2002; Zhang et al., 2008), mood control (Encinas et al., 2006; Jacobs et al., 2000; Malberg et al., 2000; Santarelli et al., 2003; Snyder et al., 2011), pattern separation (Aimone et al., 2011; Pan et al., 2012; Sahay and Hen, 2008; Sahay et al., 2011; Wojtowicz et al., 2008; Zhao et al., 2008), and stress response (Heine et al., 2005; Joels et al., 2007; Lucassen et al., 2015; Snyder et al., 2011; Surget et al., 2011). Adult neurogenesis is very-well established in the human hippocampus as well (Djuric et al., 2008; Eriksson et al., 1998; Manganas et al., 2007; Pereira et al., 2007; Quinones-Hinojosa et al., 2006; Sierra et al., 2011; Spalding et al., 2013), thus sparking interests with regards to the potential of utilizing adult neurogenesis for regenerative medicine and treatment of neuropsychiatric disorders (David et al., 2010; Mainen et al., 1999; Manganas and Maletic-Savatic, 2005; Abiega et al, 2016). If adult neurogenesis is to be used as a therapeutic modality for brain repair, it is very important to understand the unique properties of individual cell types that are responsible for this phenomenon. However, the ever-proliferating and differentiating spectrum of cells in both adult neurogenic niches poses a great challenge to study adult neurogenesis one cell type at a time.

Classification of different cell types in both adult neurogenic niches, from primary stem cells to their end-progeny, is hard. More and more it has become evident that these cells are heterogeneous populations with different lifespans, lineage plasticity and regenerative potential, that all depend on age (Alvarez-Buylla et al., 2008; Bonaguidi et al., 2012; Bond et al., 2015; Chojnacki et al., 2009; Giachino and Taylor, 2014). Criteria used to classify different cell types in both adult neurogenic niches depend not only on marker combinations but also on morphology of the cells. Although there is a consensus for establishing the main cell types of the adult neurogenic niches (Figures 1, 2), consensus for defining the neural stem/progenitor subtypes, lineages and some of their properties (self-renewal, cell cycle, quiescence) is still far away. Although experimental differences (e.g. timing and dose of tamoxifen, different cell cycle indicators, etc.) may account for some of the discrepancy, transgenic mouse lines are the primary suspect accounting for most of the observed differences: lineage tracing mouse models generated based on the same gene but utilizing different regulatory regions produce different experimental outcomes. A striking example is *Nestin*, the main powerhouse for generation of transgenic mouse lines. Nine different *Nestin*^{CreERT2} lines have been designed using *Nestin* promoter; however, only a subset of them are capable of targeting neurogenic regions of the adult brain with significant differences in efficiency (Sun et al., 2014). As many transgenic mouse models have been developed for labeling and tracing of different cell types in the adult neurogenic niches (Table 1, Figures 1, 2), it is important to understand their advantages and disadvantages. Here, we review mouse models most widely used for studies of adult neural stem/progenitor cells and their lineage.

Nestin

Arguably the most popular mouse models to study adult neurogenesis use *Nestin* regulatory elements as drivers of reporter gene expression. *Nestin* was cloned by finding the target protein of Rat401 antibody (Hockfield and McKay, 1985), namely the antigen enriched in the proliferative zone of the neural tube. It was subsequently named based on its activation in neuroepithelial stem cells (Lendahl et al., 1990). Nestin is an intermediate filament protein expressed in many tissues in addition to neural tissue, including muscle (Day et al., 2007), retina (Mayer et al., 2003), testis (Lobo et al., 2004), hair follicle (Li et al., 2003), and others (Wiese et al., 2004). The first study that characterized the regulatory regions of the *Nestin* revealed the challenges of using these regulatory regions for transgenic approaches. Initially, two enhancer regions localized to the first and second intron were characterized (Zimmerman et al., 1994). Subsequently, it was discovered that the enhancer element in the second intron of the human *Nestin* contains TR (Thyroid hormone receptor), RXR (Retinoid X receptor), RAR (all-*trans* retinoic acid receptor), and COUP-TF (Chicken ovalbumin upstream promoter-transcription factor) binding motifs that control *Nestin* activation in the embryonic brain (Lothian et al., 1999). In addition, enhancers located in the second intron of the rat *Nestin* seemed to be active in a region-specific manner: one was active throughout the developing brain, while the other was specific for the ventral midbrain (Yaworsky and Kappen, 1999). Interestingly, in these early years of the *Nestin* characterization, no study reported the expression of nestin in the adult neurogenic regions (Lothian et al., 1999; Yaworsky and Kappen, 1999; Zimmerman et al., 1994). In 2000, Yamaguchi and colleagues generated the first *Nestin*::GFP mouse and reported the expression of GFP in adult dentate gyrus, SVZ and rostral migratory stream (RMS) (Yamaguchi et al., 2000). Later, this mouse was used to demonstrate that neural stem cells (NSCs) in the SGZ shared a lot of features with astrocytes, such as the expression of glial fibrillary acidic protein (GFAP) and passive and non-inactivating currents with a linear current-voltage relationship (Filippov et al., 2003). The same group also thoroughly characterized the morphological properties of those NSCs, including the characteristic tree-like branching endings in the molecular layer of the dentate gyrus (Filippov et al., 2003).

The second mouse model that used *Nestin* as a driver of the fluorescent reporters was generated by Mignone and collaborators (Mignone et al., 2004). In their transgenic *Nestin*::GFP mouse, Mignone and colleagues used the enhancer located in the second intron in addition to *Nestin* promoter. The GFP accurately marked both neurogenic regions of the adult brain and GFP+ cells efficiently formed neurospheres after sorting. In SVZ and RMS, *Nestin*::GFP expression was localized to Type A, B, and C cells (Mignone et al., 2004), whereas within the dentate gyrus, it marked NSCs, amplifying neuroprogenitors (ANPs), as well as other non-progenitor cell types including pericytes, endothelial cells, and oligodendrocyte progenitors (Encinas et al., 2011). Although cytoplasmic GFP is good for visualization of the morphological features of the cells where it is expressed, it is not ideal for quantification because of the abundance of expressing cells, particularly in young animals. Thus, another mouse model was generated, using the cyan fluorescent protein (CFP) fused with the nuclear localization signal (*Nestin*::CFP^{nuc} transgenic mouse). In this mouse, it was easy to visualize the neurogenic areas as dotted patterns, which allowed the

unambiguous enumeration of the nuclei of Nestin-expressing cells (Encinas et al., 2006). Thus, for quantitative studies of the SGZ neuroprogenitors, the *Nestin*::CFP^{nuc} is a valuable mouse model.

Soon after *Nestin*::GFP mouse models were published, the first inducible *Nestin* mouse line was generated (Beech et al., 2004). It expressed tetracycline transactivator (tTA) under the control of a wide genomic region covering the 5.8kb upstream and 5.4 kb downstream of *Nestin*, and was then crossed with the *TetOP*-mCREB-FLAG mouse (Chen et al., 1998) to visualize the *Nestin* expressing cells and their progeny in the absence of doxycycline (tet-off). Using this mouse, it was demonstrated for the first time that Nestin expressing cells in the SVZ were capable of giving rise to periglomerular cells in the olfactory bulb (Beech et al., 2004). Surprisingly, granule cells in the olfactory bulb, another type of interneurons known to be sourced from the SVZ (Lois and Alvarez-Buylla, 1994; Luskin, 1993), were not labeled in this mouse model. This study was thus important because it pointed to two observations that the field still continues to tease out: 1) NSC population in the SVZ is heterogeneous; and 2) correct labeling of the stem/progenitor cell population is not enough to ensure that the lineage tracing will proceed as expected.

Several other transgenic mice using tetracycline responsive element were generated. Yu and collaborators developed a line with eGFP sequence upstream of the rtTA element (*Nestin*-rtTA-M2-eGFP) and crossed it with *TetOP*-Cre (Perl et al., 2002) and *Rosa26*-LacZ (Soriano, 1999) to demonstrate the temporal induction of Cre in neurogenic regions (Yu et al., 2005). Although eGFP^{+} cells have been observed in the SGZ and SVZ, no lineage tracing data in the adult mice have been reported using this mouse model. Dupret and collaborators developed a tet-on model using the second intron of rat *Nestin* (Dupret et al., 2008). In this mouse, GFP was seen only in the SGZ but not SVZ, suggesting that *Nestin* dependent transgenic reporter and inducible lines have considerable variations in their targets, depending on the genomic element used to drive the expression of transgene. Another *Nestin*::CreER^{T2} line, expressing CreER^{T2} under the control of neural specific *Nestin* enhancer (Zimmerman et al., 1994), was used to show that *Smoothened* mediated *Hedgehog* signaling is important for SVZ neurogenesis (Balordi and Fishell, 2007). Later, the same inducible line was used in two other studies that reached controversial conclusions. Encinas and collaborators performed a comprehensive double labeling study with two BrdU analogs, CldU and IdU, and developed an algorithm that estimated that SGZ NSCs, after entering into cell cycle, repeatedly divide three times and then terminally differentiate into astrocytes, suggesting that these NSCs are disposable (Encinas et al., 2011). On the other hand, Bonaguidi and collaborators used an induction protocol to activate Cre in sparse, individual NSCs and traced their respective lineages. They concluded that SGZ NSCs have the ability to both self-renew and give rise to multilineage progeny (Bonaguidi et al., 2011). These two disparate findings then led Dranovsky and collaborators to generate yet another *Nestin*::CreER^{T2} mouse, based on the pNerv-SXN vector, where brain-specific enhancer of *Nestin* located in the second intron (Josephson et al., 1998) drives the expression of CreER^{T2} (Dranovsky et al., 2011). They showed that NSCs have the ability to produce expanding and persisting populations of both neurons and stem cells, but that this effect depends mostly on the external experiences of the animal. Social isolation and X-ray

irradiation seemed to facilitate accumulation of NSCs while enriched environment shifted the balance in the favor of newborn neuron production (Dranovsky et al., 2011).

Nestin-dependent inducible lines have thus been invaluable for deciphering mechanisms underlying the complex nature of adult neurogenic niches, at the same time raising controversial questions. This is not surprising, as recent report suggests (Sun et al., 2014). Namely, all these lines show variable stem cell labeling efficiency and sometimes suffer from leakage to other cell types, which might all contribute to different findings despite the use of the "same" transgenic line. This is important to remember when authenticating each line, as strain, age, promoter, induction protocol used and other factors may affect the outcome of the experiment.

GFAP

One of the indelible markers commonly used to identify adult NSCs of the SGZ is glial fibrillary acidic protein (GFAP). GFAP labels radial processes that originate from the apical surface of the NSCs and span throughout the granular cell layer. It is not expressed in amplifying neuroprogenitors (ANPs) and this distinct expression pattern has been invaluable to differentiate between these two types of proliferating cells.

GFAP expression in the NSCs turned out to be critical for their characterization and naming. Cameron and colleagues showed for the first time that [^{3}H]thymidine$^+$ cells in the adult rat SGZ contained GFAP$^+$ cells resembling radial glia, with triangular cell bodies and a thin radial process (Cameron et al., 1993). These were SGZ primary NSCs, and "radial glia-like" cells is still in use to name these primary SGZ stem cells. Despite the fact that GFAP$^+$ cells in the SGZ were shown to proliferate, the authors of the first *GFAP*::GFP mouse (Zhuo et al., 1997) did not report on the GFP expression in the dentate gyrus. It took several years to begin to utilize this line for studies of NSCs, but eventually it found the application particularly for studies of the SVZ neurogenic niche: it was used to describe its vascular nature (Shen et al., 2008; Tavazoie et al., 2008) and to isolate and study both activated (Pastrana et al., 2009) and quiescent progenitors (Codega et al., 2014). Another GFAP reporter line, based on the human promoter, has been generated (Nolte et al., 2001) and although it has been extensively used in the astrocyte field, it has not been very popular for studies of the adult neurogenesis (Beckervordersandforth et al., 2014; Sultan et al., 2013).

First direct proof of "astrocytes" giving rise to neurons came in 2001. With the help of BrdU labeling and retroviral lineage tracing, Seri and colleagues found that GFAP$^+$ "astrocytes" in the SGZ were capable of proliferating *in vivo* and generating neurons (Seri et al., 2001). Using *GFAP*::GFP adenovirus, the same group defined the morphology of NSCs (Seri et al., 2004), and later that same year, a new line, *GFAP*::TK (thymidine kinase), was generated to transgenically ablate the dividing GFAP$^+$ progenitors (Garcia et al., 2004). This seminal study demonstrated that GFAP$^+$ progenitors are the principal source of adult neurons in both SVZ and SGZ. To further prove this observation, an inducible Cre recombinase (CreER^{T2}) controlled by the human *GFAP* promoter was used for lineage tracing of GFAP$^+$ cells and confirmed that those cells can give rise to neuronal precursors and neurons (Ganat et al., 2006). The same line was subsequently used to conditionally ablate *Notch1* in NSCs and

their progeny, revealing the role of Notch signaling in regulation of the cell fate and dendrite morphology of newborn neurons (Breunig et al., 2007).

Although human *GFAP* promoter has been useful in the generation of mouse models that allowed the studies of NSCs, abundant GFAP expression in astrocytes has generated a major problem for purification and lineage tracing of NSCs. To overcome this problem, a split-Cre approach, in which two lentiviral constructs (one containing the C-terminal of the Cre driven by *Prominin1* p2 promoter and one containing the N-terminal of the Cre driven by human *GFAP* promoter) have been used to target specifically the SGZ NSCs (Beckervordersandforth et al., 2014). Immunofluorescence against h-*GFAP*::GFP and Prominin1 showed that the combinatorial approach labeled NSCs with radial morphology; however these represented only 30% of the labeled cells.

Despite being expressed in astrocytes, abundantly present in both adult neurogenic niches, *GFAP* based models have been useful for adult neurogenic studies. For isolation of SVZ NSCs, lack of specificity of *GFAP*::GFP has been compensated by EGFR and/or CD133 as additional markers for NSC purification (Codega et al., 2014). For lineage tracing, in comparison to *Nestin* based models, *GFAP* based models have the advantage of avoiding the initial activation of Cre in ANPs. Thus, this enables lineage tracing directly from the origin, the NSC. However, these studies suffer from estimating the contribution of astrocytes to the final lineage outcome, and consequently, data interpretation and particularly quantitative studies of potential transformation of NSCs into astrocytes are jeopardized.

Sox proteins

Sox (sex determining region Y box family) proteins that bind to DNA via their high-mobility group (HMG) domains are conserved transcription factors that take role in cell fate specification and differentiation of many tissues (Abraham et al., 2013a; Abraham et al., 2013b; Kamachi and Kondoh, 2013). The most well-known member of this family, *Sox2*, has been characterized as one of the Yamanaka factors required for generation of induced pluripotent stem cells (Takahashi and Yamanaka, 2006). *Sox2 is* required for embryonic stem cell pluripotency and thus, it is one of the earliest known genes to be activated in the vertebrate neural tube (Uwanogho et al., 1995). In addition, it is also essential for maintenance of many adult tissue resident stem cells (Arnold et al., 2011), including both SVZ and SGZ NSCs (Ferri et al., 2004). The first studies of adult neurogenic niches using Sox2 expression came from $Sox2^{\beta\text{-Geo}}$ knock-in mice (Zappone et al., 2000). Ferri and colleagues showed that X-gal staining was localized to mainly SGZ of the dentate gyrus and the lateral ventricle walls, as well as that Sox2 was expressed in $BrdU^{+}$ $GFAP^{+}$ NSCs of both SGZ and SVZ niches. Moreover, in $Sox2^{\Delta ENH}$ mice, in which neural specific enhancer of Sox2 is deleted, there was a dramatic reduction in the number of proliferating cells in both niches, indicating the specificity of Sox2 expression in neural stem and progenitor cells (Ferri et al., 2004). Further characterization of Sox2 regulatory regions revealed that another enhancer element, Sox2 regulatory region2 (SRR2) that spans +3300 to +4124bp respective to the translation initiation codon, is able to discriminate between SVZ and SGZ. *Sox2*::β-geo transgenic line, which utilized SRR2 element to drive β-geo reporter, showed strong expression pattern in the SVZ and rostral migratory stream, but showed a weak labeling of

cells in the SGZ (Miyagi et al., 2006). This report indicates that the regulatory regions governing Sox2 expression are very important to consider when choosing the best mouse model for a given experiment.

First *Sox2*::GFP transgenic mice were generated in 2003 (D'Amour and Gage, 2003) and have been used to characterize the $Sox2^+$ cells in the hippocampal niche (Suh et al., 2007). Three types of cells were expressing *Sox2*::GFP in the dentate gyrus, NSCs, ANPs, and astrocytes. The same group also generated *Sox2*::Cre-GFP retro and lenti viruses to show that $Sox2^+$ cells can give rise to neurons, astrocytes and other cells that retain Sox2 expression. Thus, this study was the first to hint at the self-renewal ability of $Sox2^+$ cells in the SGZ (Suh et al., 2007). Finally, conditional removal of *Sox2* was achieved in *Sox2*::$CreER^{T2}$ line (Favaro et al., 2009), which utilized the telencephalic specific enhancer-promoter region (Zappone et al., 2000). In the embryonic brain, this removal resulted in aberrant dentate gyrus (Favaro et al., 2009). In the adult brain, it led to significant loss of hippocampal NSCs. These effects were attributed to Shh pathway, as *Sox2* is required for transcription of Shh (Favaro et al., 2009).

Sox1, another well-known member of Sox family, is one of the earliest genes to be expressed in the ectodermal cells that are committed to neural fate (Collignon, 1992). Its expression correlates with the dividing neural precursors of the embryonic central nervous system but not with the differentiation along the dorso-ventral axis (Pevny et al., 1998). First $Sox1^{GFP}$ mouse, a knock-in construct that replaced *Sox1* locus with GFP, was used to identify the neural genes from embryonic neuroepithelial cells. Interestingly, GFP was also localized in SGZ cells that resembled NSCs (Aubert et al., 2003). Characterization of these $Sox1^{GFP+}$ cells in SGZ revealed that 35% of the population had $GFAP^+$ radial processes (and thus were most likely NSCs), another 30% were $GFAP^-$ (most likely ANPs) and the remaining 35% were uncharacterized cell type(s). Despite labeling quite a bit of NSCs and ANPs, $Sox1^{GFP}$ is expressed in only 40% the total population of NSCs and ANPs, suggesting that it labels only a subset of them (Venere et al., 2012). By generating a *Sox1* driven tet-on dependent lineage tracing line (*Sox1*-tTA;tetO-Cre), Venere and colleagues were able to show that Sox1 expressing cells were able to generate granule neurons and hilar astrocytes. In SVZ however, $Sox1^{GFP+}$ cells mostly co-localized with PSA-$NCAM^+$ late progenitors/neuroblasts and not with early progenitors (Venere et al., 2012), arguing that the role of this gene depends on the neurogenic niche.

ASCL1 (Mash1)

Achaete-Scute Family BHLH Transcription Factor 1 (*Ascl1*) or *Mash1* (mammalian *Ascl1*) is a member of the basic helix loop helix family of transcription factors. It is one of the key members of the proneural transcription factors, and it is necessary and sufficient to promote neurogenesis (Bertrand et al., 2002). *Ascl1* sequentially activates target genes by increasing the accessibility of target genes both in proliferating and differentiating neuroprogenitors (Raposo et al., 2015). *Ascl1* has also been extensively used to reprogram somatic cells to induce formation of neuroprogenitors and neurons (Berninger et al., 2007; Karow et al., 2012; Pollak et al., 2013; Vierbuchen et al., 2010). Interestingly, retrovirus-mediated overexpression of *Ascl1* in the adult SGZ NSCs resulted in generation of oligodendrocytic

lineage at the expense of newborn granule neurons, suggesting the complex nature of differentiation cascade governed by *Ascl1* (Jessberger et al., 2008).

The first GFP reporter mouse model, *Ascl1*^{GFPnuc} knock-in, replaced one allele of *Ascl1* coding sequence with the nuclear localized GFP (Leung et al., 2007). Two seminal studies were published using this mouse model: Leung and collaborators demonstrated that the horizontal basal cells are the stem cell population of olfactory neuroepithelium (Leung et al., 2007), while Kim and collaborators showed that *Ascl1* expression was limited to transient ANPs in both SVZ and SGZ (Kim et al., 2007). Later, weak expression pattern of the *Ascl1* was reported in the subset of the SGZ NSCs, using an inducible *Ascl1*^{CreERT2} knock-in mouse (Kim et al., 2011). Namely, after a short term induction (1 week), labeled cells included Type 1 cells (NSCs) in the SGZ and a subset of GFAP$^+$ progenitors in the SVZ (Kim et al., 2011). Lineage tracing indicated that *Ascl1* expressing cells were able to generate only newborn neurons and not astrocytes, supporting the observation that *Ascl1* labeled mostly ANPs. Compared to other lineage tracing lines, this particular transgenic mouse model provided superbly clean labeling of neuronal progeny, demonstrating almost complete repopulation of the granule cell layer three months following the induction (Yang et al., 2015). Thus, this mouse model may become invaluable for quantitative studies of intermediate and late stages of neurogenesis as well as of newborn neuron integration.

GLAST

GLAST1 (Glial High affinity glutamate transporter) or *SLC1A3* (solute carrier family 1, member3) gene encodes an astrocyte specific high affinity glutamate transporter, which buffers excess of extracellular glutamate from the tissue. Early *in situ* hybridization data showed that *GLAST* mRNA was localized in the ventricular zone of the fetal brain (Shibata et al., 1996; Sutherland et al., 1996) and radial glia cells in the developing spinal cord (Shibata et al., 1997). Characterization of radial glia throughout embryonic development suggested that not all radial glia in the embryonic brain express *GLAST*, but that *GLAST*$^+$ cells consist of functionally distinct subsets of precursor cells with different cell cycle characteristics (Hartfuss et al., 2001). In addition, neurospheres generated from the subependymal zone of adult mice contained *GLAST*$^+$ progenitor cells (Hartfuss et al., 2001). Moreover, GLAST was expressed in the human fetal telencephalon radial glia cells too (Zecevic, 2004).

Early postnatal data on the expression of *GLAST* in BrdU$^+$ and Ki67$^+$ cells of dentate gyrus showed that majority of the proliferating cells were GLAST$^+$ and S100β$^+$ (Namba et al., 2005). This suggested that *GLAST* expression is not only specific for embryonic radial glia but also present in the adult neurogenic regions, which held in many species including mouse, rat, cat, marmoset, and pig (Williams et al., 2005).

In 2006, first inducible line for *GLAST* (*Glast*-CreER^{T2}) targets many of the astrocytes and NSCs of both dentate gyrus and SVZ that give rise to granule neurons in olfactory bulb (Mori et al., 2006). Later, this inducible line was used to detail the contribution of *GLAST* and *Nestin* lineages to adult hippocampal neurogenesis under different conditions (DeCarolis et al., 2013). In this study, authors showed that although both *Nestin* and *GLAST*

lineages gave rise to granule neurons, contribution of the latter seemed to continuously increase over time while contribution of the former reached a plateau. The difference between the contributions of two lineages to neurogenesis became more apparent when animals were exposed to experimental manipulations, either ablation (by anti-mitotic drug, AraC) or stimulation (running) of neuroprogenitors. After either experimental condition, labeled NSCs in *Glast*-CreER^{T2} line appeared to contribute to neurogenesis, while those labeled in *Nestin*-CreER^{T2} did not (DeCarolis et al., 2013). Further characterization of *Nestin*::GFP mice showed that, although GLAST^{+} GFAP^{+} radial cells were mostly *Nestin*::GFP^{+}, some GLAST^{+} GFAP^{+} radial cells were *Nestin*::GFP^{-}, suggesting that not all cells with radial morphology express *Nestin*::GFP. These data emphasized that careful reevaluation of the conventional morphology/marker based classification of the cell types, especially for NSCs, in adult neurogenic niches is a necessity. *GLAST*^{CreERT2} line thus provides undoubtedly critical tool for understanding the heterogeneity of the NSC population.

Hes5

Notch signaling is an evolutionarily conserved pathway (Andersson et al., 2011) that plays a key role in development, through diverse effects on survival, differentiation and proliferation (Alunni et al., 2013; Breunig et al., 2007; Giachino and Taylor, 2014), that depend on signal strength (Chapouton et al., 2010; Gama-Norton et al., 2015; Ninov et al., 2012; Shimojo et al., 2008) and cellular context (Basak et al., 2012; Farnsworth et al., 2015; Lugert et al., 2010). Hairy and enhancer of split (Hes) genes are downstream targets of Notch pathway. They encode transcriptional repressors that predominantly control the proneural basic helix-loop-helix genes and thus regulate the maintenance of undifferentiated cells (Kageyama and Ohtsuka, 1999; Ohtsuka et al., 2001).

Hes5 starts to be expressed at E8.5 in the midbrain/hindbrain mouse region and continues to be expressed exclusively in the developing nervous system (Akazawa et al., 1992; Hatakeyama et al., 2004; Ohtsuka et al., 2001). First reporter mouse, *Hes5*::GFP, has been developed by Basak and colleagues and replicated *in situ* data (Basak and Taylor, 2007). *Hes5*::GFP expression was completely abolished in Notch1 deficient E9.5 embryos, suggesting that *Hes5*::GFP can also be used to report Notch1 activity *in vivo* (Basak and Taylor, 2007). Further characterization of this mouse in SGZ revealed that *Hes5*::GFP is expressed in cells that have both radial (54%) and horizontal (46%) morphologies. However, only 60% of *Hes5*::GFP^{+} cells overlapped with Sox2, BLBP, and GFAP, indicating that *Hes5*::GFP labels only a subset of the NSC population (Lugert et al., 2010). This is a very important finding, which suggests that either only some NSCs have active Notch signaling or that dynamics of *Hes5*::GFP expression reflects potential oscillations in Notch signaling, labeling only the NSCs with high Notch activity. Given that *Hes5*::GFP^{+} cells consists of both quiescent and actively dividing cells that respond selectively to physiological (running) and pathological (kainic acid induced seizures) stimuli, different levels of Notch in these cells is a plausible explanation. Generation of *Hes5*::CreER^{T2} line enabled further characterization of Hes5^{+} stem/progenitor cell population and their lineage (Lugert et al., 2012). The *Hes5*::CreER^{T2} line provided new data on the proliferation dynamics of different ANP subtypes. It has been accepted that Ascl1^{high} Type2a cells are the driving force of

proliferation in the SGZ niche. In contrary, Lugert and colleagues argued that Tbr2^{+} Type2b cells that originated from Ascl1^{high} Type2a cells are highly mitotic and responsible for the expansion of the precursor pool before further differentiating into post-mitotic neuroblasts (Lugert et al., 2012). Collectively, these data suggested that Notch signaling might be one of the candidate factors that contributes to the heterogeneity of NSCs. Thus, utilization of *Hes5*::CreER^{T2} and *Hes5*::GFP mice with different conditional alleles of Notch pathway elements will be useful for understanding the Notch dependent and potentially Notch independent nature of NSCs.

Tbr2 (EOMES)

Eomesodermin (Eomes, Tbr2) is a member of T-box family and crucial for embryonic development. It is expressed in mouse oocytes and also detected in the pre-implantation embryos by *in situ* hybridization (McConnell et al., 2005). This observation was verified in *EOMES*::GFP mouse, where it was also shown that eomesodermin was expressed in trophectoderm, primitive streak and telencephalon (Kwon and Hadjantonakis, 2007). In the developing neocortex, Tbr2 expression is associated with downregulation of Pax6 and transitioning of radial glia to intermediate progenitor cell stage (Englund et al., 2005). Similarly, in the adult hippocampus, Tbr2 is specific for intermediate progenitors in the SGZ (Hodge et al., 2008). There, Tbr2^{+} cells represent a highly heterogeneous population: they colocalize with PSA-NCAM, Dcx, Sox2 (weak overlap), Ascl1 (weak overlap), Pax6, NeuroD1, and proliferation marker PCNA, but not GFAP. This expression pattern thus indicates that Tbr2 is present in a wide spectrum of the differentiating cells, from ANPs to neuroblasts (Hodge et al., 2008).

On the other hand, another transgenic reporter mouse, *Tbr2*::GFP, generated by GENSAT (Gong et al., 2003) suffered from substantial leakage to other cell types (Hodge et al., 2008). Although all Tbr2^{+} cells were *Tbr2*::GFP^{+}, they only constituted 30% of the *Tbr2*::GFP^{+} cells. GFP was expressed in immature neurons, colocalizing with calretinin, and in granule cell, colocalizing with NeuN (Hodge et al., 2008). The widely different expression of GFP in two transgenic mice, *EOMES*::GFP and *Tbr2*::GFP, indicates the variability most likely due to the use of BAC clones and prompts careful authentication of such lines to avoid misinterpretation of data. In the SVZ, Tbr2^{+} cells were detected in the dorsal subregion of subependymal zone and in the rostral migratory stream. Short term lineage tracing revealed that Tbr2^{+} cells gave rise to glutamergic olfactory bulb interneurons (Brill et al., 2009). In the SGZ, the neurogenic potential of Tbr2^{+} cells was demonstrated in the first inducible knock-in line, *EOMES*^{CreER}, in which Tbr2^{+} cells gave rise to Dcx^{+} immature neurons (Pimeisl et al., 2013). Although neuronal lineage of Tbr2^{+} cells is a well-accepted finding in the neurogenesis field, proliferation potential of these cells is still debated (Berg et al., 2015; Lugert et al., 2012).

Another Tbr2 dependent lineage tracing mouse line, *Tbr2*::CreER^{T2}, was used to show that Tbr2+ cells do not undergo significant amplification, but rather differentiate and generate 1.2 immature neurons per cell by 15 days following induction (Berg et al., 2015). As Cre is expressed mostly in homogenous population of unipotent Type2b cells that develop into immature neurons, but not into astrocytes or other cell types, *Tbr2*::CreER^{T2} is a unique

mouse model that can find applications for studies of newborn neurons with similar birthdays.

Spot14 (Thrsp)

SPOT14, or Thyroid hormone responsive protein (Thrsp), is involved in *de novo* lipogenesis and mainly expressed in the lipogenic tissues such as liver, fat, and lactating mammary gland (Jump and Oppenheimer, 1985). It regulates the activity of fatty acid synthase (Fasn), the key enzyme in biosynthesis of fatty acids, by reducing the availability of its substrate, malonyl-CoA. Lipid metabolism and signaling has been highly implicated in the function of stem cells, including neural stem cells (Allen and Maletic-Savatic, 2011; Allen et al., 2013; Arnold et al., 2015; Maletic-Savatic et al., 2008; Manganas et al., 2007; Walker et al., 2016). In 2013, Knobloch and colleagues showed that Fasn is highly expressed in the adult neural stem/progenitor cells of both SGZ and SVZ but downregulated after differentiation (Knobloch et al., 2013). *SPOT-14::*GFP reporter mouse showed that Spot14^{+} cells have radial (43.1%) and non-radial morphology (56.9%), and that GFP expression overlapped with Sox2, GFAP and Nestin. Only 1.7% of the radial population and 7.8% of the non-radial population were Ki67^{+}, indicating that Spot14^{+} cells are mostly quiescent (Knobloch et al., 2013). Long term (1 and 3 months) lineage analysis in *Spot14::*CreERT2 mouse confirmed that Spot14^{+} cells constitute neurogenic stem/progenitor cells in the adult brain (Knobloch et al., 2013). Further characterization of Spot14^{+} population revealed that their numbers decline with aging, and that they responded to both positive (running) and negative (temozolomide) neurogenic regulators (Knobloch et al., 2014). Since Spot14 has been shown to be responsible for regulating the quiescence of stem cells via limiting lipid synthesis (Knobloch et al., 2013), transgenic lines that depend on the regulatory regions of Spot14 would be useful for future studies aimed at investigations of the metabolic aspects of the stem cell quiescence.

Gli1

Sonic hedgehog (Shh) pathway is important for adult neurogenesis (Lai et al., 2003; Machold et al., 2003). Gli1 (GLI-Krupperl family member 1) has been used as a sensitive readout of the Shh activity. *Gli1* promoter was thus used to drive the expression of CreER^{T2} in the *Gli1^{CreERT2}* line (Ahn and Joyner, 2004), in order to study the role of Shh in SGZ NSCs. Indeed, Shh-responsive NSCs had the ability to self-renew as they expanded in number and generated neurons (Ahn and Joyner, 2005). Encinas and collaborators crossed *Gli1^{CreERT2}* with the RCE (*Rosa26/CMV-loxP-stop-loxP-GFP*) reporter line (Balordi and Fishell, 2007) to drive the expression of GFP exclusively in the SGZ NSCs (Encinas et al., 2011).

Other mouse models

Due to limitations of aforementioned mouse models either for specificity or efficiency of labeling of neural stem/progenitor cells, groups all over the world took different approaches to generate other valuable mouse models. Among those, recently developed *Prss56^{CreERT2}* line stands out, as it provides labeling of NSCs and respective lineages not only in the adult

SGZ and SVZ, but also in the hypothalamus ventricular zone (Jourdon et al., 2015). Further, *Hopx*, atypical homeodomain only protein, previously reported to be expressed in the stem cell populations of intestine (Takeda et al., 2011) and hair follicle (Takeda et al., 2013), is also a potential marker of SGZ but not SVZ stem/progenitor cells (Li et al., 2015). In *Hopx*$^{3FlagGFP/+}$ line, GFP expression localized to a subset of Sox2^{+} cells of the SGZ as well as GFAP^{+}, Nestin^{+} and BrdU retaining cells. *Hopx*$^{ERCre/+}$ lineage tracing showed that Hopx expressing cells consist of almost exclusively quiescent NSCs (Shin et al., 2015), which have the ability to give rise to neuronal lineage in the dentate gyrus but not in the olfactory bulb (Li et al., 2015). Thu, this unique mouse model may provide key knowledge on the biology of quiescence. Tctex-1, dynein light chain, is expressed in the neurogenic regions of the adult brain (Chuang et al., 2001; Dedesma et al., 2006). Further characterization of Tctex-1 expressing cells showed that they are mostly ANPs and neuroblasts but not NSCs (Tseng et al., 2010). On the contrary, two different *Tctex-1::GFP* lines generated in the same study showed conflicting outcomes: in one line (Line 4), GFP was expressed in NSCs and early ANPs while in the other line (Line 17), it was expressed in late ANPs and neuroblasts. This variable expression patterns even in transgenic models that use the same constructs again prompts full authentication of the mouse models, prior to start of any experimentation.

Albeit we focused here mainly on the mouse models used to study neural stem and progenitor cells, various other models have been developed to study newborn neurons (Figures 1, 2). Among those, Pomc-based (*Pomc*::eGFP (Cowley et al., 2001), *Pomc*-Cre (Balthasar et al., 2004)) and Dcx-based (two *Dcx-eGFP* (Couillard-Despres et al., 2006; Walker et al., 2007), and two *Dcx-DsRed* (Couillard-Despres et al., 2006; Wang et al., 2007)) lines stand out. Those models have been instrumental for our understanding of the differentiation and integration of neuroblasts and granule neurons (Hunt et al., 2012; McHugh et al., 2007; Nakashiba et al., 2012) as well as for distinguishing the NSC population and their progeny from each other (Bracko et al., 2012). However, complete review of these mouse models is beyond the scope of this review.

CONCLUSION

Despite its early discovery (Altman, 1962), adult mammalian neurogenesis has gained recognition only in the early 1990s, but since then, there has been a substantial increase in the number of reporter and inducible mouse lines to study this phenomenon. Finding the right genes and their regulatory regions to drive the expression of fluorescent reporters or the Cre variants with optimum specificity and efficiency has been the major challenge. Thus, characterization of enhancer elements is very important to increase the specificity and efficiency of the current models. Finding new markers for different cell types is also important for not only developing new tools but also for understanding the stem/progenitor cell heterogeneity. Single-cell RNA sequencing studies offer great opportunities for finding new markers for different cell types. A recent study has demonstrated the utility of the single cell RNA sequencing for delineating the transcriptional profiles of NSCs along their developmental trajectory (Shin et al., 2015).

Most of the transgenic models that we summarized here use GFP or eGFP as their reporters. Although stability and signal intensity of GFP is an advantage, sometimes it poses a

challenge. *Tbr2*::GFP is a good example: while Tbr2 is expressed in ANPs, GFP overlaps with calretinin and even with NeuN, and is thus found in neuroblasts and neurons in the dentate gyrus (Hodge et al., 2008). Using destabilized GFP protein fused with the PEST sequence, with a half-life of 2hr (Li et al., 1998) might be an alternative strategy to limit the leakage of the reporter gene to progeny. Developing additional reporter mouse lines that utilize other parts of the spectrum, such as *Nestin*::CFP^{nuc} (Encinas et al., 2006), and *BLBP*::mCherry (Giachino et al., 2014) would be extremely useful for the validation of our current marker paradigm and also for understanding the cellular heterogeneity of stem/progenitor cell population.

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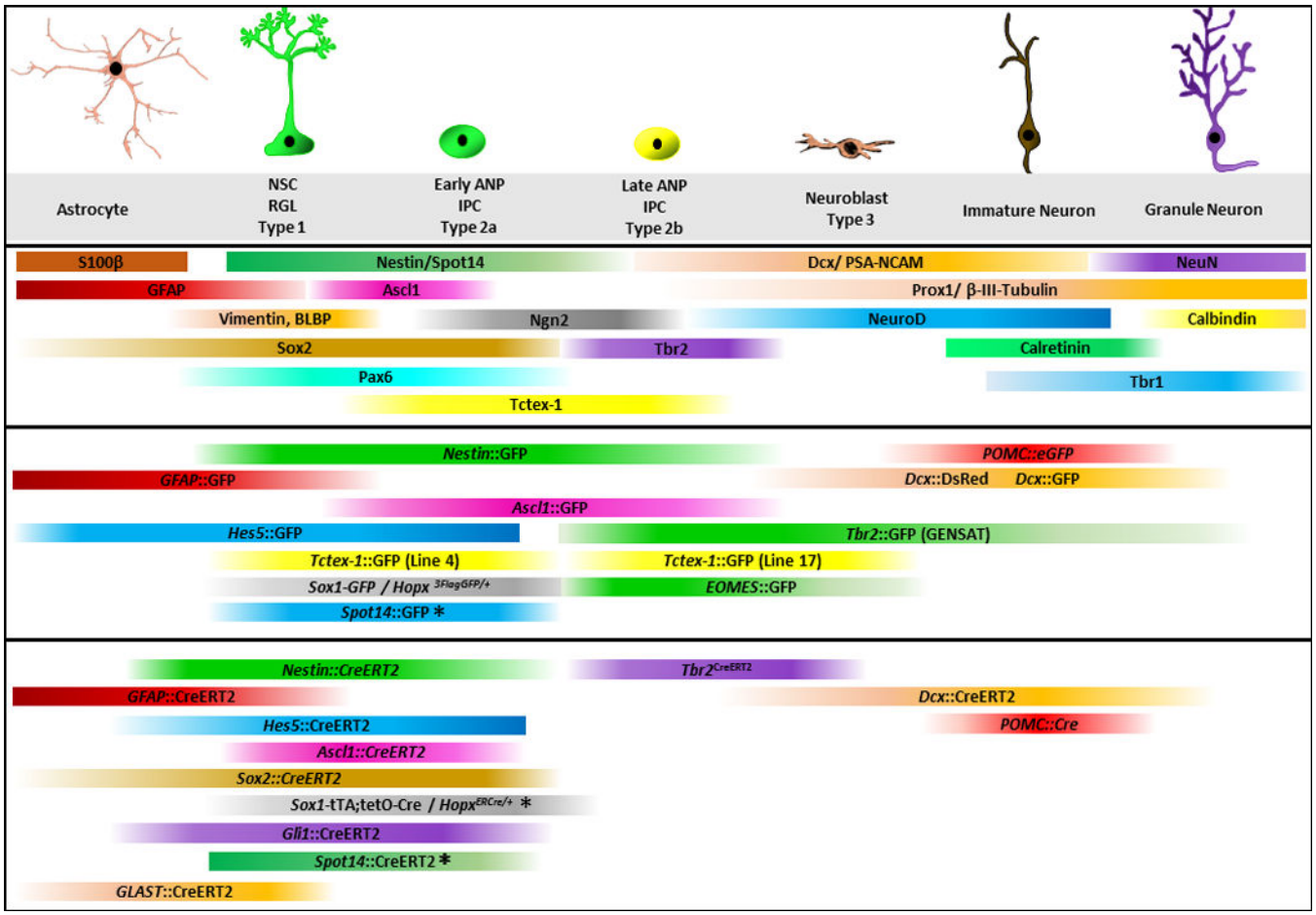

Figure 1. Summary of immunohistochemical markers, reporter and lineage tracing mouse models used to identify different cell types of the adult hippocampal neurogenic niche

NSC, neural stem cells; RGL, radial glia like cells; ANP, amplifying neuroprogenitors; IPC, intermediate progenitor cells. Upper part: Markers, Middle part: Reporter lines; Lower part: Lineage tracing lines. * denotes the mouse models that target mostly quiescent neural stem cells

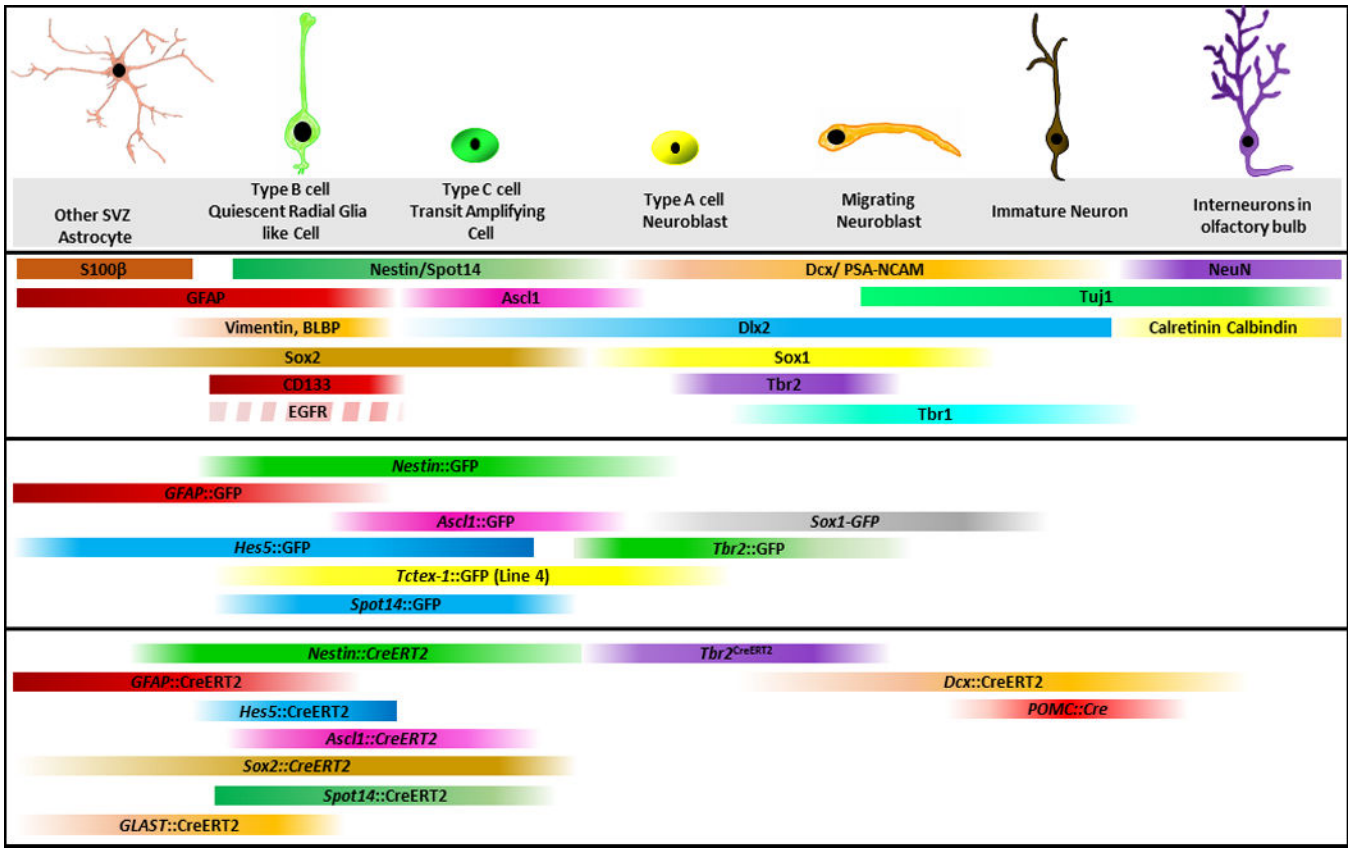

Figure 2. Summary of immunohistochemical markers, reporter and lineage tracing mouse models used to identify different cell types of the adult subventricular zone neurogenic niche

Broken strip (EGFR) indicates expression in only subset of Type B cells. $EGFR^{+}$ population is actively cycling whereas $EGFR^{-}$ population consists of quiescent SVZ neural stem cells. SVZ=subventricular zone; RMS=rostral migratory stream; OB=olfactory bulb. Upper part: Markers, Middle part: Reporter lines; Lower part: Lineage tracing lines.

Table 1
List of reporter mice used in adult neurogenesis research

NSC=neural stem cells, ANP = amplifying neuroprogenitors, NB=neuroblasts, IN=immature neurons, GZ=granule cells, SGZ=subgranular zone, SVZ=subventricular zone. When not specified, the mouse model is used for studies of both SGZ and SVZ neurogenesis.

	Line	Use	Reference:
Nestin	*Nestin*::lacZ	Characterization of regulatory regions of *Nestin*	(Johansson et al., 2002; Zimmerman et al., 1994)
	Nestin::CFP^{nuc}	Quantification of NSCs and progenitor cells	(Encinas et al., 2006)
	Nestin::GFP, *Nestin*::eGFP	Population studies of NSCs and progenitor cells	(Kawaguchi et al., 2001; Mignone et al., 2004; Yamaguchi et al., 2000)
	Nestin::tTA, *Nestin*-rtTA, *Nestin*-rtTA-M2-eGFP *Nestin*-Cre, *Nestin*-CreER; *Nestin*-CreERT2	Lineage tracing	(Beech et al., 2004; Mitsuhashi et al., 2001; Yu et al., 2005) (Betz et al., 1996; Kuo et al., 2006); (Dranovsky et al., 2011; Imayoshi et al., 2006; Lagace et al., 2007)
GFAP	*GFAP*::GFP, *GFAP*::eGFP GFAP::AmCyan1, AsRed2, mRFP1	Population studies of astrocytes and NSCs	(Nolte et al., 2001; Platel et al., 2009; Zhuo et al., 1997); (Hirrlinger et al., 2005)
	GFAP::TK	Specific ablation of NSCs	(Garcia et al., 2004)
	GFAP-Cre, *GFAP*-CreERT2	Lineage tracing of NSCs	(Casper and McCarthy, 2006; Ganat et al., 2006; Marino et al., 2000)
Sox1	*Sox1*-GFP	Population studies of a subset of NSCs and ANPs	(Aubert et al., 2003)
	Sox1-tTA;tetO-Cre	Lineage tracing of NSCs and ANPs	(Venere et al., 2012)
Sox2	*Sox2*$^{β\text{-}Geo}$	Strong activity in SVZ but weak in SGZ	(Zappone et al., 2000)
	Sox2::GFP, *Sox2*-eGFP	Population studies of NSCs, ANPs, and astrocytes	(D'Amour and Gage, 2003; Ellis et al., 2004)
	Sox2::Cre, *Sox2*::CreER, *Sox2*::CreERT2	Lineage tracing	(Favaro et al., 2009; Hayashi et al., 2007; Kang and Hebert, 2012)
Ascl1	*Ascl1*-GFPnuc	Strong expression in ANPs but weak in NSCs	(Leung et al., 2007)
	Ascl1-CreERT2	Lineage tracing in SGZ	(Kim et al., 2011)
Glast	*Glast*::eGFP *Glast*::dsRed	Population studies of astrocytes and NSCs	(Gong et al., 2003) (Glowatzki et al., 2006; Regan et al., 2007)
	Glast-CreERT2; *Glast*::CreERT2	Lineage tracing	(Mori et al., 2006); (Slezak et al., 2007)
Blbp	*Blbp*::GFP, *BLBP*::eGFP *Blbp*::eYFP, *Blbp*::dsRed2 *Blbp*::mCherry	Population studies of astrocytes and NSCs	(Anthony et al., 2004; Gong et al., 2003; Schmid et al., 2006); (Giachino et al., 2014)
	Blbp::Cre	Lineage tracing	(Anthony et al., 2004; Hegedus et al., 2007)
Hes5	*Hes5*::GFP	Population studies of a subset of NSCs and ANPs	(Basak and Taylor, 2007)
	Hes5::CreERT2	Lineage tracing	(Lugert et al., 2012)
Tbr2	*EOMES*::GFP	Labeling of late ANPs and early NBs	(Kwon and Hadjantonakis, 2007)
	Tbr2::GFP	Labeling of late ANPs, NBs, INs and some GCs	(Gong et al., 2003)

	Line	Use	Reference:
	EOMES-CreERT2 *Tbr2*::CreERT2	Lineage tracing of late ANPs and NBs	(Pimeisl et al., 2013) (Berg et al., 2015)
Spot14	*Spot14*::GFP	Labeling of subset of NSCs and ANPs	(Knobloch et al., 2013; Knobloch et al., 2014)
	Spot14::CreERT2	Lineage tracing	(Knobloch et al., 2013)
Gli1	*Gli1*::CreERT2	Lineage tracing of NSCs in SGZ	(Ahn and Joyner, 2004)
Prss56	*Prss56-CreERT2*	Lineage tracing of NSCs in SGZ	(Jourdon et al., 2015)
Hopx	*Hopx*-3FlagGFP/+	Labeling of NSCs of SGZ	(Li et al., 2015)
	Hopx-ERCre/+	Lineage tracing of NSCs in SGZ	(Li et al., 2015)
Tctex-1	*Tctex-1*::GFP, *Tctex-1*::DsRed	Labeling of NSCs, ANPs and NBs of SGZ	(Tseng et al., 2010)
Pomc	*Pomc*::eGFP	Labeling of NBs/INs	(Cowley et al., 2001)
	Pomc-Cre	Lineage tracing of NBs/INs	(Balthasar et al., 2004)
Dcx	*Dcx-eGFP* *Dcx-DsRed*	Labeling of NBs/Ins Labeling of NBs/Ins	(Couillard-Despres et al., 2006; Walker et al., 2007); (Couillard-Despres et al., 2006; Wang et al., 2007)