Review

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TSC-mTORC1 Pathway in Postnatal V-SVZ Neurodevelopment

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Abstract: In restricted regions of the rodent brain, neurogenesis persists throughout life, hinting that perhaps similar phenomena may exist in humans. Neural stem cells (NSCs) that reside within the ventricular-subventricular zone (V-SVZ) continually produce functional cells, including neurons that integrate into the olfactory bulb circuitry. The ability to achieve this feat is based on genetically encoded transcriptional programs that are controlled by environmentally regulated post-transcriptional signaling pathways. One such pathway that molds V-SVZ neurogenesis is the mTOR pathway. This pathway integrates nutrient sufficiency with growth factor signaling to control distinct steps of neurogenesis. Alterations in mTOR pathway signaling occur in numerous neurodevelopmental disorders. Here, we review the role of the mTOR pathway in this process and discuss the use of this region to study the mTOR pathway in both health and disease.

Keywords: neurogenesis; mTOR; TSC; mTORC1; TSC1; TSC2

1. Introduction

Multipotent neural stem cells (NSCs) generate vast quantities and types of neurons within the brain. NSCs produce most neurons embryonically however, they persist at least until the end of infancy in discrete brain regions. Joseph Altman was the first to find groups of dividing cells in the ventricular-subventricular zone (V-SVZ), which surrounds the lateral ventricles (LVs) of the postnatal brain1. These V-SVZ cells were labeled by the DNA precursor thymidine which was passed to cells that mature into GABAergic granule cell neurons (GCs) of the olfactory bulb (OB)2–4 (Figure 1). Others identified that these V-SVZ cells behave as NSCs and generate transit amplifying cells (TACs), which are highly proliferative progenitors5. TACs produce neuroblasts that migrate anteriorly along the rostral migratory stream (RMS) into the OB6. This seminal finding pointed toward the idea that a pool of cells and factors might facilitate neurogenesis in the adult brain. While the extent to which neurogenesis persists postnatally in humans is still unclear, genetic diversity, including pathogenic variants, could prolong neurogenesis in humans. The theoretical benefit of this cellular plasticity is the molding of neuronal circuitry to adapt to environmental conditions. In theory, the tradeoff of continued cell division is the genetic vulnerability of having an increased mutational burden and susceptibility to errors in building circuits. Thus, intrinsic genetically encoded mechanisms and environmental signals must carefully balance the costs and benefits of ongoing neurogenesis. The presence of NSCs within the V-SVZ provides a unique opportunity to study signaling pathways and to model diseases. This opportunity is derived from the fact that neonatal LVs are readily accessible for the delivery of molecules, proteins, plasmids, and viruses to manipulate NSCs. Moreover, no surgery is required. Owing to their sessile nature and anatomically restricted positions, specific pools of NSCs can be manipulated to study normal physiological and pathophysiological responses. Here, we discuss the cytoarchitectonic map of the V-SVZ, the cell types

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generated by NSCs, and the effect of altering a critical regulator of cell and circuit development, the mTOR signaling pathway within different cell types.

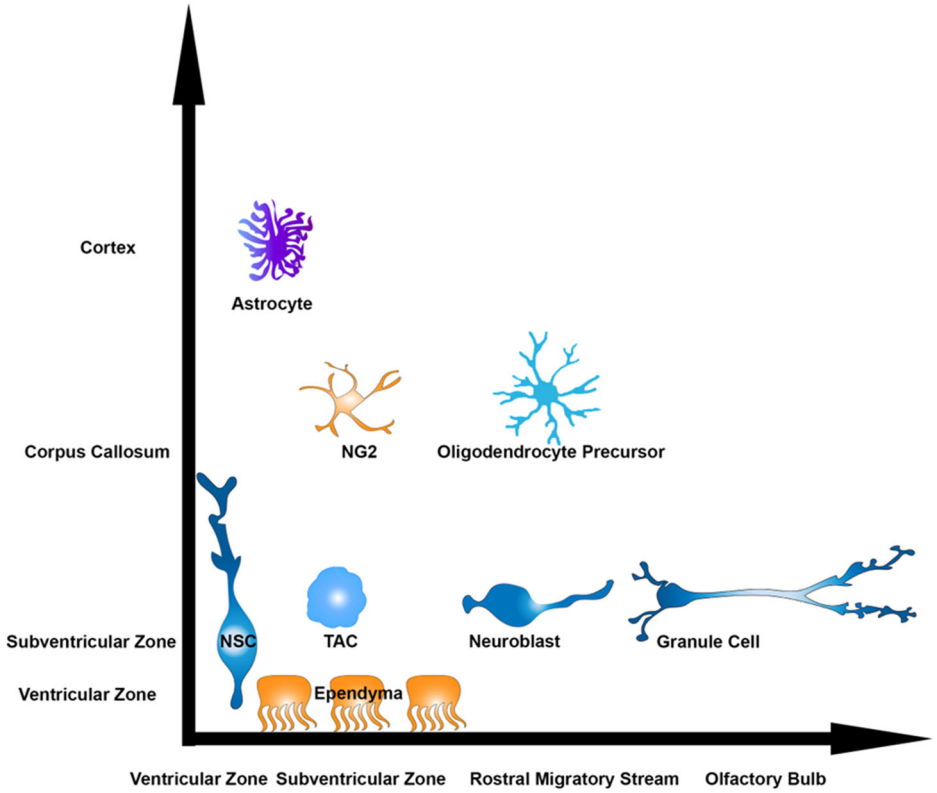

Figure 1. *Neonatal Neurogenesis.* Numerous cell types are generated from the postnatal?? V-SVZ. NSCs may be quiescent or induced to divide and generate astrocytes, ependyma, NG2, or oligodendrocyte lineage cells. In addition, V-SVZ NSCs generate rapidly dividing transit amplifying cells (TACs), which produce neuroblasts that mature into neurons in the olfactory bulb, namely granule cells.

2. Heterogeneity in the V-SVZ

The V-SVZ is a three-dimensional topographic compartment having a cytoarchitecture that is patterned and arealized along a fourth dimension, time7. Patterning of the V-SVZ is likely the remnant of the morphogenic gradients and transcriptional identities of NSCs that exist during embryogenesis8. The result is that different regions of the postnatal V-SVZ generate different cell types. For example, dorsal radial glia are a type of NSC in the embryonic brain that generate cortical excitatory neurons starting around embryonic day (E) 12 in mice9. However, in the perinatal brain, they produce glia10,11. Later, dorsal NSCs in the V-SVZ produce dopaminergic periglomerular (PG) neurons in the OB12. This appears directly related to precise transcriptional programs dictated by the expression of the transcription factors Pax6 and Dlx212. Dorsal NSCs may also generate some excitatory glutamatergic PGs that express the transcription factor Tbr113. In comparison, NSCs at the medial-septal wall produce calretinin positive PGs and GCs14. On the other hand, the lateral wall and dorsolateral corner of the ventricles produce OB GCs and dopaminergic PGs14. There are now recognized V-SVZ microdomains that are responsible for generating cells having unique GC laminar positioning and morphologies15. For example, a small ventrally located NKX2.1 microdomain derived from the embryonic medial ganglionic eminence generates postnatal GCs16. The lateral ganglionic eminence (LGE) also contains microdomains that produce striatal glia and OB GCs17.While both populations of NSCs express Dlx5/6 in the LGE, Isl1+ cells migrate to the striatum whereas Er81+ cells generate OB GCs. Transplantation experiments further support the likelihood that the potential and capacity to generate specific cell types is eventually independent of postnatal

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location and mostly specified by transcriptional programs established embryonically14. This is analogous to the cell intrinsic mechanism of NSC specification in the cortex18. On the other hand, the programs that regulate V-SVZ NSC pools have yet to be fully recognized. For example, PDGFRβ-positive stem cells within the septal and dorso-septal wall generate oligodendrocyte progenitor cells (OPCs)19. In addition, a newer intraventricular localized pool of stem cells within the lumen of the lateral ventricles was identified in the same study19. These findings indicate that diverse NSCs are found along the ventricular walls and produce different cell progeny.

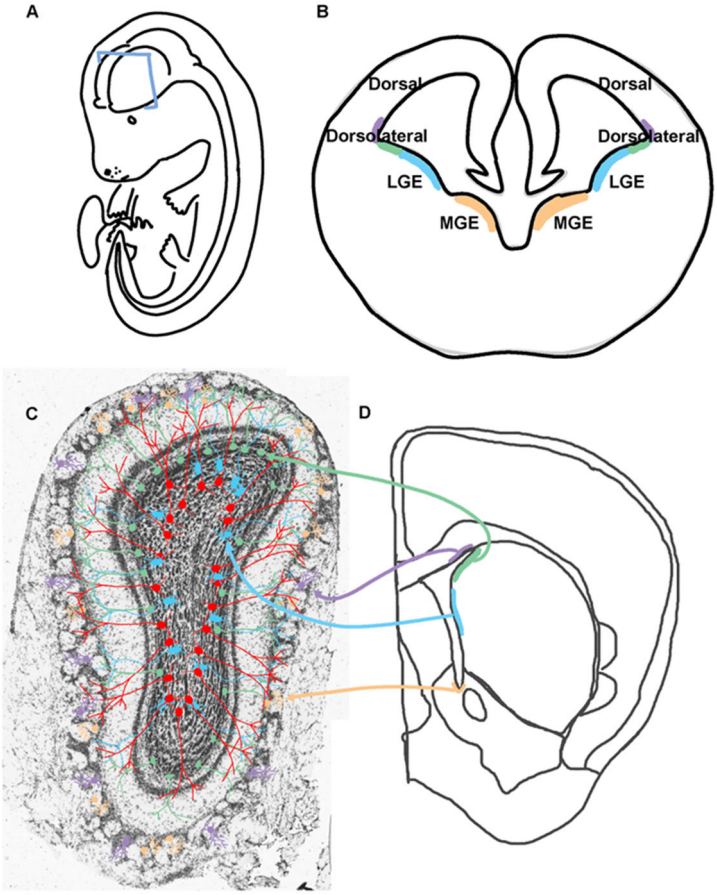

Figure 2. Origins of Postnatal OB Neurogenesis Diversity.**A.** Schematic of an embryonic mouse with a blue rectangle indicating where the coronal section of B is taken. B. Coronal section of mouse embryonic having V-SVZ regions labeled including the lateral and medial ganglionic eminences (LGE, MGE). The color corresponds to the cell types and regions that are generated in C and D. C. OB neurons originating from specific regions in the postnatal V-SVZ are color coordinated and originate from those regions indicated in B and D. D. Coronal hemi-section of an adult brain with V-SVZ regions highlighted that generate the neurons in C.

3. Targets of Postnatal Neurogenesis

It takes nearly 1 week for neuroblasts to migrate from the V-SVZ to the OB20,21. There, 94% of neuroblasts immediately begin to mature into GCs as evidenced by the production of basal dendrites that form synapses with centrifugal fibers and receive GABAergic input within 14 days22–24. GC apical dendrites project into the external plexiform layer, where reciprocal synapses start by 21 days, and glutamatergic input occurs approximately one month after GCs have been generated in the V-SVZ22,23,25. GCs are found within the GC layer, mitral/tufted cell layer, and the external plexiform layer15. The newly born GCs have distinct basal and apical dendrite morphologies and laminar positions, albeit the developmental relationship between the morphologies of these cells has not been completely characterized14,15. For example, many of the morphologies overlap at different developmental periods, shorter dendrites may reflect that these “different GCs” represent different

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states of the same cell, such as stages of development. However, these cells also express select proteins including calretinin and calbindin indicating that both the morphological and molecular characteristics change.

GCs form dendrodendritic synapses within the external plexiform layer that lies beneath glomeruli26,27. There, the dendrites of mitral cells synapse with the dendrites of GCs28. Most GCs are axon-less inhibitory neurons26. The release of glutamate from mitral/tufted cell dendrites caused by orthodromic retrograde backpropagating potential activates GCs that subsequently release GABA from their dendrites28. GC dendrite tiling prevents signaling between nearby mitral cells from different glomeruli. The lateral inhibition of mitral cells mediated by GC therefore increases contrast between signals. The addition of new GCs and dendrites to the circuitry optimizes olfactory processing24. The significance of this is that continued addition of GCs in the OB is a form of structural plasticity that facilitates perceptual learning29.

Postnatal V-SVZ NSCs may also produce additional groups of functional neurons. For example, a seminal finding found that lateral adult V-SVZ NSCs generate striatal GABAergic neurons in humans and this is reduced in Huntington's disease30. The ability of V-SVZ NSCs to produce striatal neurons is evolutionarily conserved, including in rodents and rabbits. In rats, the production of GABAergic striatal neurons that are parvalbumin positive starts around postnatal (P) 9 and progressively increases for an additional 2-3 weeks whereas the production of calretinin neurons peaks at P531. Ventral V-SVZ NSCs also continually produce neurons within the nucleus accumbens of mice32. Striatal neurogenesis is subject to environmental regulation, including pathological insults. For example, middle cerebral artery occlusion causes neuroblasts to migrate from the SVZ into the adult striatum33. The mechanism by which new striatal neurons are added in the mouse may differ under normal physiological versus pathological conditions.

The human V-SVZ also appears to produce neurons until ~18 months34,35. An evolutionarily novel bifurcation of the RMS called the medial migratory stream (MMS) pours into the ventromedial prefrontal cortex34. Details regarding the integration, maturation, and function of MMS-derived neurons are unknown. While rodents have additional postnatal waves generating GABAergic neurons that leave the RMS to populate the lower cortical layers and integrate into medial prefrontal, cingulated, and infralimbic cortices, their significance remains unclear36. It appears that dorsal V-SVZ NSCs in rodents can also produce cortical astrocytes37

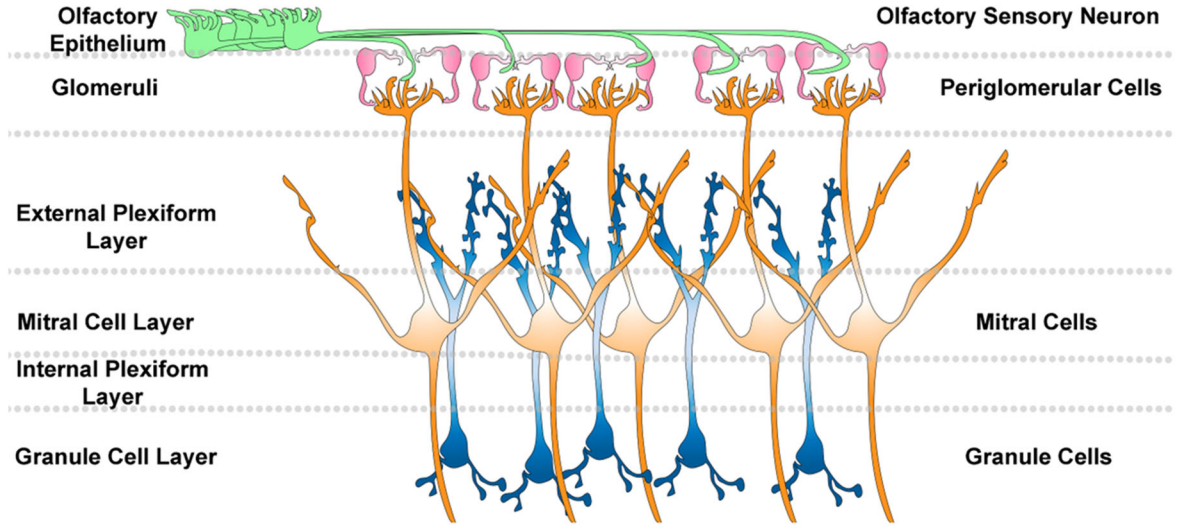

Figure 3. *Olfactory Bulb Circuitry.*Olfactory epithelial sensory neurons project axons onto the olfactory bulb. Thes axons form spheres called glomeruli that are surrounded by juxta/periglomerular cells. Stimulation of the sensory neurons can activate mitral cells that contain dendrites. Granule cells in the granule cell layer form dendrodendritic synapses with the mitral cells and release GABA to regulate mitral cell excitation.

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4. Techniques for Studying V-SVZ NSCs

We will briefly summarize the use of various methods to manipulate NSCs and daughter cells such as, components injected in the LVs including drugs or extracellular vesicles (EVs), neonatal electroporation, and viruses. Postnatal V-SVZ NSCs have a basal fiber that projects to the vasculature and an apical projection that interdigitates between ependyma and the ventricular lumen forming the hub of a pinwheel structure38. This ventricular contact allows one to manipulate NSCs. Injection of different components (e.g., drugs or plasmids) into the ventricles allows the determination of their effects on the behavior of NSCs and the production of cellular progeny. For example, the intraventricular injection of soluble factors into CSF within the LVs has been used to test the effect of growth factors on neurogenesis39. Lipophilic dyes and fluorescent beads have also been injected into the ventricle to label NCSs and study neurogenesis40. EVs have also been injected into the LVs and were taken up by microglia. The EVs were engineered to contain specific microRNAs acting as a microglia morphogen41. Consistent with this, it was demonstrated that NSCs release EVs that are taken up by microglia41. However, there are some limitations to intraventricular injections. First, the adult LVs are surrounded by multi-ciliated ependymal cells, which may prevent efficient uptake of some components. Second, the flow of CSF throughout the ventricular system results in the diffusion of injected components, which can affect many cell types in other brain regions. An example of an affected cell type are choroid plexus epithelial cells, which generate CSF and are found within the LV. Injection of CRE recombinase fused to a TAT peptide into the lateral ventricles demonstrated the selective uptake into choroid plexus epithelial cells42,43. Thus, injection into the LVs has the capacity to affect cells besides NSCs. Another approach that has been extensively used is the neonatal electroporation of plasmid DNA into the ventricles13,44,45. While this approach lacks specificity in uptake besides being restricted to cells with ventricular contact (i.e., ependymal cells versus NCS), the use of specific promoters or the introduction of inducible plasmids into mice having CRE expression within NSCs can overcome this46. Another option is to sort cells or nuclei using markers to study specific cell populations but this requires generating transgenic mice and large numbers of mice due to the small size of the V-SVZ47. An important limitation of using episomal plasmids is that they are diluted in dividing cells following electroporation48,49. Some NSCs may retain the plasmids long-term especially if they become quiescent. Electroporation of CRE recombinase or transposases can alter genomic DNA and prevents this dilution issue50,51. In addition, dilution may be an advantage. For example, the electroporation of tamoxifen-inducible CRE-ERT2 and a conditional plasmid into NSCs is accompanied by rapid dilution from actively dividing NSCs leading to plasmids expression only in the first cohort of daughter cells, including OB GCs. Injection of tamoxifen weeks later can allow for selective recombination in mature GCs allowing to manipulate them and distinguish their roles in the OB circuit from other cell types52. Another limitation of electroporation is that the injection of plasmid DNA into the LVs may cause immune reactions of intraventricular epiplexus immune cells53. The LVs, choroid plexus, and V-SVZ are enriched in immune cells during the perinatal period41. Another way to manipulate NSCs and their progeny postnatally is to use promoter driven tamoxifen inducible CRE-ERT2 mice. A popular example is the use of mice containing the rat nestin promoter driven CRE-ERT254 since nestin is expressed in NSCs. Finally, a last approach to manipulate NSCs and neurogenesis is the use of viral targeting40. In mature mice, there is not extensive proliferation besides in the neurogenic zones allowing for the use of retroviruses. Replication deficient retroviruses can be used to genomically modify NSCs55. This in theory will not lead to targeting quiescent NSCs, which is a limitation for studying the mechanisms that push quiescent NSCs to become active. Other types of viruses such as adenovirus were injected into the parenchyma of the V-SVZ to label NSCs and demonstrate that specific microdomains generate different types of neurons14.

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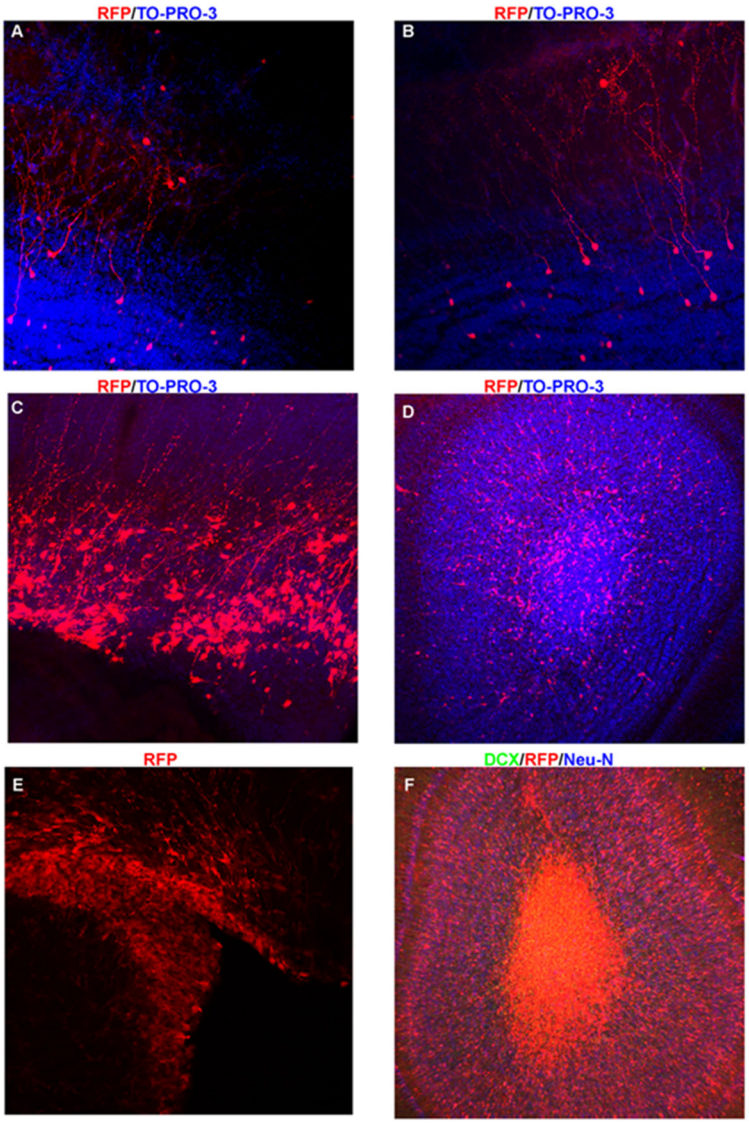

Figure 4. *Techniques for Studying V-SVZ NSCs and Cell Progeny*.A, B. Images of a postnatal day 30 olfactory bulb and corresponding V-SVZ cell progeny including GCs and PGs. C. P6 V-SVZ dorsal region following electroporation of RFP plasmid at P0. D. OB demonstrating that neuroblasts from the mouse in C are still migrating to their final destination and do not have the extensive arbors demonstrated in A, B. E. P10 V-SVZ of a *nestin*-CRE-ER^{T2} mouse crossed to an inducible RFP mouse demonstrating robust labeling of the V-SVZ. F. P10 OB demonstrating that the vast majority of cells are still migrating into the OB. Note the large number of cells in the core which are DCX positive (green) and Neu-N negative (blue).

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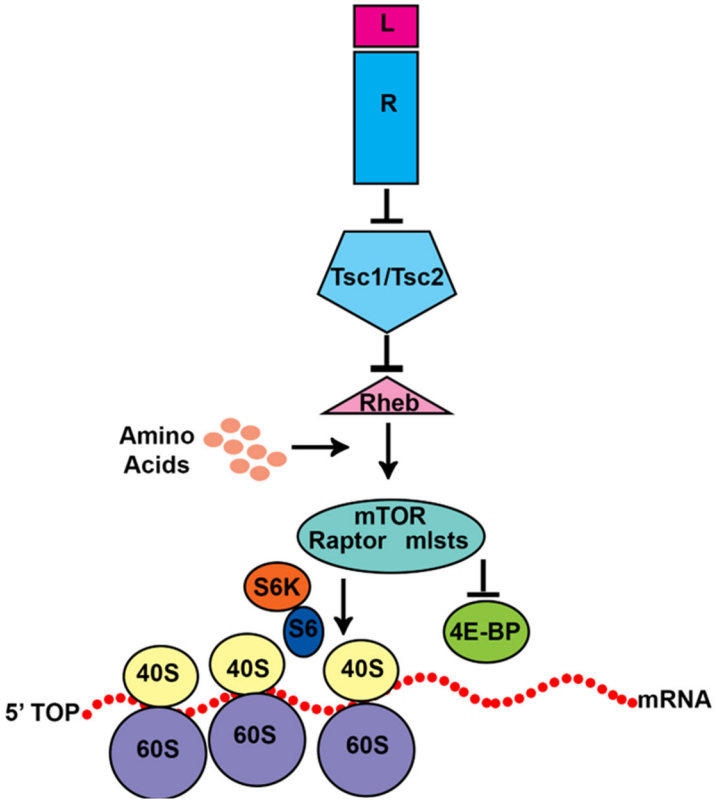

Figure 5. TSC-mTORC1 Pathway.Ligand (L) activation of receptors (R) leads to inhibition of tuberin bound to hamartin which are encoded by Tsc2 and Tsc1. Normally, tuberin/hamartin inhibit the GTPase Rheb from activating mTORC1. mTORC1 contains mTOR, which is a protein kinase that phosphorylates proteins to stimulate translation of mRNA containing a 5'TOP motif.

5. The mTOR Pathway

Rapamycin was originally discovered in 1965 as a compound derived from Streptomyces hygroscopicus, a bacterium found on Easter Island (also known as Rapa Nui). Initially, it was reported that rapamycin had antifungal properties and was used an antifungal agent. 56. Later on, it was shown that rapamycin works by causing the FK506-binding protein (FKBP12) to bind to and inhibit the mammalian target of rapamycin (mTOR)57. mTOR is a catalytic subunit of two heteromeric kinases termed mTOR complex (mTORC) 1 and 258. Rapamycin causes immediate and partial inhibition of mTORC1, however, at greater doses and over time may inactivate mTORC257,59–64. Each mTORC contains two mTOR kinase domains containing complex specific adapters65–67. The mTORC1 adapter is RAPTOR whereas RICTOR is the mTORC2 adapter68,69.

mTORC1 stimulates cell growth by inducing cap-dependent mRNA translation. This is achieved by mTORC1 inhibitory phosphorylation of eukaryotic initiation factor 4E (eIF4E) binding protein (4EBP)70,71 and phosphorylation of p70S6 kinase (p70S6K), which activates the ribosomal protein S6 (S6)60,72. mTORC1 is activated by GTP bound RHEB73–76. The GTPase RHEB is inhibited by tuberin (TSC2) and hamartin (TSC1), which are encoded by TSC1 and TSC273–76. Tuberin has a catalytic GAP activity that causes RHEB to hydrolzye GTP75. Hamartin and TBC1D7 seem to stabilize Tuberin77. Loss of hamartin or tuberin can cause abnormal brain development as discussed below.

6. Tuberous Sclerosis Complex (TSC)

Patients who are afflicted with TSC are frequently born with malformations of cortical development as well as abnormal growths along the LVs that were both originally called hamartomas78,79. The growths along the V-SVZ are subependymal nodules (SEN), which are benign slow growing tumors. Once these nodules reach a specific size, they are called subependymal giant

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cell astrocytomas (SEGAs)80. The underlying cause of TSC is inactivating mutations in the TSC1 or TSC2 genes found on chromosomes 9q34 and 16p13.3, respectively81,82. These mutations, including nonsense and missense mutations, deletions, and large rearrangements, cause the loss of TSC1 or TSC283. and uncontrolled mTORC1 activity83,84. Although the events causing V-SVZ SEN and SEGA remain unclear, some mechanisms can be appreciated from studying the role of mTOR in neurogenesis.

7. The TSC-mTORC1 Pathway in V-SVZ Neurogenesis

During development, cellular identity is tightly linked to the expression of distinct transcription factors that promote the availability of mRNAs. Indeed, single cell and single nuclei sequencing have consistently demonstrated the importance of transcriptional programs for establishing identity. This is no different in the postnatal V-SVZ85–87. Since growth factors such as EGF can titrate neurogenesis, environmental signals appear to be overlayed onto genetically encoded programs39. Thus, post-transcriptional mechanisms, including regulation of translation could in theory mold neurogenesis. The uncoupling of mRNA availability from translation occurs as human NSC differentiate into neurons88. This is important because cells might need to rapidly stop translating NSC mRNAs. Many of the differentially translated mRNAs are regulated by mTORC1. Indeed mTORC1 controls mRNA translation at different phases of V-SVZ neurogenesis89. For example, translation of the stem cell factor Sox2 mRNA is regulated by mTORC189. Persistent activation of mTORC1 causes aberrant Sox2 translation90. Therefore, controlling mTORC1-dependent mRNA translation occurs during neurogenesis.

The ability of extracellular factors such as EGF to regulate neurogenesis spurred investigations that identified mTORC1 hyperactivity in dividing Ki67+ cells and Mash1+ TACs produced by NSCs91. Rapamycin treatment reduced the density of TACs and dividing cells. In culture, rapamycin also induced quiescence in neurospheres and prevented neural differentiation91. It is important to mention that rapamycin does not completely inhibit mTORC1 phosphorylation of all substrates92. Thus, how mTORC1 inhibition affects these events is unclear. Despite this, it was known that quiescent NSCs become proliferative when they express EGFR. In fact, introducing mutant active EGFR pushes quiescent NSCs (qNSCs) to divide93. However, tumors are not generated by mutant active EGFR expression alone94. Indeed, EGF infusion into the ventricle only generates V-SVZ (subependymal) polyps 39. Subsequent experiments demonstrated that as NSCs go from a quiescent to an activated state, they activate mTORC146. This is consistent with the fact that tuberin is inhibited by CDK4/6 during the cell cycle and mTORC1 is activated95. Rapamycin also blocked NSC production of TACs and 4E-BP phosphorylation46. This study also demonstrated that RHEB knockdown prevents NSCs from generating TACs and neurons whereas as phospho (mTOR)-resistant 4E-BP1 enhanced NSC self-renewal46. The interpretation of this data is that RHEB activation of mTORC1 and phosphorylation of 4E-BP1 allows for NSCs to undergo symmetric terminal division producing highly proliferative TACs and neurons. This occurs at the expense of self-renewing divisions and maintenance of the NSC pool. RHEB activation of mTORC1 and phosphorylation of 4E-BP1 does not cause NSCs to divide but rather differentiate. These results indicate that mTORC1 is necessary for balancing NSC self-renewal and production of TACs. Excessive mTORC1 activity might in theory cause NSCs to become depleted. Consistent with this hypothesis, Tsc1 deletion from V-SVZ NSCs reduces the size of the OB GC layer over time96.

Tsc1 in qNSCs does not appear to push them to divide as reported with expression of a constitutively active RHEB97. Removal of Tsc1 from V-SVZ NSCs does however cause widespread alterations, including V-SVZ SEN and heterotopic nodules along the RMS, in the OB, and in the striatum96,98. Mice also had ventrally located nodules and developed hydrocephalus96. Ventral and dorsal V-SVZ NSCs vary in mTORC1 activity99. Considering this, the effect of loss of Tsc2 in ventral or dorsal NSCs was examined using transgenic mice expressing Nkx2-1 or Emx1 promoter-driven CRE. This study found that Nkx2-1 deletion of Tsc2 preferentially caused nodules to form along the lateral V-SVZ99. Emx1 is expressed in NSCs that generate excitatory cortical neurons and in postnatal

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dorsolateral V-SVZ NSCs that generate OB GCs100,101. As expected, Emx1-CRE Tsc1 deletion expanded the V-SVZ and RMS and caused a disorganized OB GC layer which was more spread out102. More Tsc1 mutant dorsolateral NSCs retained BrdU or were Ki67 at early stages and this effect was reduced at later ages. This is also consistent with the effects of mTORC1 hyperactivity on balancing self-renewing cell divisions with exhausting terminal cell divisions. Likewise, loss of Tsc2 by CRE electroporation (in conditional Tsc2 mice) also caused SENs, including those that protrude or are found within the ventricles103. One relevant finding from this study was that striatal astrocytes that are typically generated from the V-SVZ NSCs did not fully differentiate in the striatum and spuriously translated mRNAs associated with stemness following Tsc2 deletion103. These immature cells appeared to aberrantly produce neurons having a striatal-like morphology. The aberrant expression of immature markers in cortical tubers is also documented in TSC patients104. These results further support the need to tightly regulate mTORC1 activity at precise steps of development to prevent the expression of immature proteins in differentiated cells. In addition to loss of TSC genes, simultaneous Tsc1/Pten deletion has been performed using Nestin-CRE-ERT2 mice102. Mice injected with tamoxifen at P10 had nodular/bulbous nodules along the ventricles ~30 days later and often died likely due to cerebellar developmental complications105. To circumvent this issue, tamoxifen was injected later (P15 or P24) followed by examination of the brains months later. Upon inspection, SENs reminiscent of those in TSC patients had developed along the caudate nucleus of the striatum105.

The neuroblasts that are generated from V-SVZ NSCs have low mTORC1 activity and mRNA translation46,90,91. The presence of heterotopic clusters of neurons within the RMS following removal of Tsc1 from V-SVZ NSCs supports a role in migration and mirrors defects of cortical lamination caused by Tsc1 deletion from cortical radial glia48,98. Tsc1 null neuroblasts seemed to migrate slower than heterozygous neuroblasts but in fact likely lost direction due to the abnormal formation of multiple processes98. The migratory defects were mimicked by neuroblasts expressing constitutively active RHEB which also led to ectopic clusters of neurons106. At the molecular level, in vitro analysis of Tsc1 null neuroblasts demonstrated that there was a reduction in autophagic flux and impaired nuclear import of the transcription factor TFEB 107. Restoring TFEB activation in Tsc1 null neuroblasts rescues the migratory defect107.

Many of the neuroblasts that did not reach the OB became GCs in the RMS and their somas become enlarged following Tsc1 or Tsc2 removal or expression of a constitutively active RHEB using neonatal electroporation52,98,106,108 These changes all increased mTORC1 signaling as determined by phosphorylated S6 staining. The involvement of mTOR was demonstrated by neonatal CRE electroporation of mice having conditional mTOR leading to reduction of soma sizes109. While removal of mTOR does not reveal which mTORC is responsible for this effect, rapamycin treatment phenocopies the reduction in size suggesting a role of mTORC1109.

Since neurogenesis is ongoing, it is unclear whether affecting the mTORC1 pathway in mature GCs would have the same effect as changing it in NSCs. In one study, inducible CRE-ERT2 and GFP plasmids were electroporated into neonatal V-SVZ NSCs of Tsc2 conditional mice. The plasmid DNA (indicated by GFP) was diluted from actively dividing cells and ~30 days later, mice were injected with tamoxifen leading to Tsc2 deletion and RFP expression upon recombination in mature GCs. Tsc2 removal had a smaller effect on mTORC1, soma size, and dendrite arbors than when recombination was initiated in neonatal V-SVZ NSCs52. This is consistent with the idea that there may be discrete periods in which Tsc1/2 play more prominent roles110. What signals are turning Tsc1/2 or mTORC1 on and off during these periods is unclear. One possibility is that amino acids such as leucine, which is transported by Slc7a5 and additional transporters, activate mTORC1 and are critical, as their loss leads to OB GC death108,111.

These studies also demonstrated that loss of Tsc1, Tsc2, or increasing Rheb activity, enhanced dendrite arbors of OB GCs52,98,112. mTOR complex components raptor and rictor are well-known to be required for the development of GC dendrite arbors109. mTOR inhibition by rapamycin rescues the increased growth caused by expressing constitutively active Rheb113. Thus, the connectivity of mutant GCs might also be changed when the TSC-mTORC1 pathway is altered. Indeed, overactive

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Rheb also increased the frequency of inhibitory postsynaptic currents in ectopic GCs106, suggesting an increase in GABAergic synaptic connections. While the electrophysiological properties of action potentials in these mutant OB GCs did not change, the resting membrane potential was hyperpolarized. Further experiments are needed to determine how OB neuron firing, network activity, and olfaction are affected in these models, which could yield insight into the sensory changes that occur in patients.

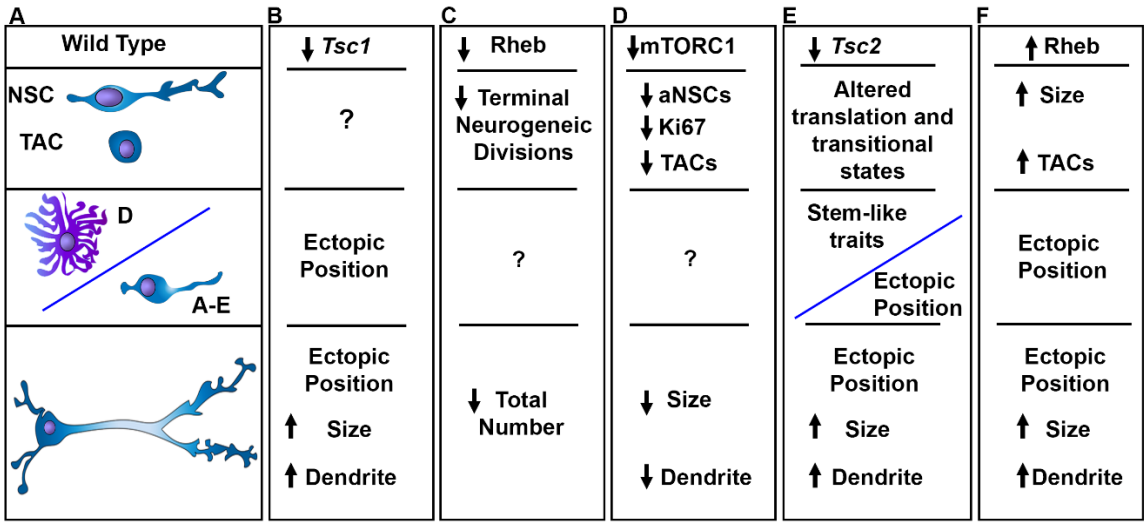

Figure 6. Alterations in mTORC1 Signaling Affect V-SVZ Neurogenesis. A. Wild type NSCs go from quiescence to an activated state and produce astrocytes and/or transit amplifying cells that generate neuroblasts which mature into granule cells and periglomerular cells. B. Loss of Tsc1 leads to ectopic heterotopias and subependymal nodules as well as fewer GCs in the OB, cytomegaly, and dendrite arborization. C. Reducing Rheb decreases the production of neuroblasts and decreases the total number of neurons produced. D. Decreasing mTORC1 activity by rapamycin reduces the number of dividing NSCs and fewer TACs. Moreover rapamycin and raptor knockdown reduce soma size and dendrite arbors. E. Loss of Tsc2 causes altered transitional states identified by single nuclei RNA sequencing and prevents proper differentiation leading to the production of partially differentiated cells expressing stem cell proteins and causes the formation of V-SVZ hamartomas and SEGA-like lesions. Moreover, OB neurons were cytomegalic and had increased dendrite growth. Ectopic expression of mutant active Rheb increased the size of NSCs and increased the total number of TACs associated with the formation of nodules and ectopic neurons that were cytomegalic and had hypertrophic dendrites.

8. Conclusions

In conclusion, the V-SVZ contains a mosaic of NSCs that produce different cell types owing to their embryonic ontogeny. NSCs may be easily altered, including through genetic manipulations to study molecules that may be relevant in normal developmental processes or in specific diseases. This is exemplified by studies that have examined the role of the TSC-mTORC1 pathway in the context of V-SVZ neurogenesis.

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