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The Roles of the Stem Cell-Controlling Sox2 Transcription Factor: from Neuroectoderm Development to Alzheimer's Disease?

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Abstract Sox2 is a component of the core transcriptional regulatory network which maintains the totipotency of the cells during embryonic preimplantation period, the pluripotency of embryonic stem cells, and the multipotency of neural stem cells. This maintenance is controlled by internal loops between Sox2 and other transcription factors of the core such as Oct4, Nanog, Dax1, and Klf4, downstream proteins of extracellular ligands, epigenetic modifiers, and miRNAs. As Sox2 plays an important role in the balance between stem cells maintenance and commitment to differentiated lineages throughout the lifetime, it is supposed that Sox2 could regulate stem cells aging processes. In this review, we provide an update concerning the involvement of Sox2 in neurogenesis during normal aging and discuss its possible role in Alzheimer's disease.

Keywords Sox2 · Transcription factors · Neural stem cells · Neurogenesis · Aging · Alzheimer's disease

Introduction

Sox2 (sex-determining region Y (SRY)-box 2) is a transcriptional factor that is essential for maintaining self-renewal/proliferation/pluripotency of undifferentiated embryonic stem cells (ESCs) and multipotency of neural stem cells (NSCs). The Sox family of protein was identified in 1990 after the seminal discovery of the mammalian testis-determining factor SRY that carries a characteristic high-mobility group (HMG) domain that binds DNA in a sequence-specific manner [1, 2]. Four years later, Sox2 was inadvertently discovered when Dailey and colleagues identified that fibroblast growth factor 4 (FGF4) activity was regulated by an embryonically expressed factor (then called Fx) in embryonic carcinoma F9 cells [3].

Sox2 is a well-established and crucial regulator of cell fate decisions during development (Figs. 1a and 2) but also plays an important role in adult tissue homeostasis and regeneration. As a matter of fact, Sox2 is required for the totipotency of cells during embryonic preimplantation period [4], the pluripotency of ESCs [5] and the multipotency of NSCs [6, 7] (Fig. 2). Moreover, Sox2 displays the remarkable property, when co-expressed with other synergistic factors, to reprogram somatic cells into induced pluripotent stem cells (iPSCs) [8, 9] (Fig. 1b). This makes Sox2 a key factor for the control of stem cells fate and more generally neurogenesis.

Sox2 is part of the core of the pluripotency network that operates together with other transcription factors, such as Nanog and Oct4, to promote potency of stem cells (for review, see [10]). Interestingly, this network is under the control of some intracellular signaling pathways initiated by extracellular ligands such as Wnt, Notch, FGF, leukemia inhibitory factor (LIF), and bone morphogenetic protein (BMP). It can also be regulated by epigenetic modifiers and several microRNAs (miRNAs) (Fig. 2).

Thus, as Sox2 maintains stem cell potency and self-renewal throughout the lifetime, it is tempting to envision that it may be involved in stem cell aging processes. This possibility gains support when we consider that, although aging mechanisms are different in mitotic and non-mitotic cells in some

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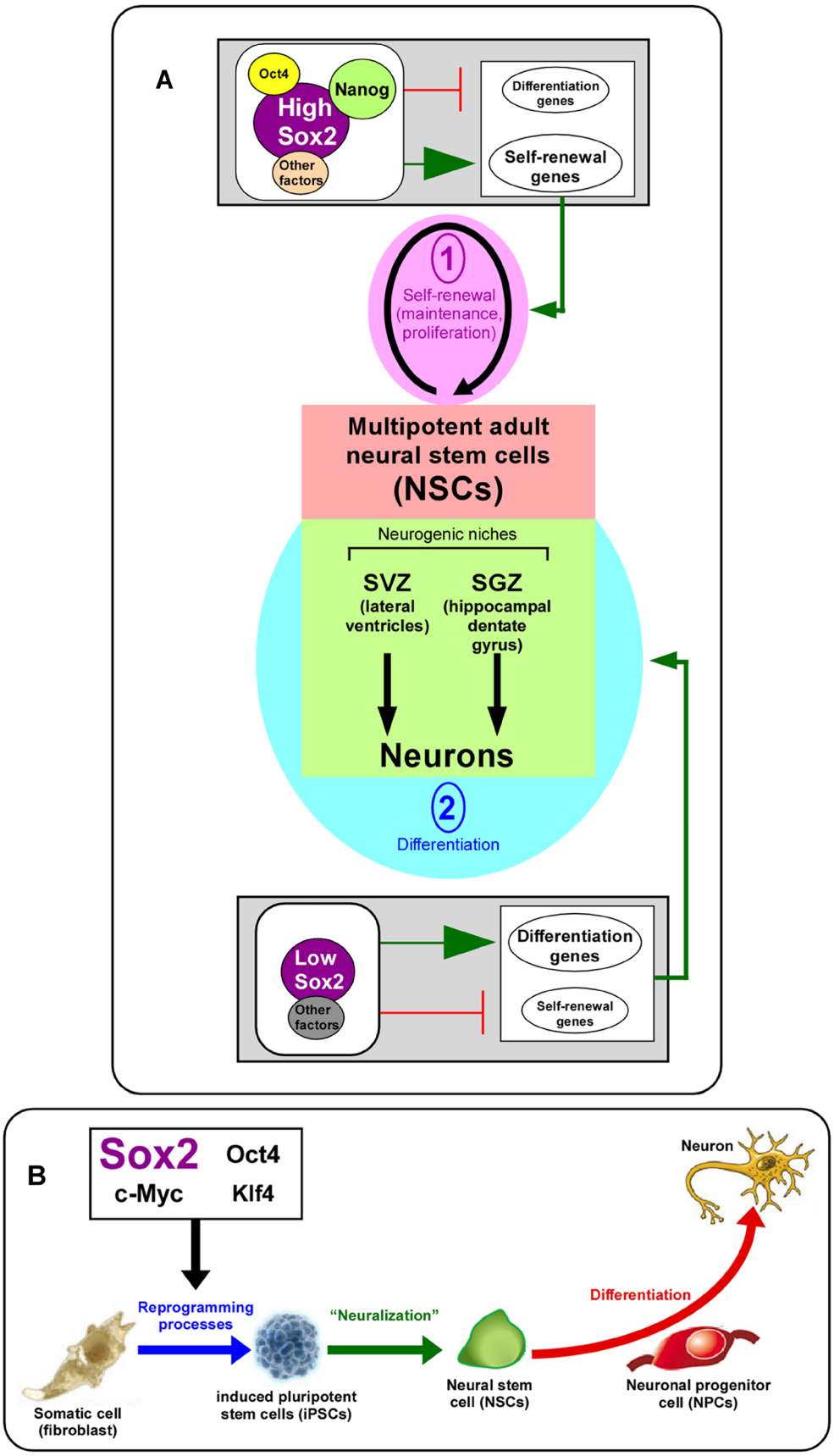

Fig. 1 Sox2 as a key component of stem cells fate and iPSCs reprogramming. **a** NSCs can self-renew (*pink circle*) or differentiate into neurons in the neurogenic niches (*blue circle*). Sox2 plays a central role in the fate of embryonic and neural stem cells through the control of the balance (activation/inhibition) of several self-renewal and differentiation genes. **b** When added, alone or in combination with Oct4, Klf4, and c-Myc, Sox2 initiate the reprogramming of somatic cells into iPSCs that can be then forced to become neurons by means of specific treatments

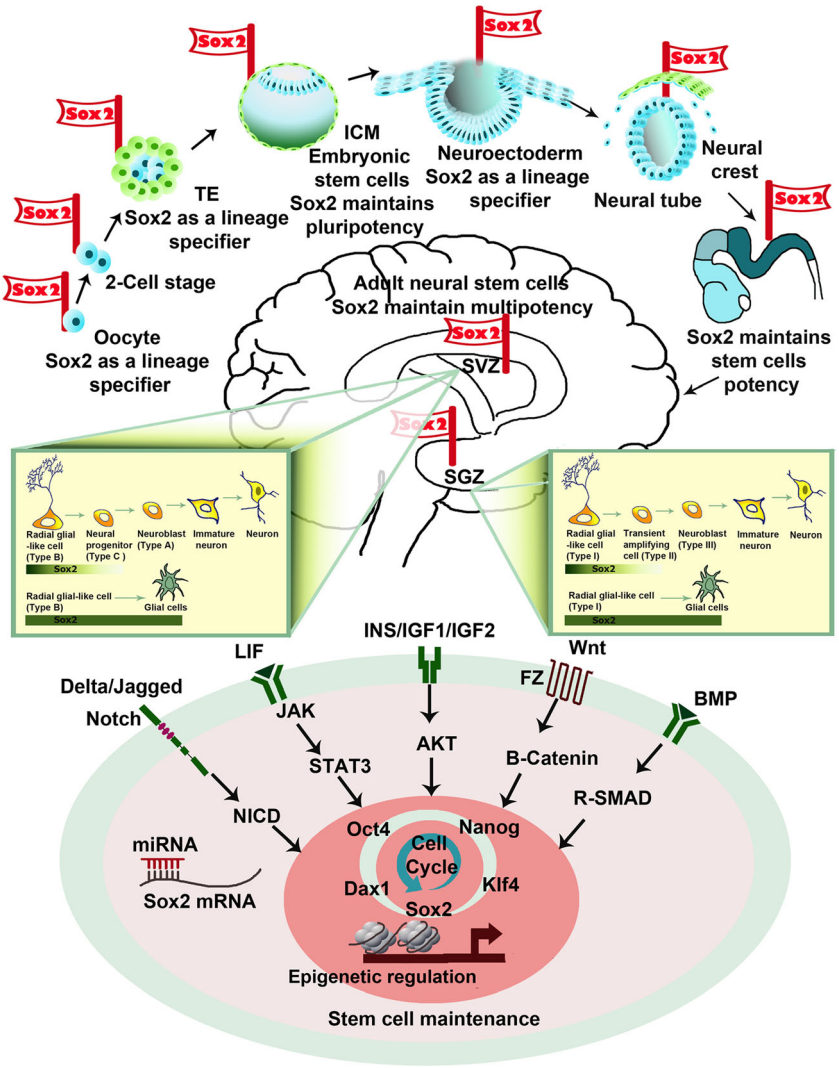

Fig. 2 Roles of Sox2 in the central nervous system throughout the lifetime. Sox2 is expressed throughout the life from oocyte stage to adult neural stem cells to maintain neural stem cells potency. Sox2, together with some transcription factors such as Oct4, Nanog, Klf4, Dax1, and others constitute a core network. This network is under the control of autoregulation mechanisms, epigenetic effects, post-translational modulations by miRNAs, and some signaling pathways initiated by extracellular ligands such as LIF (JAK/STAT), FGFs (Akt), Wnt (β-catenin), Delta/Jagged (NICD) and BMP (R-SMAD). According to the time, Sox2 makes toti-, pluri- or multi-potency under the effect of these ligands. *LIF* leukemia inhibitory factor, *FGFs* fibroblast growth factors, *BMP* bone morphogenetic protein, *TE* trophectoderm, *ICM* inner cell mass, *SVZ* subventricular zone, *SGZ* subgranular zone, *NICD* Notch intracellular domain, *Akt* protein kinase B, *STST3* signal transducer and activator of transcription 3, *JAK* Janus-associated tyrosine kinase, *INS* insulin *IGF* insulin growth factor, *FZ* frizzled, *R-SMAD* receptor-activated Smad proteins

aspects, there exist some correlations between Sox2 and some age-related factors.

The Roles of Sox2 in Neuroectoderm Development and Adult Neurogenesis

The expression of Sox2 has been observed in cytoplasm and nuclei of oocyte, two-cell stage to morula cells, in some trophectoderm (TE) cells, and all nuclei of inner cell mass (ICM) [11] as well as presumptive neuroectoderm (Fig. 2). In 9.5-day postcoitum mice, Sox2 RNA is seen throughout the brain, neural tube, sensory placodes, and branchial arches [12]. Knockdown and overexpression studies have shown the important role of Sox2 in preimplantation processes in mouse. Although the maternal Sox2 protein has been supposed to compensate for the loss of the function of Sox2 transcripts in mouse Sox2 homozygous mutant embryos [12], Sox2 knock-down by small interfering RNAs (siRNAs) in two-cell embryo mostly leads to a decrease in Sox2 level at morulae stage, developmental arrest at the morulae/blastocyst transition, and inability to form TE [11]. In addition, Sox2 overexpression in 1-cell embryo results in developmental arrest at two-cell stage and changes the reprogramming gene expression [4]. Moreover, Sox2 is clearly involved in stage-transition gene regulatory networks prior to implantation and then in the fate decision of three lineages of blastocyst to address the inner cells to epiblast [13]. Finally, in mice inner cell mass, Sox2 expression maintains pluripotency of ESCs and down-regulation of Sox2 promotes them to trophectoderm-like cells fate [14].

ESCs maintain their pluripotency until deciding to differentiate into the progenitors of mesendoderm or neural ectoderm according to the levels of Sox2 and Oct4 expression. For instance, high Sox2 and low Oct4 levels drive ESCs to neural ectoderm fate [15]. Sox2 is expressed in chick embryo throughout the neural tube and is then restricted to the medial ventricular zone and along the entire dorsoventral axis of the developing spinal cord to maintain neural characteristics of

nervous system progenitors by prevention of terminal differentiation [16]. As a matter of fact, Sox2 is expressed in proliferating central nervous system (CNS) progenitors and downregulated during their final cell cycle, and its expression inhibits neuronal differentiation and results in the maintenance of progenitor characteristics. As a corollary, inhibition of Sox2 signaling results in a loss of progenitor markers and the onset of early neuronal differentiation markers [12].

Importantly, beside its preponderant role in neuroectoderm development, Sox2 is also required for maintaining multipotency and self-renewal of adult NSCs (Fig. 2). In the CNS, NSCs are mostly located in the subgranular zone (SGZ) of the dentate gyrus and the subventricular zone (SVZ) although NSCs have been also isolated from dorsal root ganglia (DRG) [17], trigeminal ganglia [18], enteric nervous system (ENS) [19], and spiral ganglion in the peripheral nervous system (PNS) [20].

In the dentate gyrus, multipotent type-1 neural progenitor cells (NPCs) express Sox2 with other specific proteins such as glial fibrillary acidic protein (GFAP) [21], nestin and brain lipid-binding protein (BLBP) [22]. These cells, which divide at slow rate, display strong "stemness" properties and express Sox2 at high level. Type 2a hippocampal progenitor cells express high Sox2/low doublecortin (DCX) level, while type 2b show low Sox2/high DCX expression [22]. Type 2a and 2b progenitor cells then give rise to type 3 cells expressing DCX [23].

In SVZ, radial glia-like cells (type B cells) that express Sox2 and GFAP exhibit glial properties of both astrocytes and prenatal radial glia [6, 24] and act as NSCs. Transient amplifying cells (type C) are found in the rostral migratory stream (RMS) as bipotent cells, express oligodendrocyte transcription factor 2 (Olig2), achaete-scute homolog 1 (Ascl1), Dlx2, and paired box gene 2 (Pax2) [25, 26], and give rise to DCX-expressing type A neuroblasts [27].

Finally, immature neurons migrate toward olfactory bulb in rostral migratory chains surrounded by astrocytes to be neurons [28]. Sox2 expression has been reported in the undifferentiated proliferating Ki67- and BrdU-positive population cells in the SVZ and SGZ in adults [6, 7]. Neurosphere analysis of the properties of Sox2-positive and -negative transgenic models shows that Sox2-expressing cells have the capability of self-renewal and conversion to secondary neurospheres [29]. Although the differences in transcription factor levels between pluripotency and multipotency have not been clarified so far, adult Sox2-positive NSCs mostly stay in quiescence and, when activated, choose different fates: astrogliogenic asymmetric cell division, symmetric self-renewal to expand stem cells pool, or neurogenic fate [30].

In the PNS, Sox2 is also expressed in sensory progenitor cells [31]. Embryonic ENS neurogenesis starts with the migration of vagal and sacral neural crest cells toward the gut [32]. Uncommitted ENS progenitor cells that express Sox2 and Sox10 [33] and respond to Notch [34] and endothelin 3 [35] give rise to committed Phox2b-positive cells and migrate by downregulating Sox2 and expressing endothelin receptor type B (EDNRB) and RET receptor tyrosine kinase in an environment rich in glial cell line-derived neurotrophic factor (GDNF) and endothelin 3. Embryonic vagal and sacral neural crest cells migrate and colonize the entire length of the gut, and multipotent ENS progenitors remain, postnatally to adulthood, able to differentiate into neuronal and glial lineages [36].

In addition to ENS, NPCs have been also isolated from the embryonic [37] and adult DRG [17]. First, embryonic DRG stem cells are positive for Sox2 and Sox10 (which downregulate Sox2 expression during their migration) [31] and express neurogenins (NGNs) [38] and brain-specific homeobox/POU domain protein 3a (Brn3a) during their three-wave migration [39]. They then express TrkA, TrkB, TrkC, Runx1, Runx3, and Ret to differentiate into various sensory neurons [40]. Second, adult DRG progenitor cells that express Sox2, Pax6, Notch1, MASH1 together with glial GFAP/Olig1 migrate, produce neurospheres, and finally differentiate into neurons by increasing the expression of NeuroD, neurogenin1, and other neuronal markers [38].

Pluripotency maintenance is controlled by a network of genes and transcription factors, mostly Sox2, Oct4, Nanog [5], and lineage specifiers of ESCs [41]. Sox2 and its partner, Oct4, bind with transcriptional cis-regulatory Octamer/Sox element in the promoter of Nanog and control its expression. Nanog also regulates both Oct4 and Sox2 expression. These transcription factors bind with some gene promoters and control self-renewal and pluripotency of ESCs via internal negative/positive feedback circuits and autoregulatory loops [42, 43]. In addition to these transcription factors, other proteins such as Dax1 and Klf4 also play a role as main pluripotency regulatory factors with a potential of autoregulatory loops. Some ChIP experiments, together with other methods, show the occupancy of promoter/enhancer regions of these transcription factors by protein complexes or cis-regulatory elements [44, 45]. Sox2, Nanog, Oct4, Dax1, and Klf4 repress or activate their targets in association with cofactor complexes or histone modifiers. Interestingly, these transcription factors can share common targets. Although Sox2 regulates the expression of many target genes during the maintenance of stem cells, a biphasic effect has been evidenced for Sox2-dependent self-renewal/maintenance and differentiation. At endogenous levels, Sox2 associates with Oct3/4 and activates the genes responsible for cell maintenance. However, elevated Sox2 levels induce a decrease of these genes because of an activation of protein kinase B (Akt) signaling, an inactivation of forkhead box O1 (FoxO1) and consequently a decrease of endogenous Sox2 [46, 47]. Moreover, a concomitant augmentation of Sox2 and Oct4 disrupts the self-renewal of ESCs and induces their

differentiation. In contrast, elevating Sox2 along with Oct4, Klf4, and c-Myc does not disrupt self-renewal and does not promote differentiation [48]. Finally, Sox2 has been shown to maintain retinal NPCs in an undifferentiated state in a dose-dependent manner [49].

Altogether, because Sox2 can trigger opposite effects according to its level of expression, it is of utmost importance to know how this transcription factor interacts with other partners. Indeed, it has been established that Nanog-Oct4-Sox2 clusters recruit other proteins such as P300, a histone acetyltransferase [44], and some of the interactive proteins that enhance genomic stability such as stem cell co-activator (SCC)/XPC-RAD23B-CETN2 (XPC) complex (SCC/XPC) [50]. But, the most important aspect of Sox2 regulation recently emerged with the demonstration that Sox2 was tightly linked with some so-called pluripotency extracellular ligands. The most common extracellular factors that influence stem cells pluripotency include LIF [51], FGF [52], WNT/β-catenin [53], and BMP [54]. As an example, in LIF downstream signaling, Sox2 activation has been shown to occur through Jak/Stat3 and Klf4 activation, whereas Nanog is upregulated via PI3k/Akt which affects the core transcriptional network of pluripotency in mouse ESCs [55]. Moreover, Klf4 in association with Oct3/4 and Sox2 upregulates Lefty1 expression to maintain self-renewal [56].

The Connection Between Sox2 and Extracellular Signals

Several Sox2 regulatory mechanisms involving receptor-mediated signaling pathways have been evidenced (Fig. 2). This is the case for Akt, a downstream protein of insulin signaling pathway that is involved in neurogenesis. Mammalian insulin, insulin-like growth factor 1 (IGF1), and insulin-like growth factor 2 (IGF2) promote the MAPK/ERK pathway and activate Akt via PI(3,4) P2 and PI(3,4,5)P3. Activation of Akt modulates protein synthesis and autophagy in mammalian target of rapamycin (mTOR)-dependent and -independent manner [57]. The activity of this pathway must be maintained at optimal level for cellular homeostasis [58]. Akt-overexpressing adult hippocampal NPCs show slight increase in Sox2 expression during proliferation and loss of Sox2 expression in differentiation. It has been proposed that Akt modulates Sox2 mRNA levels rather than Sox2 protein stability [59]. Akt phosphorylates Sox2 at Thr118 and enhances self-renewal and pluripotency in mouse ESCs without phosphorylation of Oct4 [60]. As mentioned, Akt activation due to Sox2 overexpression has been shown to decrease endogenous Sox2 levels because of the phosphorylation of FoxO1 and its sequestration in cytoplasm. Nuclear FoxO1 binds to Sox2 promoter and leads to increased endogenous Sox2 expression, while phosphorylation of FoxO1 by Akt localizes it into the cytoplasm and prevents Sox2 expression [47]. FoxO1 knockdown results in the downregulation of Sox2, Oct4 and Nanog expression, and spontaneous differentiation in human ESCs, and this effect is enhanced by direct binding of FoxO1 to regulatory regions of these pluripotency markers [61]. In nervous system, FoxO-null brains reveal a decrease in Sox2-positive NSCs in SVZ [62]. Because autophagy is a downstream step of Akt signaling pathway, it has been shown that Sox2 overexpression induces autophagy by targeting autophagy-related protein 10 (ATG10) and Lc3 (ATG8b) expression, downregulation of total protein levels of Akt, p70S6K, and mTOR, and increasing phosphorylation of phosphatase and tensin homolog (PTEN). Sox2-induced autophagy promotes cellular senescence in cancer cells, and insulin treatment reverses this effect [63].

Wnt is a secreted lipid-modified protein that binds to frizzled (FZ) receptor and low-density lipoprotein receptor-related proteins and activates dishevelled (DVL) which promotes nuclear accumulation of β-catenin in canonical pathway. In the absence of Wnt, phosphorylated β-catenin makes a complex with glycogen synthase kinase 3β (GSK3β), adenomatosis polyposis coli (APC), and AXIN and is ubiquitinated for proteosome-mediated degradation. Wnt stimulation inhibits β-catenin phosphorylation by GSK3β which results in its translocation into the nucleus and interaction with T-cell factor/lymphoid enhancer factor (TCF/LEF) element in DNA [53]. In mouse ESCs, Wnt/β-catenin pathway upregulates Stat3 via interaction of β-catenin with TCF/LEF and promotes LIF downstream signaling to prevent differentiation and maintain pluripotency [64] and increases the efficacy of LIF signaling pathway. However, in adult NSCs niche, Wnt signaling increases neurogenesis through activation of β-catenin in SVZ [65] and SGZ [66]. Sox2-positive neurospheres are the major stem/progenitor cells which are stimulated by Wnt3a to increase proliferation and neurogenesis in postnatal mice olfactory epithelium [67]. The interaction between Wnt and Sox2 has been reported in mouse neural crest-derived osteoblast lineages [68], human and mouse osteosarcoma cell lines [69], xenopus retinal progenitor cells [70], as well as in postnatal and adult mouse NSCs [67, 71]. In the osteoblast lineage, Sox2 inhibits Wnt signaling pathway through the upregulation of APC and GSK3β, downregulation of Fzd receptor, and interaction with β-catenin to inhibit differentiation [68]. In xenopus retina, Sox2 inhibits Wnt/β-catenin and blocks neural differentiation, whereas its downregulation by proneural proteins results in neural differentiation [70]. The antagonizing effect of Sox2 and Wnt signaling pathway has been proposed to occur via the competition of β-catenin and Sox2 for the binding to Sox2 and TCF/LEF-binding sites (Sox/LEF) of target genes. Thus, while β-catenin displays a positive effect, Sox2 associated with histone deacetylase HDAC1 represses Sox/LEF element in the promoters of differentiation-specific genes in adult neural stem cells [71]. However, in neural crest-derived

osteoblasts, Sox2 directly inhibits Wnt signaling via its c-terminal domain [72].

Notch signaling has been proposed to be a mediator of the Wnt-Sox2 cross talk in neuroepithelial cells [70]. Notch is a transmembrane receptor which is classified into four types (Notch1–4) with many ligands including Jagged (Jag1 and Jag2) and delta-like proteins in mammals. Binding of these ligands to the extracellular domain of Notch triggers an intra membrane cleavage by γ-secretase and the release of the Notch intracellular domain (NICD). NICD then translocates into the nucleus and controls the transcription of a certain number of genes. Although Notch signaling plays an important role in lateral inhibition during the development of the nervous system [73], it is also expressed in adult NSCs with an effect on their maintenance [74]. Indeed, Notch1 expression has been observed in neural precursor cells and astrocytes in SVZ and neuroblasts within the RMS, and Jagged1 and Delta1 are expressed in SVZ of adult mouse brain [75]. Importantly, Notch determines neural progenitor fate in SVZ of adult rat brains [76] and controls proliferation and differentiation through maintaining neural progenitor characteristics in a dose-dependent manner. Low levels of the active form of Notch1 promote proliferation, whereas high levels lead to growth arrest [77]. Sox2 and Jag1 are coexpressed in neurosensory development, and Jag1 maintains Sox2 expression within restricted domains of the optic epithelium through a Notch-mediated lateral induction [78]. The demonstration that activated Wnt signaling induces proneural genes in retina and leads, through Sox2 and Notch, to progenitor maintenance [70] that illustrates the fact that NPCs undergo self-renewal and differentiation through a functional interaction between Wnt, Sox2, and Notch.

The Connection Between Sox2, Epigenetic Modifications, and miRNAs

The self-renewal, maintenance, and differentiation of NSCs are regulated by epigenetic mechanisms that modulate DNA without altering genomic sequences. DNA methylation and histone acetylation play an important role in activating and silencing Sox2 expression in undifferentiated NSCs and differentiated neurons. DNA methylation mostly occurs in the cytosine residues of CpG islands by DNA methyltransferases (DNMT1, DNMT2a, and DNMT2b in mammals), while histone acetyltransferases (HATs) and histone deacetylases (HDACs) catalyze histone acetylation and deacetylation. Sox2 regulatory region 1 (SRR1) and SRR2 enhancers, located 4 kb upstream and downstream from transcription start site (TSS) of Sox2 gene respectively, are involved in the epigenetic regulation of Sox2 expression. SRR1 includes POU transcription factor motif, and SRR2 contains Octamer/Sox2-binding sequence in ESCs [79], and these enhancers are also present in NSCs or NPCs [80]. In one hand, in differentiated neurons, CpGs are highly methylated at SRR1 and SRR2, whereas in NPCs, these enhancers have undergone H3 histone acetylation and demethylation [81], and it has been shown that $P27^{kip1}$ decreases Sox2 expression via its binding to Sox2-SRR2 enhancer [82]. In the other hand, Sox2 binds to distal enhancers of many genes in ESCs and NPCs, and mapping of the binding sites within 1 kb from TSS has shown that the most occupied sites in ESCs and NPCs are different [83].

The association of Sox2 with the histone deacetylase HDAC1 has been evidenced in ESCs and NSCs. HDAC1 is one of the class I HDAC family which is found in repressive complexes such as Sin3, NuRD, CoREST, and PRC2 [84]. In addition to HDAC1, Sox2 also binds to HDAC2 and has been shown to be part of protein complexes by using multiple domains to interact with its partners [85]. Embryonic and trophoblast stem cells express high level of Sox2 and HDAC1. In ESCs, HDAC1 occupies the promoters of most of the pluripotency-related genes including Sox2 and supports self-renewal and pluripotency [86]. Sox2/HDAC represses Sox/LEF element in the promoters of differentiation-specific genes such as Neuro1 in adult NSCs [71]. Sox2 has been found to be associated with the mSin3A-HDAC complex [87], which consists of HDAC1/2, Sin3A/3B, RbAp46/48, and SAP18/30, and interacts with Nanog in mammals. Nanog maintains self-renewal of NSCs by activating specific target genes under the control of the binding of Sox2 and Oct4 to its Octamer/Sox element [88], while during differentiation, Nanog is downregulated [89]. The mSin3A-HDAC complex binds to the Nanog promoter of ESCs and interacts with Sox2 to stimulate Nanog expression during proliferation, whereas this interaction is destroyed during differentiation [87].

The maintenance of stem cells is mostly controlled by polycomb group (PcG) protein-mediated histone modifications and DNA methylation, whereas trithorax group (TrxG)-mediated histone modification plays a role in differentiation [90] via acetylation of H3K27 (H3K27ac), H3K4me3, dimethylation of Lys36 on histone H3 (H3K36me2), and/or nucleosome-remodelling activities [91]. The repressive function of Sox2 on target genes is addressed by polycomb repressive complex 2 (PRC2), one of the PcG proteins. In the epigenetic control of repression, enhancer of zeste homologue 2 (EZH2), a component of PRC2, methylates lysine 27 of histone H3 (H3K27me), and PRC2 then recruits polycomb repressive complex 1 (PRC1).

The PRC1 complex contains Bmi-1 and also Ring1A proteins which are ubiquitin ligases for H2AK119, and these chromatin modifications results in the repressive function of Sox2, whereas these modifications are lost via some activators during differentiation [92, 93]. Bmi-1, as a member of PRC1, binds to repressive tri-methyl lysine 27 of histone H3 (H3K27me3) during the

epigenetic control of stem cell self-renewal [94], and overexpression/knockdown of Bmi-1 has demonstrated its role in self-renewal of NSCs [95, 96]. Bmi-1 suppresses $P16^{INK4a}$ and $P19^{Arf}$ expression, promotes stem cell self-renewal in the central and peripheral nervous system [97], and affects aging process via Ink4a/Arf locus [98]. Importantly, Sox2 increases the expression of Bmi-1 in osteoblast progenitor cells [68].

In addition to the epigenetic control of Sox2 in the nucleus, it can also be modulated by miRNAs at a post-transcriptional level. MicroRNAs, which are transcribed as primary transcripts (pri-miRNAs) by RNA polymerase II, are processed by a microprocessor complex containing Drosha and DGCR8 in the nucleus and matured by Dicer and transactivation response (TAR) RNA-binding protein (TRBP). Mature miRNAs are then incorporated into the RNA-induced silencing complex (RISC) including argonaute proteins and the single-stranded miRNA and recognize target mRNAs through the seed match sequences. It inhibits the expression of the target mRNA through deadenylation followed by mRNA degradation and blockade of translation at the initiation step or at the elongation step [99]. Several connections between Sox2 and some miRNAs have been illustrated recently. First, endogenous miR-145 represses the Oct4, Sox2, and Klf4 3′-UTR reporters in human ESCs under self-renewal conditions [100]. Second, Oct4, Sox2, and Nanog bind to the promoter region of the miR-302 cluster of miRNAs in human ESCs and regulate transcription of miR-302 which leads to the translational repression of targets such as cyclin D1 and provides a link between the transcription factors of pluripotency and cell cycle regulators in pluripotent cells [101]. Third, Nanog, Oct3/4, Rex1, and Sox2 have been identified as regulators of the miR302-367 cluster in ESCs. The comparison of transcriptional activity between the 525-bp (PROM-525) and 974-bp (PROM-974) fragments in the promoter of this cluster shows that Oct3/4 and Nanog inhibition has a negative effect on PROM-974 activity and that they act as transcriptional activators of the miR302-367 gene. In contrast, repression of Sox2 is associated with a significant increase in PROM-974 activity, thereby suggesting a potential negative regulation on the miR302-367 promoter [102]. Fourth, Sox2 expression is inhibited by miR-126 via targeting the Sox2 3′-UTR through two binding sites in gastric cancer cells [103]. Fifth, miR-296, miR-470, and miR-134 are significantly upregulated during self-renewal because of their effects on Nanog, Oct4, and Sox2, while miR-134 can silence Sox2 in ESCs [104]. Finally, miR-137 is a direct target of Sox2 and methyl CpG binding protein 2 (MeCP2) that inhibit neuronal differentiation and maturation in adult SGZ NSCs [105].

Sox2 in the Aging Nervous System

Neurogenesis in the Adult Brain and During Aging

Although the occurrence of adult neurogenesis along the SVZ-olfactory bulb axis of the brain has been evidenced more than 50 years ago [106, 107], it long remained controversial, and the cells responsible for continued neuronal and glial production were not identified. The two main properties of NSCs are their multipotency and their dual capacity of self-renewal and differentiation. During the past years, many intrinsic factors (growth factors, morphogens, neurotransmitters, and others) have been shown to regulate the decision of NSCs to proliferate or differentiate (see [108] for review). Thus, NSCs appear as a long-life source of neurons and glia (for recent review see [109]), a concept that makes obsolete the dogma that the CNS lacks regenerative power.

Very interesting is the fact that extrinsic factors such as aging, stress, and inflammation can also modulate the fate of NSCs. Although most of the studies demonstrate a decrease in proliferative activity of neural precursors with aging [110–112], some show a constant proliferation capacity throughout life [113]. Several processes have been considered to be involved in the aging of NSCs such as reduced commitment and fate changes, increased cell death, an imbalance between symmetric and asymmetric division or gliogenesis versus neurogenesis, increased quiescence, failure of the stem cells self-renewal, senescence, telomeres shortening, and telomerase deficits [114–117]. However, validation of such molecular mechanisms is still under discussion.

Aging, Oxidative Stress, and Sox2

Reactive oxygen species (ROS) producing oxidative stress are considered as the main cause of aging in non-mitotic cells, whereas the reactivity of stem cells is mostly different. For instance, it has been documented that hematopoietic stem cells (HSCs) self-renewal increases under low level ROS condition [118]. However, NSCs, when compared with HSCs, are mostly in a quiescent state, and their self-renewal, proliferation, and multipotency increase in response to elevated endogenous ROS levels. High level of ROS has been observed in DCX-positive cells rather than in Sox2- or GFAP-positive cells in SVZ [119]. In SGZ, ROS is transiently produced and reaches its highest level in intermediate precursor cells that exhibit the highest rate of proliferation, while inhibition of neurogenesis leads to a decline of oxidative stress markers [120]. The high level of endogenous ROS which is associated with higher neurosphere formation, proliferation, and multipotency of NSCs has been evidenced to be dependent on NADPH oxidase (NOX) enzymes and PI3/Akt pathway [119]. However, the effects of free radicals on the markers of NSCs may demonstrate the role of multipotency transcription factors in aging.

As far as Sox2 is concerned, Sox2-positive cells mostly observed in low ROS conditions in SVZ [119] and low levels of O_2, when compared with higher levels, enhance the expression of Sox2 and Oct4 via hypoxia-inducible factor 2α (HIF-2α) in human glioblastoma cells [121]. Thus, Sox2-positive cells, which mostly include NSCs, have been suggested to maintain low levels of ROS in quiescent state to keep their stemness property. In these cells, oxidative response is mediated by FoxO3 [122], and the balance between Akt/FoxO and JNk/FoxO has been supposed to address cells to quiescence or senescence [123]. Because a direct interaction between FoxO1 and Sox2 has been documented [47], it is proposed that the role of Sox2 in NSCs maintenance under low level ROS is correlated to FoxO proteins.

Aging, Senescence Processes, and Sox2

Senescence, a hayflick limitation and exhaustion of cell division, has been considered as an aging mechanism in mitotic cells. The number of senescent cells increases during aging, and senescence is considered as a cell cycle arrest. Indeed, cell exhaustion and senescence mechanisms include inhibition of cyclin-dependent protein kinases (CDKs)/cyclins and modulation of the mechanisms in charge of chromosome cycle (DNA replication, nuclear envelope breakdown, chromosome condensation, and spindle assembly) [124]. Moreover, telomere shortening through p53 pathway, stress-induced senescence through p16-pRB pathway, oncogenes or loss of tumor suppressor genes, oxidative stress, loss of enriched environment and cellular contacts are considered as senescence mechanisms [125, 126]. It has been evidenced that telomeres shortening and telomerase deficits mediated by p53 regulation and Notch signaling pathways impair neurogenesis and neuritogenesis in NSCs [115]. Moreover, the plasticity of the histone modification marks, H3K9m3 and H4K30m, shows more similarity at telomeric regions of iPSCs and ESCs compared with differentiated mouse embryonic fibroblasts (MEFs). Interestingly, telomerase activity increases in human iPSCs induced by Oct3/4, Sox2, Klf4, and c-Myc in human dermal fibroblasts [9]. However, the role of Sox2 in telomere elongation remains poorly defined.

In senescence-induced $p19^{ARF}$/p53/p21 pathway, the tumor suppressor protein p53 is activated downstream to DNA damage through some checkpoint kinase pathways such as DNA-dependent protein kinase (DNA-PK), ataxia telangectasia mutated (ATM), ATM rad-3 related (ATR), checkpoint kinase 1 (CHK1), checkpoint kinase 2 (CHK2), and MAPK-activated protein kinase 2 (MK2) to induce senescence or transient cell cycle arrest as a tumor suppression [127]. P53 knockdown increases self-renewal, proliferation, and apoptosis mostly via p21 in mice NSCs [128]. Moreover, p53 downregulates E2f target genes and activates cellular senescence via $p19^{ARF}$, $p16^{INK4a}$, or p21 [125]. It has been documented that p21 inhibits Sox2 expression since p21-deficient mice demonstrate high population of GFAP/Sox2-positive B-type NSCs with higher amount of Sox2, p53, and p19ARF proteins compared to wild-type NSCs. In these cells, a decrease of γH2AX-positive cells under Sox2 knockdown condition has been determined, and DNA damage occurs concomitantly with Sox2 overexpression in p21-null mice NSCs. Finally, elevated Sox2 levels trigger growth arrest and impairment of self-renewal, DNA damage, and senescence in a p53-dependent manner [129].

In $p27^{Kip1}$-mediated senescence pathway, overexpression of PTEN leads to the upregulation of the CDK inhibitor $p27^{Kip1}$ and to the negative regulation of PI3K/Akt signaling pathway [130]. Interestingly, $p27^{Kip1}$ has been considered as a Sox2 repressor, and $p27^{Kip1}$ null MEFs can be reprogrammed to iPSCs cells. In $p27^{Kip1}$-null iPSCs cells, H3K9me3 and H3K27me3 that are both repressive modifications, increase at Sox2-SRR2 enhancer similarly to retinoic acid-induced differentiation condition of MEFs. Additional experiments showed that $p27^{Kip1}$ directly binds to the Sox2-SRR2 enhancer sequence and decreases Sox2 expression [82].

Ink4a/Arf locus encodes $p16^{INK4a}$ and $p19^{Arf}$, which are mediators of cellular senescence, and their expression increases during aging [131]. In $p16^{INK4a}$ deficient mice, the number of newborn neurons increases, and $p16^{INK4a}$ upregulation causes a decline of NPCs in SVZ during aging [132]. Bmi-1, which suppresses $p16^{INK4a}$ and $p19^{Arf}$ expression, is downregulated during aging, which results in an increase of p53 positive effect on the promoter regions of antioxidant response genes, promotes oxidative stress in brain cortical neurons, and triggers aging processes [133]. Interestingly, it has been identified as a critical regulator of Sox2-dependent self-renewal in osteoblasts [68].

Aging, iPSCs Reprogramming, and Sox2

During reprograming, Oct4, Klf4, and Sox2 repress Ink4a/Arf locus whereas aging upregulates it. Thus, Ink4/Arf locus expression is considered to be responsible for the decreased reprogramming associated with aging [134]. Induction of reprogramming factors (Sox2, Oct4, Klf4, and c-Myc) triggers senescence via upregulation of $p16^{INK4a}$, $p21^{cip1}$, and p53 which results in DNA damage. Because inducing telomerase activity results in declined senescence, the cost of this rejuvenation is an increased tumorigenesis. For this reason, tumor formation is a barrier for reprogramming to pluripotent stem cells. In this context, Sox2 has been evidenced to modulate the expression of tumor progression genes and plays a role as an oncogene in esophageal and lung squamous cell carcinoma [135, 136]. Among reprogramming factors, increased Sox2 has been shown to correlate with an accumulation of p53 [129], and Sox2 has been reported as a single factor for the

reprogramming of mouse and human fibroblasts into NSCS without tumor formation [137].

Aging, Intracellular Signaling, and Sox2

Reduction of PI3/Akt pathway enhances translation of anti-stress proteins and autophagy-dependent clearance of misfolded proteins (via a reduction of FoxO1 and an augmentation of mTOR downstream signaling) and extends lifespan [63] (Fig. 3). Moreover, lysosomal autophagy protects cells against oxidative stress and enhances the degradation of dysfunctional mitochondria [138]. It has been evidenced that autophagy is promoted by Sox2 via the upregulation of ATG10 and LC3, which triggers senescence by increasing $p16^{INK4a}$, p21, and p53 in cancer cells [139]. Although Sox2 overexpression has been reported to upregulate Akt in ESCs [47], Sox2-induced autophagy has been shown to promote senescence in cancer cells through downregulation of Akt but not class III PI3K signaling [139].

Wnt/β-catenin signaling pathway promotes the expression of differentiation genes, and Wnt expression is decreased in hippocampal astrocytes during aging, thereby driving NPCs to quiescence [140]. Interestingly, Sox2 reduces Wnt signaling through the upregulation of APC and GSK3β and the downregulation of Fzd in osteoblast lineage [68] and the binding to Sox/LEF element via Sox2/HDAC1 in adult NSCs [71]. This Sox2-dependent pathway may thus be considered as a cause of the reduction of Wnt signaling during aging. In addition, in aging HSCs, Wnt signaling shifts from canonical to non-canonical pathway through the upregulation of Wnt5a and the downregulation of Wnt3a [141]. In the nervous system, Wnt3a expression, as well as the number of Wnt3a-secreting astrocytes, decreases in adult hippocampal NSCs, thereby affecting the expression of some pro-neural genes such as NeuroD1 and long interspersed nucleotide element 1 (LINE-1) and leading to a decline of neurogenesis during aging [142].

Notch1, which is expressed in neuroblasts and astrocytes in SVZ, as well as Jagged1 and NICD that regulate progenitor fate, all decreases in SVZ of aged rat brain when compared with young adult [76]. For this reason, it has been hypothesized that Notch1 signaling could play an important role in the aging-dependent declined of neurogenesis in SVZ [76] although a direct relationship between Sox2 and Notch signaling pathway remains to be firmly established.

Aging, LINE-1 Transposable Element, and Sox2

LINE-1 is a transposable element, the gene of which includes two open reading frames (ORF1 and ORF2) encoding proteins that bind to nucleic acids as well as other elements presenting reverse transcriptase and endonuclease properties. After transcription, LINE-1 mRNA is translocated into the cytoplasm for translation of ORF1 and ORF2 proteins which reintegrate LINE-1 into the genome via target primed reverse transcription (TPRT) process [143]. LINE-1 activity in the brain is greater than in other parts of the body and is mostly expressed in the spinal cord and the dentate gyrus [144]. It creates DNA double-strand breaks [145], point mutations, rearrangements, damaged chromatin, and retrotransposition, which lead to genome instability [146] and an imbalance between damage and repair during aging [147]. It has been proposed that in contrast with the impact of beneficial genetic variation on evolution, LINE-1 activation has a cost on longevity and causes aging [143]. Interestingly, methyl-CpG-binding protein (MECP2) and Sox2 are able to repress LINE-1 transcription through Sox/LEF-binding sites on LINE-1 promoter sequence [71]. Indeed, two Sox-specific SRY-binding sites are present in the LINE-1 5′-UTR close to the CpG islands and during differentiation, Sox2 and MECP2 expressions are lower in neural progenitor cell [144]. Indeed, it has been shown that the neuronal specificity of somatic LINE-1 retrotransposition in NPCs is partially due to the transition of a Sox2/HDAC1 repressor complex to a Wnt-mediated TCF/LEF transcriptional activation [71].

A Role for Sox2 in Alzheimer's Disease?

Alzheimer's disease (AD) is the most common form of neurodegenerative syndrome worldwide and is characterized by a progressive loss of memory and cognitive functions ultimately leading to dementia, vascular hemorrhage, and death.

At the brain level, post-mortem AD patients manifest a massive neuronal loss with particular damages in the regions that are responsible for memory and language. The affected brain areas display two main pathological hallmarks: (i) extracellular amyloid plaques that are mainly composed of the amyloid-β peptide and (ii) intraneuronal neurofibrillary tangles (NFT) that are due to aggregation of the hyperphosphorylated tau protein. Although they can rarely be (less than 1 %) of genetic origin (familial forms due to mutations on some genes), most of AD cases are sporadic. Nevertheless, all AD forms are characterized by the abnormal aggregation of a set of peptides called amyloid-β peptides (Aβ) that is intimately linked to the onset of the disease.

AD, the Amyloid Hypothesis, and βAPP Processing

According to the amyloid hypothesis, β-amyloid peptide (Aβ) that is produced from the β-amyloid precursor protein (βAPP) accumulates because of an imbalance between its production and clearance and initiates subsequent deleterious events (tau hyperphosphorylation, inflammation and neuronal death) that ultimately lead to memory deficits and dementia.

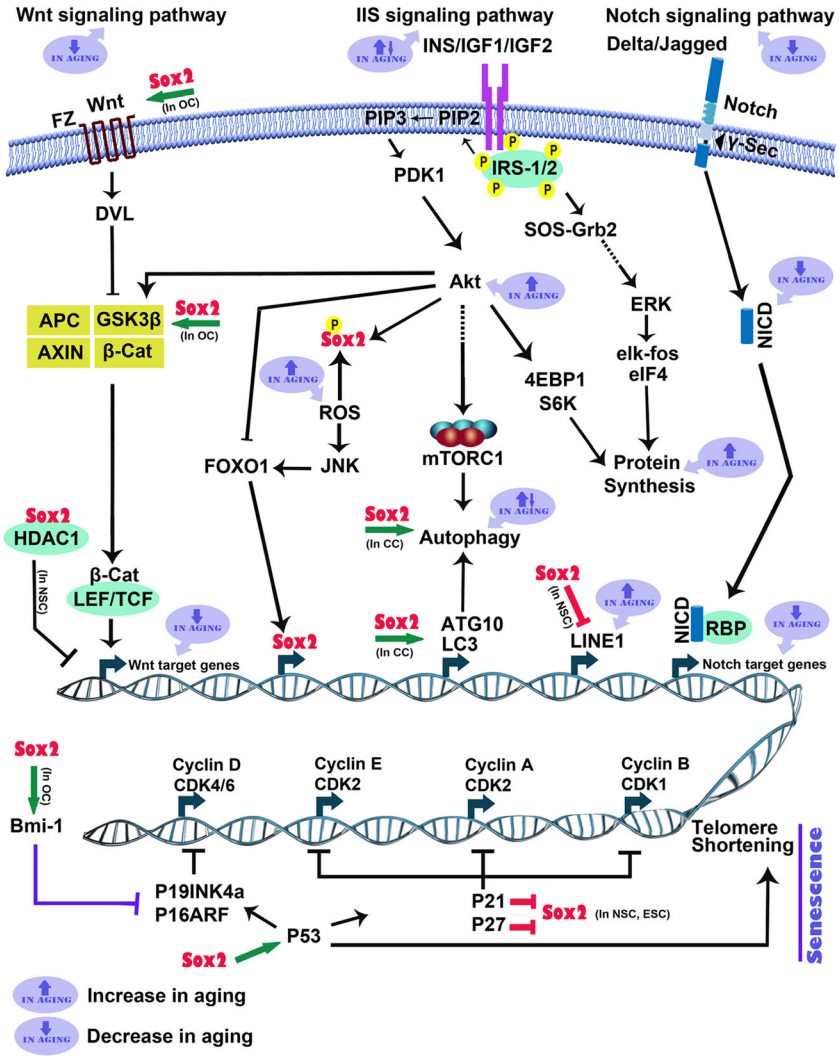

Fig. 3 The functional cross-talk between Sox2 and some signaling pathways that are involved in the aging processes. Wnt/β-catenin signaling pathway efficacy which promotes differentiation genes through the binding of β-catenin with TCF/LEF decreases in hippocampal astrocytes during aging. Sox2 inhibits Wnt signaling pathway by upregulation of APC and GSK3β, downregulation of FZ receptor, interaction with β-catenin to inhibit differentiation in the osteoblast lineage and repression of Sox/LEF element associated with HDAC1 in the promoters of differentiation-specific genes in adult neural stem cells. In mammalian insulin/IGF signaling pathway, Akt is upregulated during aging, which increases mTORC1 and authophagy and protein synthesis. It phosphorylates Sox2 at Thr118 to modulate Sox2 protein stability and inhibits FoxO1 which increases endogenous Sox2 expression. Sox2 induces autophagy via upregulation of ATG10 and LC3 and results in senescence in cancer cells. Sox2 suppresses LINE-1 expression which has upregulation during aging. In senescence pathways, Sox2 increases the expression of Bmi-1 which suppresses $P16^{INK4a}$ and $P19^{Arf}$ expression. On the other hand, p21 and $p27^{kip1}$ which mediate senescence pathways inhibit Sox2 expression. Elevated Sox2 levels trigger impairment of self-renewal and senescence in a p53-dependent manner. Notch signaling efficacy also declines in aging via decrease in Notch, Jagged1, and NICD in neuroblasts and astrocytes in SVZ. *TCF/LEF* T-cell factor/lymphoid enhancer factor, *APC* adenomatosis polysis coli, *GSK3β* glycogen synthase kinase 3β, *FZ* frizzled, *β-cat* β-catenin, *HDAC1* histone deacetylase 1, *IGF* insulin-like growth factor, *IIS* insulin/IGF-like signaling, *IRS* insulin receptor substrates, *PDK1* phosphatidylinositol-dependent protein kinase 1, *mTORC1* mammalian target of rapamycin complex 1, *FoxO1* Forkhead box O1, *CC* cancer cells, *OC* osteoblast cells, *NSC* neural stem cells, *ESC* embryonic stem cells, *NICD* Notch intracellular domain, *p* phosphorylated, *ROS* reactive oxygen species, *LINE1* long interspersed nucleotide element-1

Aβ peptides are produced through the so-called amyloidogenic pathway by the sequential cleavages by β- and γ-secretases [148] (Fig. 4). The β-secretase has been identified in 1999 by four independent research groups as a new aspartyl protease called Beta-site APP-cleaving enzyme 1 (BACE1) [149], while γ-secretase is a generic term defining an heterotetrameric complex composed of presenilin 1 or 2, anterior pharynx defective-1 (Aph-1), presenilin enhancer-2 (Pen-2), and nicastrin [150].

On the other hand, there exists an alternative non-amyloidogenic α-secretase cleavage mainly performed by two enzymes (ADAM10 and ADAM17) that are members of the disintegrin family of metalloprotease and are respectively responsible for the constitutive and PKC-regulated

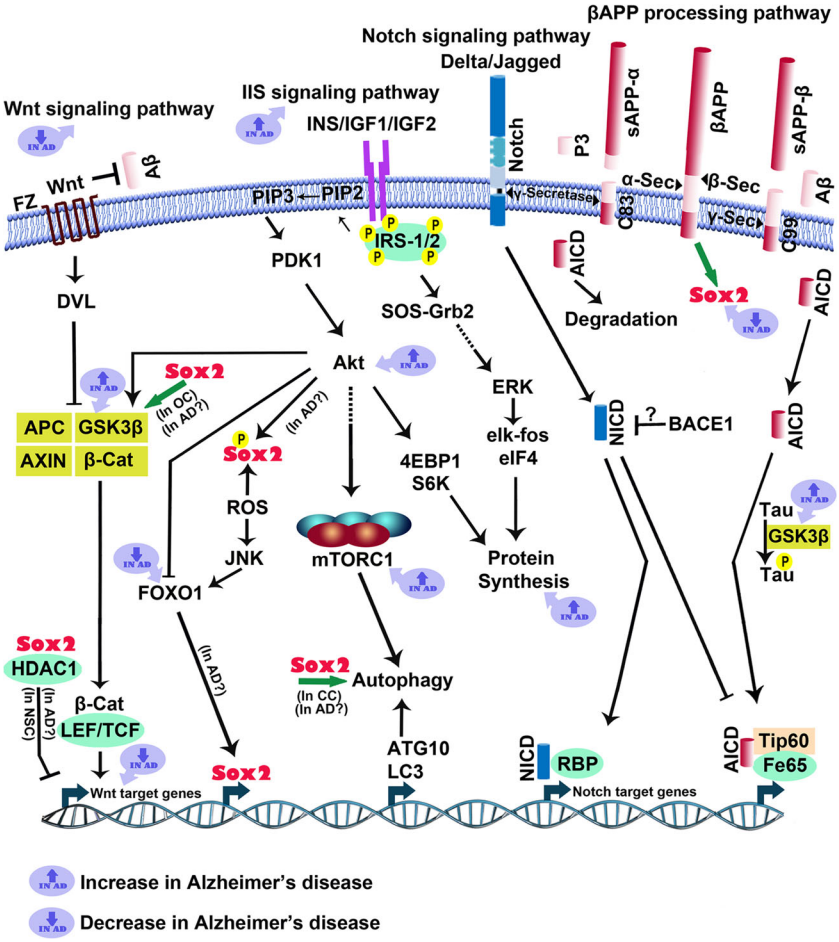

Fig. 4 The connections between Sox2 and some signaling pathways that are modified in AD pathology. Since Sox2 is decreased in AD brain and because βAPP overexpression triggers an augmentation of Sox2 levels, one can reasonably envision that Sox2 may have an impact on the development of AD. Moreover, several Sox2-connected signaling pathways are affected in AD. Thus, the efficacy of Wnt, which protects hippocampal neurons from Aβ oligomers declines in AD. GSK3β, which phosphorylates both β-catenin and tau protein increases in AD and stimulates Aβ production. Sox2 combined with HDAC1 represses Sox/LEF element in the promoters of differentiation-specific genes in adult neural stem cells. Although Sox2 inhibits Wnt signaling pathway via an interaction with GSK3b in the osteoblast lineage, its effect in AD is unknown. NICD, the downstream effector of Notch signaling, is produced by γ-secretase, a shared enzyme between βAPP processing and Notch signaling, and inhibits AICD-Tip60-Fe65 complex through physical interaction. The β-secretase BACE1 also interacts with the Jag1-Notch pathway and NICD production. Activation of Akt by insulin/IGF1 increases in AD thereby leading to more GSK3β, tau phosphorylation, and mTOR levels in the cortex. However, the level of FoxO1 expression declines as a result of overexpression of Akt in AD. Although Sox2 phosphorylation by Akt and its upregulation by FoxO1 have been evidenced in cancer cells, the occurrence of such effects in AD remains to be determined. *AD* Alzheimer's disease, *APP* amyloid precursor protein, *sAPP* soluble *APP*, *AICD* APP intracellular domain, *Aβ* amyloid-β peptide, *Sec* secretase, *TCF/LEF* T-cell factor/lymphoid enhancer factor, *APC* adenomatosispolysis coli, *GSK3β* glycogen synthase kinase 3β, *FZ* frizzled, *β-cat* β-catenin, *HDAC1* histone deacetylase 1, *IGF* insulin-like growth factor, *IIS* insulin/IGF-like signaling, *PDK1* phosphatidylinositol-dependent protein kinase 1, *IRS* insulin receptor substrates, *mTORC1* mammalian target of rapamycin complex 1, *CC* cancer cells, *OC* osteoblast cells, *FoxO1* Forkhead box O1, *p* phosphorylated, *ROS* reactive oxygen species, *NICD* Notch intracellular domain

pathways [151]. This proteolytic event occurs in the middle of the Aβ sequence, thereby precluding its production. Moreover, this cleavage leads to the secretion of the large neurotrophic and neuroprotective-secreted sAPPα fragment as well as its C-terminal counterpart C83.

AD and Stem Cells

It has been documented that proliferation and differentiation of NSCs first decrease in AD before a subsequent increase as a compensatory mechanism in SVZ and SGZ. Moreover, neurogenesis marker proteins such as DCX, PSA-NCAM, TUC-4, and NeuroD are upregulated in the subgranular zone of dentate gyrus in AD hippocampus [152]. Recently, stem cell therapy for patients with AD and iPSCs usage in AD animal models have been envisioned with a particular focus on the core transcriptional network (including Sox2) that is responsible for the maintenance of pluripotency and multipotency. Because many evidences suggest that adult neurogenesis contributes to learning and memory [153], stem

cell therapy has been considered as a possible treatment for neurodegenerative disorders. In spite of the limitation in transplantation, mainly due to grafts rejection and tumor production, derived neurons or glial cells from ESCs or NSCs have been tested as an effective treatment in vivo in animal models of AD [154–157]. As a proof of concept, transplantation of ESCs-derived neurospheres into some cortical areas in nucleus basalis of Meynert lesion in AD mice model has been shown to trigger the production of ChAT-positive and serotonin-positive neurons around the graft [154]. Moreover, transplantation of NSCs with transgenic expression of human nerve growth factor (hNGF) into the brain enhances cognitive performance in rat model of AD [155], and behavioral recovery has been observed following the induction of mouse ESCs-derived NPCs into cholinergic cells and their transplantation into the mouse models of AD [156]. Finally, transplanted human NSCs line was found to differentiate in cerebral cortex, hippocampus, striatum, and septum in a rat model of AD [157].

However, because accessibility and isolation of NSCs out of their in vivo environment are problematic, an alternative to NSCs transplantation was awaited. In 2006, a huge step forward in the field of cell biology occurred with the first description of a simple method to dedifferentiate somatic cells (fibroblasts) to embryonic-like iPSCs in mouse [8]. One protocol consists of the retroviral delivery of a cocktail of just four genes (Sox2, Oct4, Klf4, and c-Myc), and this method was shown to also work for other species including humans [9]. Interestingly, it has been demonstrated recently that iPSCs induction can be performed by the sole Sox2 transcription factor [137]. These pluripotent iPSCs can then be differentiated into any kind of cells according to the treatment applied and thereby provide a simple way to obtain cultured cells issued from a whole organism. This approach allowed, via iPSCs, the obtention of genuine neurons issued from fibroblasts of AD patients. This so-called "AD modeling" process has been successfully achieved by several laboratories during the past 3 years [158].

βAPP, βAPP-Derived Metabolites, βAPP-Cleaving Secretases and Stem Cells

Several lines of evidence have established the occurrence of a functional link between NSCs fate and βAPP biology. First, neurogenesis and the number of BrdU-positive cells decrease in SVZ and SGZ in βAPP-overexpressing transgenic mice models of AD [159–161]. Second, βAPP overexpression in embryonic stem cells has been evidenced to promote differentiation with an altered morphology of human ESCs colonies, neuronal markers, and neurite outgrowths [162]. Third, βAPP and its parent protein APLP2 can respectively upregulate neuronal migration and NSCs differentiation during mammalian cortical development [163, 164]. Altogether, this most likely means that βAPP itself, Aβ, βAPP C-terminal fragments, and possibly others play a role in the AD-dependent decrease of NPCs differentiation.

As far as βAPP-derived fragments are concerned, ESCs express the three secretases responsible for βAPP processing and, as a consequence, produce detectable levels of Aβ, C99, and sAPPα [165]. Not surprisingly, it has been established that Aβ and sAPPα treatments modulate the proliferation/differentiation of ESCs into neural progenitor cells in various manners (induction of proliferation by soluble Aβ and fibrillar Aβ, induction of differentiation by sAPPα, and inhibition of proliferation by oligomeric Aβ) [165].

Considering Aβ, although a neurogenic effect of oligomeric Aβ42 has been described [166], a correlation between the impairment of the differentiation into neurons and Aβ production/deposition has been evidenced [159, 167]. Another study established that Aβ decreases neurogenesis via apoptosic pathways and downregulation of β-catenin in newborn neurons, thereby leading to Wnt/β-catening signaling impairment in glial progenitor cells [168].

Concerning the large secreted sAPP fragments, the fact that sAPP-binding sites, which regulate proliferation of adult progenitors in response to either epidermal growth factor (EGF) or sAPP and increase the number of BrdU- and epidermal growth factor receptor (EGF-R)-positive NSCs, is present in SVZ goes in favor of a role for sAPP in neurogenesis [169]. In addition to SVZ, both sAPPα and sAPPβ regulate proliferation and differentiation of NSCs in SGZ [170] with sAPPβ being more potent than sAPPα at inducing differentiation in human ESCs [162]. Although the underlying signaling pathway is still poorly understood, it has been established that sAPPα modulates depolarization-induced neurite outgrowth via MAPK activity in NPCs-derived neurons [171].

Finally, the βAPP intracellular domain AICD impairs adult neurogenesis in AD mouse model by inducing inflammation and reducing adult hippocampal neurogenesis in an age-dependent manner [172]. Moreover, proliferation of NSCs declines in the SGZ of hippocampus of AICD transgenic mice, and AICD downregulates cell survival without specific effect on differentiation of newly generated hippocampal cells [173].

Regarding the impact of the βAPP-cleaving proteases (more commonly called "secretase" and responsible for the production of the here above mentioned metabolites) on NSCs fate, pharmacological inhibition of the amyloidogenic β-secretase BACE1 has been shown to suppress proliferation and promote NPCs formation [165], whereas another study established that BACE1 knockout increases astrogenesis and decreases neurogenesis [174]. These data appear conflicting, and further studies are now required to delineate the exact role of this enzyme in neurogenesis under normal and pathological (AD) conditions. Information concerning the involvement of presenilin 1 (PS1) (the catalytic core of the amyloidogenic γ-

secretase complex) in neurogenesis under physiological conditions are still lacking at present, and the only data published so far have reported that FAD-linked PS1 mutations impair adult neurogenesis in transgenic mouse models of AD [167, 175–178]. Finally, the role of the nonamyloidogenic α-secretases ADAM10 and ADAM17 in adult neurogenesis under normal and pathological conditions is still unknown. Concerning ADAM10, it has been suggested, but not proved, that it could play a role in neuronal maturation during cortex development via the processing of Notch [179]. As far as ADAM17 is concerned, a role for this protease in the upregulation of proliferation after stroke in the SVZ has been evidenced [180], and an increase of proliferation/decrease of differentiation via Notch signaling has been shown in glioblastoma stem cells [181].

AD and Sox2

It is widely accepted that neurogenesis contributes to learning and memory. Thus, considering the strong implication of Sox2 in regulating the fate of stem cells and given the fact that neurogenesis and cognitive functions including memory are impaired in AD, one can reasonably postulate that this transcription factor could play an important role in the development of this neurodegenerative disease. Two independent studies have supported this hypothesis. First, Sox2 deficiency not only impairs neurogenesis but also induces neuronal degeneration in the adult mouse brain [6]. Second, Sox2 levels are strongly decreased in the brain of transgenic mouse model of AD as well as in the brain of AD patients [182]. Of utmost importance is the observation that the Sox2 decrease in AD cases positively correlates with the severity of the disease [182]. These complementary data strongly support the fact that any decrease of Sox2 could favor AD pathology.

Intracellular Signaling Pathways as Common Denominators to Sox2 and AD

It is striking that most of the signaling pathways that interact with the Sox2 transcription factor are also implicated in AD (Fig. 4). First, the Sox2-regulating Insulin/IGF1/Akt signaling pathway increases in AD and leads to more phosphorylation of Akt targets such as GSK3β, Tau, and Mtor, while PTEN is downregulated in cortex of AD patients [183]. In addition, some studies showed that the inhibition of PI3K/Akt pathway increases the level of the γ-secretase complex and the ubiquitination of PS1 [184], whereas the stimulation of this pathway promotes phosphorylation and inactivation of IRS-1/2 as a mechanism of insulin resistance in AD. Moreover, an increase of inactivated phospho^{ser312} IRS-1 and phospho^{ser616} IRS-1 is observed in NFTs [185], and phospho$^{ser636/639}$ IRS-1 levels have been found to be negatively correlated with episodic and working memory [186]. The levels of FoxO1 expression decline as a result of overexpression of Akt in AD [123], whereas PTEN, PP2A, and mTOR/S6K activities negatively regulate the PI3K/Akt pathway. Finally, the activation of PI3K/Akt signaling has been shown to be sustained in the brain of patients with AD, and turning off/on of this pathway modulates LTP/LTD [63]. Thus, the rather strong correlation between Akt signaling pathway with both Sox2 and proteins involved in the development of AD makes highly plausible the hypothesis that Sox2 may play an important role in AD development.

As previously mentioned, Sox2 interacts with the Wnt signaling pathway that is also supposed to be involved in the pathogenesis of AD. Indeed, loss of Wnt signaling triggers GSK3β activation, intracellular amyloid deposition, β-catenin degradation, and activation of some apoptosis pathways and ultimately leads to AD. As a reminder, GSK-3β both stimulates Aβ production and phosphorylates Tau protein [187], and it has been evidenced that PS1 mutation enhances proliferation of NPCs via an alteration of Wnt/β-catenin signaling [188]. It has also been shown that canonical Wnt/β-catenin protects hippocampal neurons from Aβ oligomers with the blockade of neuronal apoptosis and that Wnt3a increases cell survival toward Aβ-dependent neurotoxicity, inhibits GSK-3β activity and Tau phosphorylation, and prevents Aβ-induced apoptosis [189]. In the non-canonical Wnt signaling pathway, GSK3β inhibition stabilizes β-catenin, modulates mitochondrial dynamic, prevents Aβ-dependent Bcl2 augmentation, and reduces the neurotoxicity of Aβ oligomers [190]. In addition, inhibition of GSK-3β by lithium has been shown to protect rat hippocampal and cortical neurons from Aβ-induced damage through the reduction of total Aβ in brains of APPswe+PSEN1ΔE9 transgenic mice [191]. Finally, Wnt5a prevents synaptotoxicity changes induced by Aβ oligomers on PSD-95 clustering in synaptic contact [192]. Altogether, these data established that the efficacy of the Wnt/β-catenin signaling declines in AD and that Sox2, which negatively correlates with this pathway, is likely to have an impact on AD pathology.

As far as the Notch signaling pathway is concerned, it has been well established that Notch, as well as βAPP and other trans-membrane proteins, is cleaved inside the plasma membrane by γ-secretase to give rise to NICD [193]. Noteworthy, because AICD-Tip60-Fe65 complex is suppressed by NICD through physical interaction [194] and given the fact that all three partners can have an impact on NPCs fate, one could envision a putative NICD/AICD/Sox2 regulatory loop.

βAPP and Sox2

The occurrence of a functional cross-talk between Sox2 and βAPP emerged during the past years. First, Sox2 colocalizes with βAPP and Fe65 in the NSCs niche of the fetal ventricular

zone, and TAG1-βAPP signaling negatively modulates neurogenesis in an AICD/Fe65-dependent manner [195]. Consistent with these findings, it has been established that Sox2 colocalizes with βAPP in both NSCs and NPCs of the adult SVZ [196]. Second, βAPP overexpression causes a rapid differentiation and alters the morphology of human ESCs, and it has been shown that the expression of Sox2 increases in βAPP_{WT}- and βAPP_{Swe}-overexpressing human ESCs cells when compared with controls [162]. However, a decrease of Sox2 expression has been reported in the hippocampus of βAPP-tg mice [182]. Some important issues remain to be solved, and it will be now crucial to determine, by means of genetic and pharmacological approaches, whether the observed effects are due to full-length βAPP or to some βAPP-derived metabolites. On the other hand, the described opposite effects of βAPP on Sox2 in stem cells and hippocampus mentioned above may reflect some regional or cell-specific Sox2-βAPP functional interactions in the brain. A detailed mapping of βAPP-Sox2 cross-talk in various cell lines and brain areas should answer this important question in the future.

Secretases and Sox2

Any functional cross-talk between Sox2 and secretases themselves has been documented so far, although Sox2 colocalizes with the α-secretase ADAM10 in NSCs of the SVZ [196]. However, the fact that some βAPP-derived fragments might be responsible for the observed βAPP-dependent, Sox2 regulation could illustrate an indirect involvement of these proteolytic activities. This issue deserves particular attention, and several works provide some weight to this hypothesis. First, as mentioned in a previous paragraph, transgenic mice overexpressing mutated presenilin 1 (the catalytic core of the γ-secretase complex) display a reduced number of both NSCs and NPCs in the hippocampus when compared to wild-type animals [167, 175–178]. Second, a very recent study has established that the β-secretase BACE1 can control the balance between neurogenesis and astrogenesis via the Jag1-Notch pathway and that NICD production and full-length Jag1 protein levels significantly increase in BACE1 null mice [174].

In summary, the present available data strongly support the possibility that full-length βAPP, some of the βAPP-derived metabolites and/or the proteases responsible for βAPP processing, could interact with Sox2, and we can reasonably hypothesize that this functional cross-talk could have an important role during normal adult neurogenesis and that an imbalance of this network could contribute to AD.

Conclusion

In spite of an intense multidisciplinary research, effective treatments to improve cognitive impairments in normal and pathological aging, especially Alzheimer's disease, are urgently required. Although the boundary between normal aging and age-related neurodegenerative diseases remains to be determined, some fundamental mechanisms undergo the same pathways. Stem cell therapy, which has been considered as a treatment in neurodegenerative disorders, demonstrates some limitations like insufficient survival and stability after transplantation and graft rejection or tumor production of ESCs, iPSCs, MSCs, or NSCs following transplantation [197]. Moreover, senescence is a barrier for reprogramming. In order to identify new tracks aimed at making possible AD-targeting stem cell therapy, the modeling of iPSCs-derived neurons in AD represents an important step forward.

In this context, a functional interaction between Sox2, proteins involved in AD and some signaling pathways that control normal aging and are modified in AD, is worth envisioning. Undoubtedly, Sox2 and βAPP/βAPP metabolites both interact with Wnt/β-catenin, Notch, and PI3K/Akt signaling pathways. First, during normal aging, Wnt/β-catenin signaling that promotes neurogenesis declines in neural stem cells due to the weak production of Wnt or to the increased action of negative regulators of the pathway such as Sox2. Antagonizing effect of Wnt/β-catenin on Aβ has been evidenced in AD. Second, PI3K/Akt is mostly overexpressed to address more protein synthesis and inhibits autophagy, whereas Sox2 expression, which promotes autophagy, is suppressed via the inhibition of FoxO1 by Akt. In addition, Sox2 phosphorylation is promoted by Akt signaling. However, the activity of this signaling pathway increases during aging and AD. Third, Sox2 interacts with the Notch pathway that, like βAPP, undergoes γ-secretase cleavage and with some cell cycle regulators that promote senescence.

Overall, according to the preponderant action of Sox2 in the balance between self-renewal and differentiation during neurogenesis and its involvement in some pathways correlated with normal aging and AD, it is proposed that Sox2 may play an important role in neurodegeneration and stem cell aging and that its modulation could be used in ESCs, NSCs, or iPSCs replacements that recently have been considered as a new therapeutic strategy to fight neurodegenerative diseases.

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