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MINIREVIEWS

Sox2 transcription network acts as a molecular switch to regulate properties of neural stem cells

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Abstract

Neural stem cells (NSCs) contribute to ontogeny by producing neurons at the appropriate time and location. Neurogenesis from NSCs is also involved in various biological functions in adults. Thus, NSCs continue to exert their effects throughout the lifespan of the organism. The mechanism regulating the core functional properties of NSCs is governed by intra- and extracellular signals. Among the transcription factors that serve as molecular switches, Sox2 is considered a key factor in NSCs. Sox2 forms a core network with partner factors, thereby functioning as a molecular switch. This review discusses how the network of Sox2 partner and target genes illustrates the molecular characteristics of the mechanism underlying the self-renewal and multipotency of NSCs.

Key words: Neural stem cells; Self-renewal; Multipotency; Sox2; Transcriptional network

Core tip: Neural stem cells (NSCs) are cells that are capable of both self-renewal and multipotency. In these two processes, the transcription factor Sox2 serves as a switch for the central molecular mechanism. Sox2 forms complexes with its partner factors to perform its transcription-related functions. This partner switching presumably serves as an important key to the intrinsic functions of NSCs. A detailed understanding of these molecular mechanisms will advance our understanding of basic neuroscience and increase the feasibility of employing cell reprogramming technology in regenerative medicine.

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INTRODUCTION

Neural stem cells (NSCs) are cells that are capable of self-renewal and maintaining multipotency[1,2]. NSCs differentiate into neurons, astrocytes, and oligodendrocytes. The cellular origin of mouse NSCs dates back to the initial stage of ontogeny. A blastocyst generates the primitive ectoderm, further differentiating into the neuroectoderm, which serves as a source of primitive NSCs[3,4]. The neuroectoderm then develops and differentiates into the neuroepithelium[3,4]. Primitive NSCs exhibit self-renewal with a rather limited multipotency[5]. On embryonic day 11.5 (E11.5) in the murine fetal period, differentiation into neurons dominates while differentiation into the astrocyte lineage is suppressed by DNA methylation. Then at E14.5, NSCs begin to produce neurons and astrocytes[6-8]. After birth, NSCs manifest their ability to produce oligodendrocytes[8]. NSCs also actively undergo repeated self-renewal in the region of the central nervous system after birth to generate neurons, astrocytes, and oligodendrocytes in a region-dependent manner to build the brain as an organ. It was previously believed that neurons

do not regenerate once the brain organogenesis is complete in an adult organism. However, the study[9-13] revised this dogma, and it is now known that neurogenesis takes place even in the adult brain. This process has been best studied in the subventricular zone (SVZ) of the lateral ventricle and the subgranular zone (SGZ) lining the hippocampal region, where NSCs are located and produce new nerve cells through self-renewal[1,14-20]. Understanding the molecular biology underlying the capacity of NSCs to exhibit self-renewal and multipotency is expected to stimulate our exploration of basic neuroscience and lead to practical applications in regenerative medicine, allowing lost neurons to be regenerated as desired. Although some NSCs can be cultured from body tissues as the monolayer[21-23], there are technical challenges as well as issues of productivity and quality related to the practical use of such cultured NSCs in regenerative medicine. However, a new technology was recently developed to reprogram somatic cells through the gene transfer. Using this technology, combinational transfection of the *Oct4*, *Sox2*, *Klf4*, and *c-Myc* genes into various cells can establish a type of multipotent stem cells, called induced pluripotent stem (iPS) cells[24,25]. By changing the culture conditions under which iPS cells are established, we can artificially induce differentiation into NSCs[26]. This technology has also been utilized to develop induced neuronal (iN) cells, which directly induce differentiation into neurons[27]. iN cells are obtained by transfecting the *Ascl1*, *Brn2*, and *Myt1l* genes into fibroblasts. The gene cluster serving as the switch to precisely regulate cell fate mainly includes transcription factors. One key factor that plays an important role in NSCs is the transcription factor Sox2. Transcription factors bind to response regions in the genome to initiate or terminate the expression of target genes. Concomitantly, they interact with a group of chromatin-regulating factors other than transcription factors to perform various regulatory functions. In this review, I focus on the transcription regulatory network centered around Sox2 to shed light on the molecular regulatory mechanism underlying the biology of NSCs.

NEURAL STEM CELLS AND SOX2

Sox2 belongs to the *Sry* gene family and contains a DNA-binding domain referred to as a high-mobility group (HMG) domain, which is highly conserved across the family. To date, more than 20 genes have been identified in the *Sox* gene family[28,29]. Sox2 is a maternal factor that is specifically expressed in the inner cell mass (ICM) and primitive ectoderm[30]. Sox2 expression is widely observed among the cells within the neural tube at early stages of neurodevelopment[31]. Its expression is subsequently localized to the ventricular layer in the neuronal cortex, where NSCs and their precursor cells are present after the mid-fetal period. During this period, Sox2 is not expressed in layers where terminally differentiated neurons are present[32]. In the adult brain, NSCs are localized to the SVZ of the lateral ventricle and the SGZ lining the hippocampal region, where they undergo self-renewal and perform neurogenesis[1,14]. All of such self-renewing cells express Sox2. Sox2 plays an important role in maintaining the functions of NSCs[32-35]. It has been reported that SoxB1 family members, Sox1 and Sox3, which show high sequence homology to Sox2, exhibit similar functions[36]. Sox2 functions as a maternal factor in pre-implantation embryos[30]. Zygotic knock-down of Sox2 using a specific siRNA resulted in an incomplete trophectoderm (TE) in fertilized embryos, which failed to progress beyond the morula stage[30]. Sox2 expression is detected in both the ICM and TE, and its expression becomes restricted to the ICM[29]. During embryogenesis, the ICM becomes the embryo, and the TE forms the placenta. A high level of *Sox2* gene expression has been confirmed in the neuroectoderm that gives rise to NSCs[31]. During embryogenesis, Sox2 promotes neuroectoderm cell fate by suppressing the mesodermal cell fate[37]. Moreover, Sox2 plays important roles in the differentiation of the central nervous system and peripheral nervous system during embryogenesis by controlling the proliferation and differentiation of neural stem/progenitor cells[32]. Sox2 deficiency is embryonically lethal in mice because the fetus fails to form embryonic stem (ES) cells from the ICM or produce trophoblast stem cells[30,38]. Sox2 conditional knock out (KO) mice have been reported to undergo neurodegeneration leading to dysfunctional neuronal differentiation in the adult brain[35,39]. Various research approaches have been employed to demonstrate that Sox2 expression is localized to NSCs and that its function is essential for these cells.

SOX2 AND ITS PARTNERS

Sox2 collaborates with other transcription factors[40,41]. In ES cells and NSCs, Sox2 regulates the self-renewal mechanism and suppresses differentiation in a dosage-sensitive manner[42,43]. Sox2 and a POU factor known as Oct4 form a specific partnership to coordinately regulate the mechanism that maintains undifferentiated ES cells[44,45]. The target genes of this partnership include *Nanog*, *Utf1*, and *Fgf4*[4]. Sox family members form partner complexes with POU factors, but the partnership assumes various forms depending on the cell type[41]. In NSCs, Sox2 interacts with POU factors such as Pax6, Brn1, and Brn2, where Pax6 forms complexes with Sox2 to regulate the differentiation of cells of the optic nerve and lens[46-49]. Pax6 is coexpressed in Sox2-positive cells and reportedly regulates the self-renewal and neurogenesis of NSCs in the hippocampus in the adult brain[50]. The expression of Nestin, a marker for NSCs, is coordinately regulated by Sox2 and POU factors[47,51]. Sox2 and the partner code of Brn1 and Brn2 bind to the regulatory region of the Nestin and Sox2 genes to perform an important function in the regulation of gene expression[47,51-53]. Furthermore, Sox2 can bind to Prx1 (MHox1/Prrx1) and function as its partner[54]. Because Prx1 and Sox2 are coexpressed in certain cells in the NSC region, they are expected to

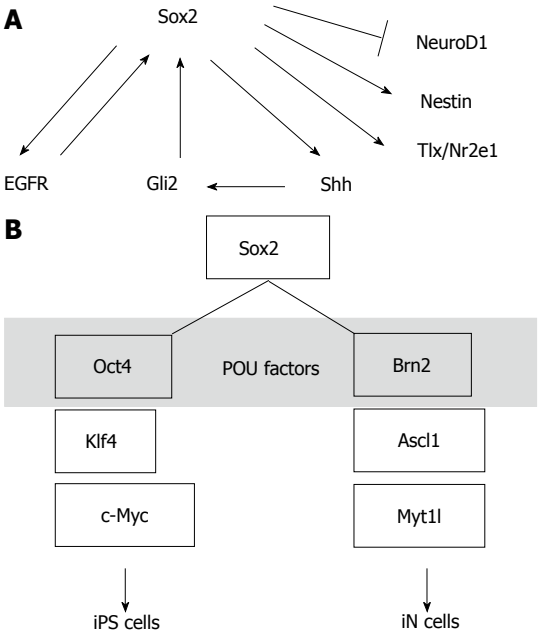

Figure 1 Diagrams of the Sox2 transcription network and reprogramming. A: Examples from the Sox2 transcription network. Sox2 activates Egfr transcription, and EGFR signaling activates Sox2 transcription. Sox2 also activates Shh transcription, and the Shh signaling downstream factor Gli2 activates Sox2 transcription. Sox2 activates the Nestin and Tlx/Nr2e1 genes but represses NeuroD1 transcription; B: Sox2 and POU factors are assumed to function as a core-partner unit in gene-induced cell reprogramming. iPS: Induced pluripotent stem; iN: Induced neuronal.

coordinately activate the target genes, and they have been suggested to be involved in the regulatory mechanism that maintains the undifferentiated state of NSCs.

SOX2 TARGET GENES AND STEM CELL FUNCTION

Sox2 is a transcription factor, and many reports have been published describing analyses of its target genes. Sox2 regulates the expression of its target gene called *Sonic hedgehog* (*Shh*) to regulate NSCs in the hippocampus[39,55,56]. Shh is a humoral factor that transmits outside signals from outside into the cell via its receptor Patched, and induces Smo/Gli signal activation[57-59]. Another transcription factor, Gli2, is a downstream target of Shh and regulates *Sox2* gene expression[60]. Therefore, these factors may constitute a positive feedback loop. Additionally, Notch and the epidermal growth factor receptor (EGFR) pathway regulate the number of NSCs and their self-renewal[61]. EGF stimulation can turn neural progenitors into multipotent NSCs through the receptor, EGFR[62]. Whereas EGFR signaling increases *Sox2* expression, Sox2 enhances *Egfr* expression, which suggests a positive feedback mechanism[63] (Figure 1A). The nuclear receptor, Tlx (Nr2e1), is an essential factor in the mechanism that maintains undifferentiated NSCs[64-66]. A possible negative feedback model of *Tlx* gene expression has been reported, in which Sox2 binds to Tlx to regulate its transcription[67]. Based on these findings, it is conceivable that the Sox2-centered feedback loop mechanism involving Sox2 target genes serves as an important system for the self-renewal mechanisms of NSCs.

It was recently reported that the crosstalk between Sox2 and Wnt signaling regulates the switching during the differentiation of NSCs to neurons[68]. Sox2 and Tcf act as molecular switches thus interacting with the overlap sequence, and this process, in turn, regulates *NeuroD1* expression[68]. Although the mechanisms underlying the molecular switching of numerous genes are being increasingly revealed, it remains unknown how such mechanisms activate differentiation switches at the appropriate times and locations in response to intra- and extracellular changes, while suppressing the expression of genes other than those involved in neuronal differentiation.

STEM CELL REPROGRAMMING AND THE SOX2 GENE NETWORK

Combined transfection of the *Oct4*, *Sox2*, *Klf4*, and *c-Myc* genes transforms somatic cells into pluripotent stem cells[24,25]. In this process, the transcriptional network is switched on to generate multipotent stem cells. It is likely that the partnership between Sox2 and Oct4 functions as the core switch[4]. The addition of Klf4 to the partner complexes presumably allows for multidimensional regulation of various modes of switching. In the multipotency induction process, the use of serum-free culture medium with EGF actively induces the formation of NSCs[26]. Conversely, induction of the iN cell phenotype is conducted using a cell engineering technology that directly transdifferentiates somatic cells into neurons[27]. Forced expression of the *Ascl1*, *Brn2*, and *Myt1l* genes can induce neuronal differentiation. However, this method is not intended for the maintenance of NSCs. Brn2 is a partner factor of Sox2[51,53]. When Sox2 is added to the group of iN-factors and cells are cultured in EGF- or bFGF-containing medium, combinations other than Oct4, Klf4, and c-Myc may be able to produce artificial NSCs. Moreover, based on the concept of the Sox2 partner code[41], the establishment of neuronal subtype-specific NSCs also seems possible, using combinations of Pax6 and Prx1 or other POU factors (Figure 1B).

CONCLUSION

I have reviewed the link between the molecular mechanisms at work in NSCs and properties of stem cells, with a focus on the network involving the Sox2-centered partner code and its target genes. The localized expression of Sox2 in NSCs/neural progenitors enhances its molecular specificity. By forming complexes with its partner factors, Sox2 exerts its transcriptional-regulation function. The partner factors involved vary depending on the molecular context of the stem cell lineage. Sox2 target genes include molecular switches controlling the *NeuroD1* gene (which is capable of inducing neuronal differentiation) as well as the feedback loop with the factors involved in self-renew-

al such as members of the EGFR signaling pathway. By manipulating Sox2 and its partner factors, researchers can now artificially induce differentiation into pluripotent, or multipotent stem cells and into neurons. Nevertheless, many questions remain unanswered regarding the Sox2-based self-renewal mechanism and the regulatory mechanism underlying multipotency. Further research using conditional KO mice is needed to explore functions of Sox2, its partner factors, and chromatin-regulating factors that interact with Sox2 and its partner factors as well as to identify the entire panel of Sox2 target genes.

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