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Dr. Jekyl-Mr. Hyde Role of Sox Family – From Neurogenesis to Cancer: A Review

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Abstract

After the historic discovery of IPSCs by Shinya Yamanaka, Sox2 became a highly important factor for its crucial role in reprogramming of somatic cells. The transcriptional control of various phases of nerve cell development, which include stem-cell maintenance, glial specification and lineage-specific terminal differentiation, are not well understood. This is where Sox proteins come into play. Recently, SOX2 expression has been corroborated in several tumor types including ovarian carcinoma, which suggests an involvement of SOX2 in regulation of cancer stem cells (CSC). SOX antibodies have been categorized as specific serological markers for Small cell lung cancer. However Sox2 reduction leads to neurodegeneration. Thus understanding the expression of this protein is very important. Here is an overview of the present knowledge we possess about the functional mechanisms of SOX family, with an effort to understand the role in both development and disease.

Keywords: IPSCs; SOX; Neurogenesis

Introduction

The Sox family of transcription factors are identified by a high-mobility-group DNA-binding domain which was first observed in the mammalian Sry protein [1-3]. There are 20 different Sox proteins in mammals and eight in Drosophila melanogaster [1]. Later in 2006, 24 different candidate factors were tested for their ability to induce pluripotency. The analysis substantiated that introduction of four transcription factors (Oct-3/4, Sox2, c-Myc, and KLF4) into mouse embryonic or adult fibroblasts by a retro-viral mediation and selection for the expression of Fbx15, a target of Oct-3/4 and Sox2, resulted in the generation of cells which are similar to embryonic stem cells in morphology, proliferation, and teratoma formation [4] and are now recognised as Induced Pluripotent Stem Cells (iPSc) [5]. Experiments to see roles of different Sox factors in development and disease have been performed.

Literature Review

Role in development

SOX 1: Initiation of the expression of SOX1 factor, has been observed at the time of neural induction, both in case of *in vivo* as well as *in vitro*, and appears to be limited to ectodermal cells committed to the neural fate [4-6]. As neural cells egress mitosis to terminally differentiate, the expression of SOX1 is subsequently downregulated [4,6,7]. The compiled data signifies that the inception of SOX1 expression is closely associated with the acquisition of neural fate by the ectoderm, both *in vitro* and *in vivo* [4,6-8]. *In vitro* SOX1 expression has been observed to initiate within 24 hours of the addition of retinoic acid and P19 aggregates coincident with the induction of neuroepithelial markers like NESTIN, Mash1 and Wnt1 [6,7]. In mouse and rat embryos SOX1 has been detected initially in late primitive streak stage embryos and is found to be restricted to the cells of the antero/distal ectoderm [6,7]. Fate mapping studies conducted prior to these, indicate that this region of the epiblast constitutes the primordium of the nervous system [6,7,9]. SOX1 gene expression has been observed all through the cells of the neural plate and early neural tube along its entire anteroposterior axis [4,6,7]. The early and uniform SOX1 expression throughout the possible CNS demonstrates that SOX1 is activated by neural promoting signals and bolsters the proposition, that a two-step response of the ectoderm to organizer signals leads to the generation of a nervous system: [4,6,7] neuralization precedes regionalization expression of SOX1 is closely associated with acquiring neural fate *in vivo* and *in vitro*. SOX1 expression can solely induce neural fate in uncommitted P19 cells [4,6,7,10]. Sox1 knockout in mice can lead to neural defects [11].

SOX 2: Sox-2 has traditionally been employed as marker for characterizing pluripotent embryonic stem cells, more recent reports have detailed the role of this transcription factor in cell fate determination, particularly neuroectoderm formation [12]. Sox2 has been identified as Sox (SRY-related HMG box) protein expressed in EC cells [3,13]. The high mobility group (HMG) domain is a DNA binding domain conserved in abundant chromosomal proteins including HMG1 and HMG2, which bind to the DNA with little or no sequence specificity, and in sequence-specific transcription factors, including SRY, SOX, and LEF-1 [3,13-16]. All SOX factors appear to recognize a analogous binding motif, A/TA/TCAAA/TG [3-4,13-16]. Just as Oct-3/4, Sox2 also marks the pluripotent lineage of the early mouse embryo [3-5,14-16], it is expressed in the ICM, epiblast, and germ cells [3-5]. Unlike Oct-3/4, however, Sox2 is also expressed by the multipotential cells of the extraembryonic ectoderm [3,13,15-17].

Sox2 expression has also been associated with uncommitted dividing stem and precursor cells of the developing central nervous system (CNS), and it can be used to isolate such cells [3,4,13,18].

Sox2 null embryos have been reported to die at the time of implantation due to a failure of epiblast (primitive ectoderm) development [17,19]. Homozygous mutant blastocysts appear morphologically normal, but undifferentiated cells fail to proliferate when blastocysts are cultured *in vitro*, and only trophectoderm and

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primitive endoderm-like cells are produced [3,13,19]. The deletion of Sox2 in ES cells has resulted in trophectoderm differentiation [20]. Therefore, Sox2, like Oct-3/4, is essential for the maintenance of pluripotency [19]. Resident astrocytes can be converted to doublecortin (DCX)-positive neuroblasts by a single transcription factor, SOX2, in the injured adult spinal cord [21,22]. Importantly, these induced neuroblasts can mature into synapse-forming neurons *in vivo* Sox2 is considered a transcription factor necessary for the proliferation maintenance of at least one type of stem cell, the epiblast stem cell [17,22]. Sox2 is found to be expressed in neural stem/precursor cells of adult mouse, and is found to be required for their proliferation and maintenance. In addition to neural proliferation defects, adult brains of Sox2 mutants have shown the loss of thalamo-striatal parenchyma, cell degeneration and neurological abnormalities [23].

SOX 4 and SOX11: Proneural bHLH transcription factors have been observed to be essential for the progression of neurogenesis and can induce cell cycle exit and commit progenitors to a neurogenic program [14-15,24-26], but how these proteins promote differentiated progeny to obtain a neuronal phenotype has remained elusive. It is seen that Sox4 and Sox11 function downstream from proneural bHLH protein as critical activators of both generic and subtype specific neuronal properties. Elimination of Sox4 and Sox11 activity did not disrupt the ability of proneural bHLH proteins to promote cell cycle exit, but blocked their capacity to establish the expression of neuronal properties. Together, these data reveal a central regulatory role of group-C Sox proteins during neuronal maturation and suggest that the induction of Sox4 and Sox11 expression reflects a critical step in the acquisition of a neuronal phenotype [27].

Expression of Sox11 was increased after SCI and mainly located in ependymal cells lining the central canal and in newly-generated neurons in the spinal cord. A lentiviral vector expressing GFP containing the Sox11 gene was introduced into the injured spinal cords to evaluate the therapeutic potential of Sox11 in mice with SCI. Sox11 markedly improved locomotor recovery and this recovery was accompanied by an up-regulation of Nestin/Doublecortin expression in the injured spinal cord. Moreover, some GFP-positive cells along the central canal expressed Nestin, a neural stem cell marker and some GFP-positive cells in the gray matter of injured spinal cords expressed Doublecortin, an immature neuronal cell marker [28].

SOX 21: The studies have suggested that the generation of neurons from precursor cells depends on Sox21 repressor activity, which promotes neurogenesis by counteracting the function of Sox1–3 [29]. Thus, whether neural cells remain as progenitors or commit to neuronal differentiation appears to be dependent on the intrinsic balance of Sox21 and Sox1–3 activity [29]. Data has shown that proneural proteins upregulate the expression of Sox21 and thereby shift the balance of Sox21 and Sox1–3 activity [29]. Sox21 has been found to have a central role during neurogenesis. Amount of Sox21 expression shows a progressive increase in progenitor cells. Until a critical level was reached at which Sox1–3–activated genes are repressed, inducing these cells to commit to differentiation [29]. Indeed, these findings favour the idea, as the expression of Sox21 was most pronounced in the lateral aspect of the ventricular zone. Hence, the activity of Sox21, and its ability to promote differentiation, seems to be reflected by its level of expression [29,30].

SOX 9 AND SOX 10: SOX10 preserves both neurogenic and gliogenic differentiation capacity from extinction by lineage restriction factors [31]. SOX10 inhibits overt neuronal and smooth muscle differentia- SOX10 prevents TGF_-induced proliferative embryos.

SOX9 is a key determinant of multipotent NSCs in both the embryonic and adult CNS. The NSC-promoting activity of SHH signalling is mediated at least in part by induction of Sox9. SOX9 has been shown to be expressed by radial glia, at least some of which possess NSC char-acteristic, and Sox9 been implicated in the switch from neurogenesis to gliogenesis in progenitors of the embryonic spinal cord [32].

Role in diseases

SOX 2 in ovarian carcinoma: SOX2 is recognised as a key regulator for maintaining the pluripotency and self-renewal of embryonic stem cells and contributes to the reprogramming of differentiated somatic cells back to a pluripotent stem cell state [11,33,34]. More recently, enhancement in SOX2 expression has been detected in several epithelial tumors which suggest that SOX2 also regulates tumorigenesis [33]. On the basis of its prominent role in pluripotent stem cell stemness, SOX2 expression has been proposed as a general feature of CSCs [33]. The reported data, however, shows that divergent SOX2 expression patterns and functions across tumors, suggesting that SOX2 adopts specific roles in individual tumor types [33]. In breast cancer cells, for instance, SOX2 has been seen to promote CSC characteristics such as *in vitro* tumor sphere formation and *in vivo* tumorigenicity [33]. When cultured under nonadherent sphere conditions that enrich for CSCs, breast cancer cells upregulated SOX2 expression. This indicated a tight link between SOX2 expression and functional stem cell state. Furthermore, immunohistochemical analysis of primary breast carcinomas has exhibited a heterogeneous SOX2 protein expression in only a minority of tumor cells consistent with the putative role of SOX2 as a breast CSC marker [33,35].

SOX 1 in small cell lung cancer (SCLC): SOX antibodies have been recognised as important markers for premature diagnosis of cancer [4]. Unlike before when testing was elaborate and determination of antibody titers was difficult [4], the newly developed ELISA has been able solve issues and is amenable to high throughput screening [4]. SOX1 antibodies have been commonly observed in small-cell lung carcinoma (SCLC) with and without paraneoplastic syndrome (PNS) and can serve as serological tumor marker [4]. Addition of other antibodies might improve its diagnostic power. Validation of an enzyme-linked immunosorbent assay (ELISA) to assess the diagnostic value of serum antibodies in SCLC and Lambert-Eaton myasthenic syndrome (LEMS) was done [4] which detected SOX or -Hu serum antibodies in 43% of SCLC patients without clinical paraneoplastic disease and in 67% of SCLC patients with LEMS [4]. Out of the four SOX proteins, antibodies against SOX1 were found most frequently (32%) in SCLC patients without PNS Cross-reactivity among SOX proteins which has been studied in greater detail [4]. Absorption with SOX1 protein showed neutralization of all SOX21 reactivity, but Vice-versa absorption with SOX21 only partially neutralized SOX-B1 (SOX1, SOX2, and SOX3) reactivity [4]. This suggested that SOX-B1 antigens, possibly SOX1 itself, were more likely to be the primary antigen eliciting the initial immune response. SOX antibodies are recognised as tumor markers and are considered to be exclusively present in patients with a tumor [4,36].

SOX 2-A frequently amplified gene in small cell lung cancer: Lung cancer is the leading cause of cancer mortality in the United States, where it is responsible for over 160,000 deaths annually. Approximately 10–15% of the new lung cancer cases diagnosed each year is SCLC [37].

SOX2 protein overexpression has previously been noted in high-

grade SCLC [38], and immunoreactive antibodies against SOX2 have been detected in sera from SCLC patients [39].

Suppression of SOX2 using shRNAs blocked proliferation of SOX2-amplified SCLC lines [39].

The siRNA-mediated knockdown of SOX2 in D121 lung carcinoma cells, which led to the decisive inhibition of these cells' migration in a transwell migration assay, suggests that this transcription factor may regulate key biological functions of these cells. SOX2 signalling pathway as well as its downstream genes Oct 4 and Nanog in the development and maintenance of cancer stem cells are still being investigated. SOX2 signaling pathway is involved in cancer stem cell development and that its deregulation can effectively suppress growth and metastasis of non-small cell lung carcinoma cells [40,41]. This novel strategy may contribute to the future development of efficacious cancer treatments [39].

Discussion and Conclusion

Transcription factors of the Sox family provide important clues about the control of events in neurogenesis [3]. In the central nervous system, Sox1, Sox2 and Sox3 are required for stem-cell maintenance, and their effects have been observed to be counteracted by Sox21 [3]. Sox9 has been seen in altering the potential of stem cells from neurogenic to gliogenic, whereas Sox10 is indispensable for terminal oligodendrocyte differentiation [3]. In the peripheral nervous system the same Sox proteins have altered functions, uncovering vital developmental differences between the CNS and PNS [3]. Some Sox genes, such as Sox7 and Sox17 are epigenetically silenced in many human cancers and they appear to act as tumor suppressors [42].

Over expression of SOX7 or SOX17 in human colon cancer cell lines has been found to have a suppressive role in the hyperactive β-catenin activity in cancerous cells as well as reduce Cyclin-D1 expression and repress proliferation [42]. The stable transfection of SOX4 was found to transform prostate cells [43], whereas antisense depletion of SOX4 from prostate or colon cancer cell lines inhibited Cyclin-D1 expression and reduced proliferation [42-44]. There are cases where the same Sox gene behaves in a different way in different cancers [42]. For instance, SOX2 has been observed to be frequently over expressed in aggressive human breast carcinomas, where it promotes β-catenin stimulated proliferation [45], whereas in gastric cancer, Sox2 is often down regulated and when over expressed in those cells represses Cyclin-D1 expression and proliferation [42,46]. Even during formation of iPSCs Yamanaka discovered that though Sox2 in an inevitable factor it also leads to teratoma formation. Role of Sox family, its various interactions with pathways as well as its presence in disease and disorders is yet to be completely understood by scientists. Its importance in various processes cannot be denied. Also how various animals having a capacity to regenerate balance between the stem cell proliferation and Cancer formation properties of Sox family is an enigmatic mystery yet to be unravelled.

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References

1. Bowles J, Schepers G, Koopman P (2000) Phylogeny of the SOX family of developmental transcription factors based on sequence and structural indicators. Dev Biol 227: 239-255.
2. Kamachi Y, Uchikawa M, Kondoh H (2000) Pairing SOX off: With partners in the regulation of embryonic development. Trends Genet 16: 182-187.
3. Wegner M, Stolt CC (2005) From stem cells to neurons and glia: A soxist's view of neural development. Trends Neurosci 28: 583-588.
4. Lipka AF, Verschuuren JJ, Titulaer MJ (2012) SOX1 antibodies in lambert–eaton myasthenic syndrome and screening for small cell lung carcinoma. Ann N Y Acad Sci 1275: 70-77.
5. Takahashi K, Yamanaka S (2006). Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell 126: 663-676.
6. Pevny LH, Sockanathan S, Placzek M, Lovell-Badge R (1998) A role for SOX1 in neural determination. Development 125: 1967-1978.
7. Larsya Penvy (1999) Genetic demonstration of requirement for NKX6.1 and NKX2.2 in ventral neuron generation. US7393686B1.
8. Rudin CM, Durinck S, Stawiski EW, Poirier JT, Modrusan Z, et al. (2012) Comprehensive genomic analysis identifies SOX2 as a frequently amplified gene in small-cell lung cancer. Nat Genet 44: 1111.
9. Zhao S, Nichols J, Smith AG, Li M (2004) SoxB transcription factors specify neuroectodermal lineage choice in ES cells. Mol Cell Neurosci 27: 332-342.
10. Gordon KJ, Kirkbride KC, How T, Blobe GC (2008) Bone morphogenetic proteins induce pancreatic cancer cell invasiveness through a Smad1-dependent mechanism that involves matrix metalloproteinase-2. Carcinogenesis 30: 238-248.
11. Nishiguchi S, Wood H, Kondoh H, Lovell-Badge R, Episkopou V (1998) Sox1 directly regulates the γ-crystallin genes and is essential for lens development in mice. Genes Dev 12: 776-781.
12. Chen S, Choo AB, Nai-Dy W, Heng-Phon T, Oh SK (2007) Knockdown of Oct-4 or Sox-2 attenuates neurogenesis of mouse embryonic stem cells. Stem Cells Dev 16: 413-420.
13. Yamanaka S (2007) Strategies and new developments in the generation of patient-specific pluripotent stem cells. Cell stem cell 1: 39-49.
14. Campolo F, Gori M, Favaro R, Nicolis S, Pellegrini M, et al. (2013) Essential role of Sox2 for the establishment and maintenance of the germ cell line. Stem Cells 31: 1408-1421.
15. Kim D, Kim CH, Kim KS (2010) Induced pluripotent stem cells. 2: 1.
16. Chew LJ, Gallo V (2009) The yin and yang of sox proteins: Activation and repression in development and disease. J Neurosci Res 87: 3277-3287.
17. Avilion AA, Nicolis SK, Pevny LH, Perez L, Vivian N, et al. (2003) Multipotent cell lineages in early mouse development depend on SOX2 function. Genes Dev 17: 126-140.
18. Li M, Pevny L, Lovell-Badge R, Smith A (1998) Generation of purified neural precursors from embryonic stem cells by lineage selection. Curr Biol 8: 971-974.
19. Yamanaka S (2008) Pluripotency and nuclear reprogramming. Philos Trans R Soc Lond B Biol Sci 363: 2079-2087.
20. Zappone MV, Galli R, Catena R, Meani N, De Biasi S, et al. (2000) Sox2 regulatory sequences direct expression of a beta-geo transgene to telencephalic neural stem cells and precursors of the mouse embryo, revealing regionalization of gene expression in CNS stem cells. Development 127: 2367-2382.
21. Masui S, Nakatake Y, Toyooka Y, Shimosato D, Yagi R, et al. (2007) Pluripotency governed by Sox2 via regulation of Oct 3/4 expression in mouse embryonic stem cells. Nat Cell Biol 9: 625-635.
22. Wang LL, Su Z, Tai W, Zou Y, Xu XM, et al. (2016) The p53 pathway controls SOX2-mediated reprogramming in the adult mouse spinal cord. Cell Rep 17: 891-903.
23. Su Z, Niu W, Liu ML, Zou Y, Zhang CL (2014) *In vivo* conversion of astrocytes to neurons in the injured adult spinal cord. Nat Commun 5: 3338.
24. Ferri AL, Cavallaro M, Braida D, Di Cristofano A, Canta A, et al. (2004) Sox2 deficiency causes neurodegeneration and impaired neurogenesis in the adult mouse brain. Development 131: 3805-3819.
25. Farah MH, Olson JM, Sucic HB, Hume RI, Tapscott SJ, et al. (2000) Generation of neurons by transient expression of neural bHLH proteins in mammalian cells. Development 127: 693-702.
26. Bertrand N, Castro DS, Guillemot F (2002) Proneural genes and the specification of neural cell types. Nat Rev Neurosci 3: 517-530.

27. Kintner C (2002) Neurogenesis in embryos and in adult neural stem cells. J Neurosci 22: 639-643.

28. Bergsland M, Werme M, Malewicz M, Perlmann T, Muhr J (2006) The establishment of neuronal properties is controlled by Sox4 and Sox11. Genes Dev 20: 3475-3486.

29. Sandberg M, Källström M, Muhr J (2005) Sox21 promotes the progression of vertebrate neurogenesis. Nat Neurosci 8: 995-1001.

30. Guo Y, Liu S, Zhang X, Wang L, Zhang X, et al. (2014) Sox11 promotes endogenous neurogenesis and locomotor recovery in mice spinal cord injury. Biochemical and biophysical research communications 446: 830-835.

31. Holmberg J, Hansson E, Malewicz M, Sandberg M, Perlmann T, et al. (2008) SoxB1 transcription factors and notch signaling use distinct mechanisms to regulate proneural gene function and neural progenitor differentiation. Development 135: 1843-1851.

32. Kim J, Lo L, Dormand E, Anderson DJ (2003) SOX10 maintains multipotency and inhibits neuronal differentiation of neural crest stem cells. Neuron 38: 17-31.

33. Bareiss PM, Paczulla A, Wang H, Schairer R, Wiehr S, et al. (2013) SOX2 expression associates with stem cell state in human ovarian carcinoma. Cancer Res 73: 5544-5555.

34. Parras CM, Schuurmans C, Scardigli R, Kim J, Anderson DJ, et al. (2002) Divergent functions of the proneural genes Mash1 and Ngn2 in the specification of neuronal subtype identity. Genes Dev 16: 324-338.

35. Scott CE, Wynn SL, Sesay A, Cruz C, Cheung M, et al. (2010) SOX9 induces and maintains neural stem cells. Nat Neurosci 13: 1181-1189.

36. Pham DL, Scheble V, Bareiss P, Fischer A, Beschorner C, et al. (2013) SOX2 expression and prognostic significance in ovarian carcinoma. Int J Gynecol Pathol 32: 358-367.

37. Titulaer MJ, Klooster R, Potman M, Sabater L, Graus F, et al. (2009) SOX antibodies in small-cell lung cancer and Lambert-Eaton myasthenic syndrome: Frequency and relation with survival. J Clin Oncol 27: 4260-4267.

38. Siegel R, Naishadham D, Jemal A (2013) Cancer statistics. CA Cancer J Clin 63: 11-30.

39. Sholl LM, Long KB, Hornick JL (2010) Sox2 expression in pulmonary non-small cell and neuroendocrine carcinomas. Appl Immunohistochem Mol Morphol 18: 55-61.

40. Zhang X, He X, Liu Y, Zhang H, Chen H, et al. (2017) MiR-101-3p inhibits the growth and metastasis of non-small cell lung cancer through blocking PI3K/AKT signal pathway by targeting MALAT-1. Biomed Pharmacother 93: 1065-1073.

41. Yoshimasu T, Matsuura N, Ota I, Tani N, Oura S, et al. (2001) Integrins α2β1, α5β1 and αvβ5 are related to tumor growthand metastasis of non-small cell lung cancer. Haigan 41: 111-115.

42. Kormish JD, Sinner D, Zorn AM (2010). Interactions between SOX factors and Wnt/β□catenin signaling in development and disease. Dev Dyn 239: 56-68.

43. Liu P, Ramachandran S, Seyed MA, Scharer CD, Laycock N, et al. (2006) Sex-determining region Y box 4 is a transforming oncogene in human prostate cancer cells. Cancer Res 66: 4011-4019.

44. Sinner D, Kordich JJ, Spence JR, Opoka R, Rankin S, et al. (2007) Sox17 and Sox4 differentially regulate β-catenin/T-cell factor activity and proliferation of colon carcinoma cells. Mol Cell Biol 27: 7802-7815.

45. Chen X, Xu H, Yuan P, Fang F, Huss M, et al. (2008) Integration of external signaling pathways with the core transcriptional network in embryonic stem cells. Cell 133: 1106-1117.

46. Otsubo T, Akiyama Y, Yanagihara K, Yuasa Y (2008) SOX2 is frequently downregulated in gastric cancers and inhibits cell growth through cell-cycle arrest and apoptosis. Br J Cancer 98: 824.