Journal of Experimental and Basic Medical Sciences 2021;2(3):318-325

Review

SOX2 Gene and Tumor Development

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ABSTRACT

The sex-determining region Y-box 2 (SOX2) gene plays an important role in both embryonic development and the postnatal period. Mutations that may occur in the SOX2 gene lead to the formation of various defects in the human brain. SOX2 gene has been shown to promote cell proliferation and tumor metastasis in various tumor types such as glioblastomas, colorectal cancer, prostate cancer, breast cancer, and stomach cancer. This article reviewed the functions of the SOX2 gene and its relationship with tumor formation.

Keywords: Glioblastoma, SOX2 gene, SRY gene, tumor

The sex-determining region Y-box (SOX) genes encode a family of highly pleiotropic transcription regulators that play essential roles during embryonic development and in the maintenance of stem cell fate. They are characterized by a high mobility group (HMG) protein DNA binding domain of about 80 amino acids forming three α-helixes, first identified in the mammalian testis determining factor or the sex-determining region of the Y (SRY) chromosome.[1] SRY-related HMG-box proteins (SOX) contain an HMG domain with at least 50% sequence identity to the HMG domain of SRY. To date, 20 different SOX genes have been found in the murine (mice or rats) and the human genome, and they have been divided into eight subgroups based on sequence identity and similar functions, respectively.[2] Each member of this family contains a well-protected domain of high mobility groups that mediates DNA binding.[3] Several SOX subgroups are formed from SOX proteins that share an HMG domain with more than 80% sequence identity, and these subgroups are termed SOX A to H based on the HMG-box domains analyzed phylogenetically. All SOX genes are divided into eight groups from A to H: A (SRY), B1 (SOX1, SOX2, and SOX3), B2 (SOX14 and SOX21), C (SOX4, SOX11, and SOX12), D (SOX5, SOX6, and SOX13), E (SOX8, SOX9, and SOX10), F (SOX7, SOX17, and SOX18), G (SOX15) and H (SOX30) found in mammals only.[4]

The SOX2 gene is located on the long arm of chromosome 3 (3q26.3-q27), has no introns, and is a member of the SOXB1 group together with SOX1 and SOX3, then it shares a sequence similarity of over 80%.[1] SOX2 not only enhances the expression of its own gene as part of the autoregulation feed-forward mechanisms, but the single exon SOX2 falls into the intron of a much larger, overlapping genetic element called SOX2OT (SOX2 overlapping transcript). This peculiar gene regulation is phylogenetically conserved between man and mouse; here, SOX2OT has recently been shown to modulate SOX2 expression in cortical neuronal progenitors.[5,6]

In terms of function, SOX proteins recognize the same short common consensus sequence (CCCATTGTTC for humans and CTTTGTC for mice).[1,5] SOX proteins can bind to ATTGTT or related sequence motifs via HMG domains composed of three alpha-strands. This binding is established by the interaction of the HMG domain with the small DNA groove that expands the small groove and causes the DNA to bend towards the main groove.[7] It has also been experimentally proven that DNA bending contributes to the regulatory functions

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Cite this article as: Daşdelen D, Demirezen A, Akdoğdu BS, Altuntaş İ, Erbaş O. SOX2 Gene and Tumor Development. JEB Med Sci 2021;2(3):318-325.

doi: 10.5606/jebms.2021.75673

Received : March 4, 2021
Accepted : March 20, 2021
Published online : March 8, 2022

of SOX proteins.[8] There is no consensus on the origin of SOX proteins. Recognition of SOX-like genes in a unicellular organism known as choanoflagellate Monosiga brevicollis provides the argument that SOX proteins can transmit from unicellular organisms to multicellular organisms.[9]

FUNCTIONAL ROLES OF SOX2 GENE

The SOX2 gene is an essential transcription factor to maintain pluripotency in embryonic stem cells (ESCs) and early embryonic cells and to induce pluripotency from somatic cells through reprogramming.[10] In mammals, SOX2 is expressed in pluripotent stem cells of the blastocyst inner cell mass from the early stages of embryonic development.[11] It is also one of the key transcription factors originally used to derive induced pluripotent stem (iPS) cells from fibroblast cells, and SOX2 is an important transcriptional regulator of the cell cycle, cell proliferation, and apoptosis.[12] In addition, SOX2 stability, subcellular localization, and utilization type control with six different types of post-translational modification distributed at least a dozen (encoded by human SOX2 317 amino acids) of 319 amino acids.[11] Data results of SOX2 have been reported in several studies, which can explain the role inconsistency of SOX2 in the cell, varying in its expression, post-translational modification, sub-localization, and interaction with other transcriptions.[13] SOX2 has also been reported to play a critical role in developmental processes, including neural stem cell specification and maintenance, and lung morphogenesis.[12] SOX2 determines the fate of the cell during mammalian development, and mutations in the SOX2 gene are associated with defects in human brain development, particularly hippocampal and parahippocampal malformations.[3] In the retina, SOX2 is expressed in retinal progenitor cells (RPCs), and its solid regulation is a critical factor for RPC differentiation during development.[14] Besides, SOX2 expression is limited to neural retinal cells and is required to maintain silence in the early postnatal period.[15,16]

Experiments in mouse models of SOX2 showed that conditional ablation of this factor compromised the proliferation and differentiation capacity of RPCs, while hypomorphic levels caused an abnormal differentiation in postnatal animals leading to various microphthalmia phenotypes.[14] RPC's complete absence of SOX2 expression eliminates proliferation capacity and differentiation ability.[17] Even decreased SOX2 expression can cause various eye defects (anophthalmia, missing eye, severe microphthalmia, small eye).[3] A study revealed that there is a cause-and-effect relationship between abnormally low SOX2 expression and defects in eye development.[18] As a result of many scientific studies, the idea that SOX2, which is transcriptional factor, has regulatory roles such as both the differentiation of RPC and the characterization of its identity has been supported. Overexpression of SOX2 has also been proven to increase cell proliferation and invasion and inhibit apoptosis by controlling transcriptional activation of programmed death ligand-1 (PD-L1), mitogen-activated protein kinase (MAPK), phosphatase and tensin homolog (PTEN).[19]

The specification of neural lineage in early embryonic development relies heavily on SOX2 activity.[17] SOX2 expression is widely expressed in neural tube cells in the early stages of neuronal development. Subsequently, SOX2 expression is limited to the ventricular layer of the neural cortex where neural stem cells (NSCs) and their precursor cells are located after the mid-fetal period.[20] The first evidence that SOX2 can function to maintain neural precursor cell properties has been obtained by gain-of-function/ectopic expression and dominant intervention studies in xenopus and chicks.[21] In the adult brain, SOX2 is expressed not only in adult neural stem cells but also in subtypes of postmitotic neurons, including pyramidal cells of the cerebral cortex, some striatal neurons, and many thalamic neurons. Accordingly, mice with greatly reduced SOX2 levels show signs of neurodegeneration in areas where SOX2 is expressed in mature neurons and shows corresponding neurological abnormalities.[22] Moreover, SOX2 has been recognized as a potent oncogene in various types of cancer, where cancer stem cells (CSCs) regulate cancer formation and are functionally associated with many other properties.[5]

Shortly thereafter, SOX2 was found to be necessary for the self-regeneration and pluripotency of ESCs.[3] Interest in SOX2 increased after the discovery by Yamanaka and colleagues, showing that SOX2, along with octamer-binding transcription factor 4 (OCT4), krüppel-like factor 4 (KLF4), and c-Myc, can reprogram somatic cells into a pluripotent stem cell state.[3,23] Working with mouse embryonic stem (ES) cells provided the first indication that levels of stem cell transcription factors such as SOX2 need to be regulated very carefully[3]. The self-renewal and pluripotency of these cells are strictly dependent on a variety of transcription factors, including SOX2 and OCT4.[3,23] A study reported that slight decreases or slight increases will cause differentiation of ES cells.[3]

In addition, KLF4, Myc, and LIN28 have been reported as critical factors for the generation of pluripotent stem cells induced from somatic cells.[23] SOX2 can also affect cell activities, including DNA processing processes, chromatin organization and assembly, and RNA processing, through complexes resulting from protein interactions. Mallanna et al.[24] Identified many proteins that interact with SOX2 using Multidimensional Protein Identification Technology (MudPIT). Identification of these proteins is important for us to gain new insight into the mechanisms that control the fate of pluripotent stem cells, identifying protein-interaction networks for pluripotency factors such as SOX2, OCT4, and homeobox transcription factor NANOG during differentiation[25] Recently, it has also been shown that SOX2 expression is required for the growth and survival of ovarian cancer cells. In many types of cancer, SOX2 acts as an oncogenic transcriptional factor, and thus SOX2 has become a new therapeutic target in these cancers.[23]

TUMOR FORMATION

Besides its various roles during mammalian development, ^{SOX2} plays a critical role in both normal adult cells and tumor cells.[3] It has been shown in various studies that SOX proteins participate in different events in cancer such as migration, progression, proliferation, regulation of cell fate, and differentiation.[9,26] SOX2 is the most studied gene and plays a role as an important regulator of many human cancers.[4] Since 2006, SOX2 has been associated with growth, tumorigenicity, drug resistance, and metastasis in at least 25 different cancers, including ovarian, lung, skin, brain, breast, prostate, and pancreatic cancers [11,27]. It has been associated with the root secretion of cancer in some, if not all, SOX2.[5]

The transcription factor SOX2, which plays an important role in controlling the developing and embryonic stem cell status, is also highly expressed in many cancers that are thought to mark CSCs.[28] However, SOX2 overexpression alone is insufficient to induce cancer. STAT3 (signal transducer and activator of transcription 3) has been shown to be upregulated with SOX2 in cancer stem cells and clustered circulating tumor cells with high metastatic potential.[29] The cooperation between STAT3 and SOX2 in the formation of cancers such as squamous cell carcinoma (SCC), glioblastoma (GBM) has been demonstrated by various studies.[30-33] Next, SCC and GBM will be explained in detail.

Cancer stem cells are considered to be at the root of tumor progression, and many studies are beginning to discover potential therapeutic drugs targeting CSCs.[34,35] CSCs are a small subpopulation of cancer cells with stem cell characteristics such as self-renewal and the ability to differentiate into multiple cell types. Radiation therapy or chemotherapy largely removes cancer cells, including cervical cancer, but some tumor cells survive and gain resistance to radiation or chemotherapy.[12] In osteosarcomas, the most common bone tumor, it marks and preserves a variable tumor-initiating cell fraction that demonstrates all the features of CSC, including high SOX2 expression, high expression of stem cell antigens, ability to form colonies in suspension, high expression of proliferation genes. It plays a role as a blockade of osteoblastic differentiation, with timely preservation.[28] Knock-down (KD) of SOX2 expression by short hairpin RNA (shRNA) eliminates tumor formation in mouse xenografts, and SOX2 KD cells behave very similarly to the non-CSC fraction of the tumor cell population.[28,36]

GLIOBLASTOMA

The SOX2 gene is one of the members of the SOXB1 group, which is essential for embryo maintenance before implantation and is important for the survival of glioma stem cells.[37-39] SOX2 is required for NSCs to maintain self-renewal in specific brain regions after birth.[37] Deregulation of SOX2 can lead to a loss of ESCs pluripotency.[39] While the increase of SOX2 is associated with the development and maintenance of various types of cancer, heterozygous inactivation of SOX2 can cause diseases such as anophthalmia, microphthalmia mild hypopituitarism, and learning difficulties.[40]

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In GBM, SOX2 is a gene associated with rootedness.[30] GBM is the most aggressive and widespread (86%) primary central nervous system tumor, and patients survive for 12–15 months despite the combination of cytoreductive surgery, chemotherapy, and radiation.[39,41,42] SOX2 is overexpressed in malignant

gliomas and its expression in normal brain tissue is rare.[43] Also, SOX2 expression correlates positively with the degree of malignancy in brain tumors.[39] SOX2 is intricately regulated by various signal pathways. Changing some of these regulators in GBM leads to SOX2 overexpression.[40] SOX2 expression is activated via four major signal pathways including Sonic Hedgehog (SHH), Wingless-related integration site (WNT), fibroblast growth factor receptor (FGFR), and transforming growth factor-beta (TGF-β). Garros-Regulez et al.[40] Instead of the WNT pathway, the epidermal growth factor receptor (EGFR) signaling pathway has been published as four main signal pathways. SHH pathway plays a role in triggering tumorigenesis in the brain, and inhibition of TGF-signaling reduces tumor formation in GBM stem cells by suppressing SOX2 activity.[39,44] In studies aimed at finding a cure, it has been shown that destroying SOX2 of tumor-initiating cells (TICs) by RNA interference reduces the proliferation and tumorigenicity of glioblastomas.[42,45] Also, silencing of SOX2 leads to reduced migration and invasion capabilities, while increasing aging and causing cell cycle arrest in G0/G1.[40]

SQUAMOUS CELL CARCINOMA

The SOX2 gene is a single exon nuclear transcription factor with complex, important, and pleiotropic effects in multiple tissues in development and homeostasis.[1,46] SCC is the second most common malignant type after adenocarcinoma.[47] Increased SOX2 expression has been demonstrated in a number of squamous cancers, including cervical SCC, but the role of SOX2 in cervical cancer metastasis is still not fully established.[48,49] Overexpression of SOX2 has also been shown to play an oncogenic role in SCCs of other organs (lungs, larynx, cervix, penis, and skin).[50] In SCCs, chromosome 3 aberrations are the most common, and SOX2 is considered the main target of the 3q amplicon.[1,51] Sequence-based studies of SCC identified a large region spanning hundreds of genes on chromosome 3q as a repetitive amplification site.[1,52] In addition, both SOX2 and tumor protein p63 (TP63) are located on the 3q arm of the chromosome, which undergoes widespread amplification in many types of squamous cancers.[32] In addition, molecular epidemiological studies have shown that the tumor protein P53 gene (TP53) is disrupted in almost all invasive SCCs.[46] It has been identified as a candidate oncogenic gene in genes such as tumor protein P63 (TP63), epithelial cell transforming 2 (ECT2), phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA), protein kinase C iota (PRKCI), and defective in cullin neddylation 1 domain containing 1 (DCUN1D1) at locus 3q26.33 with SOX2.[1,52]

Lung squamous cell carcinoma accounts for, 30% of all lung cancer.[53] SOX2 is activated in the majority (67%) of LSCCs.[51] Both SOX2 and FGFR1 are often amplified in LSCC, in some cases in the absence of mutations in cyclin-dependent kinase inhibitor 2A/B (CDKN2AB) and PTEN.[54] Yuan et al.[55] reported that there is a large increase in the expression of the transcriptional factor SOX2 related to pluripotent stem cells in SCCs compared to lung adenocarcinomas. It is explained by . About 90% of esophageal cancers are SCCs, and SOX2 expression is associated with the progression and invasiveness of esophageal SCC.[50,56]

GASTRIC CANCER

The SOX2 gene is an important transcriptional regulator of the cell cycle, cell proliferation, and apoptosis. SOX2 is also a marker of gastric differentiation and is often down-regulated in gastric cancer.[12] OCT4 and SOX2 are important transcriptional factors involved in the maintenance of pluripotency and self-renewal in cancer stem cells; Abnormal expression of OCT4 and SOX2 may contribute to carcinogenesis in a variety of cancers.[57] For example, high expressions of SOX2, OCT4, and NANOG in gastric cancer and their contribution to cancer progression and prognosis have been reported.[58] SOX2, OCT3/4, and NANOG are mainly expressed in the nucleus of stomach cancer cells. Proteins encoded by these genes can act as a transcriptional activator after forming a complex with other proteins.[59] Because these proteins function by binding together to DNA, they can be expressed mainly in the nucleus of gastric cancer cells.[60] Although the presence of cancer stem cells in gastric cancer has been suggested, the relationship between rootedness factors (SOX2, OCT4, NANOG) and gastric cancer remains unclear.[23,60]

Some reports have shown that SOX2 expression is associated with worse overall survival in gastric cancer, but other studies have also found reduced SOX2 expression in gastric carcinogenesis, which is predictive of better survival.[61] No significant association was found between SOX2 and age, sex, depth of invasion, tumor diameter, distant metastasis, or histological type, but SOX2 is dramatically associated with lymph node metastasis, and lymph node metastasis can be seen in gastric cancer patients due to the high SOX2 expression level.[62] SOX2 is an important transcriptional regulator of the cell cycle, cell proliferation, and apoptosis.[17] Increasing

evidence suggests that microRNAs (miRNAs) are abnormally expressed in many human cancers and play a role in the initiation, development, and metastasis of cancers.[63] Multiple pre-clinical studies have demonstrated the proliferation and invasion of cancer cells in both in vitro cell culture and in vivo xenograft tumor models of SOX2 knockout mediated by small interfering RNA (siRNA), shRNA, or miRNA. It has shown that it suppresses dramatically.[36] miR-126 is overexpressed in gastric cancer, and targeted SOX2, therefore, inhibiting SOX2 expression and promoting gastric carcinogenesis, as a result of upregulation of miR-126.[17]

BREAST CANCER

It is known that the transcription factor SOX2 has great importance in many types of cancer and tumor formation. For example, breast cancer, which is very common in women, is one of the most common malignant tumors among women worldwide and has become a major threat to women's health. This disease can be treated using a combination of therapy that includes surgery, chemotherapy, radiotherapy, molecular targeted therapy, and endocrine therapy.[64,65] However, 20–40% of breast cancer patients still suffer from disease recurrence and metastasis even when given treatment according to the National Comprehensive Cancer Network (NCCN) guidelines.[66]

The SOX2 gene is a member of the high mobility group box gene family associated with the sex-determining region Y and has been found to act as an oncogene in a variety of tumors.[67] Studies have shown that SOX2 is upregulated in breast cancer tissue and promotes the development of breast cancer and promotes breast cancer proliferation, invasion, and metastasis.[19,68] SOX2 increases Tamoxifen resistance in breast cancer cells. Tamoxifen, an estrogen antagonist in the breast, has been the standard endocrine therapy for women with ER-positive breast cancer for many years and remains that way for pre-menopausal and a significant number of post-menopausal patients. of interest in the context of the development of tamoxifen resistance in cancer patients. In addition, normal cells and cancer stem cells share phenotypes that may reflect the activity of common signaling pathways, such as high NANOG, OCT4, and SOX2 expression reduced by estrogen.[69] It shows that SOX2 promotes cell proliferation, migration and invasiveness by regulating the SOX2/miR-181a-5p, miR-30e-5p/tumor suppressor candidate 3 (TUSC3) axis in breast cancer cells.[19] Activation mutations of genes such as EGFR, human epidermal growth factor receptor 2 (HER2) in breast cancer have been found to transmit signals to the nucleus to upregulate the transcription of downstream genes and promote cancer cell growth.[70] Targeting signal molecules upstream or downstream of SOX2 has become an attractive alternative approach[36].

The SOX2 gene is a transcriptional factor that enables the formation or generation of embryonic stem cells and inducible pluripotent stem cells and also preserves the pluripotency characteristics of these cells. It is the only intron-free exon gene of the SOX family, which is localized on the 3q26.3-q27 segments on chromosome 3 encodes a protein of 317 amino acids, and is associated with SRY. It can bind to the promoter regions of genes belonging to embryonic stem cells and cause transactivation of genes or suppress and silence those genes. SOX2 is restricted to somatic cells of adult tissues. In embryonic/embryonal stem cells, the normal stem cell phenotype functions as transcriptional regulation in neural stem cells as well as a limited number of factors such as OCT4 and NANOG. SOX2 transcriptional factor plays a serious role in developmental events. As a result of its binding to the HMG-box domain-mediated DNA molecule, it promotes the expression of cells of various tissues and the different gene sets contained in those cells, or suppresses and silences those genes, and contributes to the specificity of target genes as a result of synchronous interaction of other transcriptional factors. As a result of the abnormal expression and irregular control of SOX2, it has been determined as a result of the research that humans trigger the formation of various malformations, degenerative diseases, or malignancies.

In conclusion, according to recent scientific studies, it has been stated that abnormal expression of transcriptional factor SOX2 is associated with cancers such as lung, brain, ovaries, bone, colon, skin, breast cancers, pancreatic, squamous, and glioblastoma and has an effect on tumor formation. Disordered expression of SOX2 has been found in most of these tumor types in the cancer stem-like cell population, and studies using various experimental models include proliferation, invasion, migration, colony formation, sphere formation due to the non-adherent stem cell class, and tumorigenicity in vivo. It has shown that it promotes key tumorigenic properties, and even accelerates tumor formation as a result of excessive abnormal expression of SOX2, its differentiation, and invasion, as well as multiple cancers that have been evaluated with poor prognosis.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

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