Interplay of SOX transcription factors and microRNAs in the brain under physiological and pathological conditions

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Introduction

Brain development and homeostasis consist of a series of coordinated events that rely on precise control of gene expression. Neural stem cells (NSCs) represent a self-renewing stem cell population that is essential for the proper development of the central nervous system (CNS) as well as adult neurogenesis (De Filippis and Binda, 2012; Obernier and Alvarez-Buylla, 2019). During development, primary NSCs directly differentiate into early neurons. With the transition from single to multi-layered nervous tissue, a novel population of NSCs is generated that gives rise to the neural progenitor cells (NPCs) contributing to the majority of neurons in the brain. At the later stages of development, NSCs also generate glial precursors, astrocyte progenitor, and oligodendrocyte progenitor cells (OPCs) that further differentiate into astrocytes and oligodendrocytes, respectively (Kriegstein and Alvarez-Buylla, 2009). In the adult brain, the majority of NSCs, found in the two neurogenic niches, the subgranular zone of the hippocampal dentate gyrus and subventricular zone of the lateral ventricle, are involved in adult neurogenesis. The generation of both new neurons and glial cells in the adult brain contributes to neural plasticity and, to some extent, to neural repair (Frisen, 2016). In addition, growing evidence indicates that impaired adult neurogenesis is associated with some neurodegenerative diseases (NDs), including Parkinson’s (PD), Alzheimer’s (AD), and Huntington’s diseases (HD) (Horguslugu et al., 2017).

Several lines of evidence have supported the hypothesis that brain tumors arise from aberrant NSCs proliferation (Oliver and Wechsler-Reya, 2004). Many brain tumors contain stem cells that share many similarities to NSCs (Nakano and Kornblum, 2006). For instance, glioblastoma (GBM), one of the most common and the most aggressive malignant brain tumors in adults, contains neural carcinoma stem cells, known as glioma stem cells (GSCs), which are responsible for tumor initiation, progression, resistance to chemo- and radiotherapy and tumor relapse (Bryukhovetskiy et al., 2020; Vieira de Castro et al., 2020). NSCs are considered one of the major candidates for the GBM cell of origin (Fan et al., 2019).

Numerous transcription regulators, including SOX proteins, play important roles during brain development and homeostasis, starting from maintenance of stemness, cell fate decision, coordination of initial phases of differentiation until the generation of mature neurons, astrocytes, and myelinating oligodendrocytes (Stevanovic et al., 2021). The SOX regulatory proteins display properties of both classical transcription factors (TFs) and architectural components of chromatin (Pevny and Lovell-Badge, 1997). Based on similarity between the proteins they encode, their structure and expression profiles, SOX/Sox genes (in human and mammals, respectively) have been divided into eight groups, A to H (Table 1), with group B further split into subgroups B1 and B2 (Bowles et al., 2000).

MicroRNAs (miRNAs) are small non-coding single-stranded RNA molecules that regulate the expression of genes at the post-transcriptional level (Dexheimer and Cochella, 2020). miRNAs act together with other gene regulatory factors to orchestrate the spatial and temporal expression important for neurodevelopment. Literature data revealed that miRNAs regulate different processes during neurogenesis, including self-renewal, cell-type specification/differentiation, and synaptic plasticity (Stappert et al., 2015). Importantly, miRNAs play roles in the conversion of NSCs into neural cancer stem cells (Diana et al., 2019).

Abstract

Precise tuning of gene expression, accomplished by regulatory networks of transcription factors, epigenetic modifiers, and microRNAs, is crucial for the proper neural development and function of the brain cells. The SOX transcription factors are involved in regulating diverse cellular processes during embryonic and adult neurogenesis, such as maintaining the cell stemness, cell proliferation, cell fate decisions, and terminal differentiation into neurons and glial cells. MicroRNAs represent a class of small non-coding RNAs that play important roles in the regulation of gene expression. Together with other gene regulatory factors, microRNAs regulate different processes during neurogenesis and orchestrate the spatial and temporal expression important for neurodevelopment. The emerging data point to a complex regulatory network between SOX transcription factors and microRNAs that govern distinct cellular activities in the developing and adult brain. Deregulated SOX/microRNA interplay in signaling pathways that influence the homeostasis and plasticity in the brain has been revealed in various brain pathologies, including neurodegenerative disorders, traumatic brain injury, and cancer. Therapeutic strategies that target SOX/microRNA interplay have emerged in recent years as a promising tool to target neural tissue regeneration and enhance neurorestoration. Numerous studies have confirmed complex interactions between microRNAs and SOX-specific miRNAs regulating key features of glioblastoma. Keeping in mind the crucial roles of SOX genes and microRNAs in neural development, we focus this review on SOX/microRNAs interplay in the brain during development and adulthood in physiological and pathological conditions. Special focus was made on their interplay in brain pathologies to summarize current knowledge and highlight potential future development of molecular therapies.

Key Words: dysregulation of miRNA expression; glioblastoma; gliogenesis; glioma stem cells; ischemic stroke; neural stem cells; neural tissue regeneration; neurodegenerative diseases; neurodevelopment; neurogenesis; SOX/miRNA interplay; traumatic brain injury

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Both, SOX genes and miRNAs are crucial regulatory components in neurogenesis and brain plasticity affecting similar processes (Stappert et al., 2015; Zhang et al., 2017; Stappert et al., 2018; Prom iodou and Matsas, 2019; Stevanovic et al., 2021). About 70% of all miRNAs are highly expressed in the CNS (Cao et al., 2016) and extensive changes in the expression of both SOX genes and miRNAs are revealed during brain development (Bylund et al., 2003; Miska et al., 2004; Bergsland et al., 2011; Hoshiba et al., 2016; Cho et al., 2019). Some of the SOX genes and miRNAs have age-specific (Smith-Vikos and Rock, 2012; Kuipers et al., 2015; Carrasco-Garcia et al., 2019; Cho et al., 2019; Goodall et al., 2019; Ketser and Pincus, 2020) and gender-specific (Guo et al., 2017b; Zale tel et al., 2018; Piscopo et al., 2021) expression in the brain. miRNAs and SOX genes are already recognized as novel diagnostic and prognostic biomarkers as well as potential therapeutic targets for various pathologies (Adlakha and Saini, 2014; Hu et al., 2019; Condrat et al., 2020; Grimm et al., 2020). Accordingly, a better understanding of the general principles of the interplay between SOX genes and miRNAs in the brain under physiological and pathological conditions could contribute to translating basic studies into novel clinical approaches, particularly in the fight against brain disorders.

### Search Strategy and Selection Criteria

The studies cited in the current review, published from 1993 to 2021, were retrieved on electronically search on Google, Web of Science, and PubMed databases using the following keywords/terms: SOX, miRNA, self-renewal, differentiation, neurodevelopment, neuroregeneration, ischemia, trauma brain injury, brain disorders, cancer, and glioblastoma. Furthermore, we also used various combinations of the above search terms to reach the literature data more specifically.

### The Roles of SOX Genes in Development and Diseases

SOX genes are widely expressed in different cells and tissues having important roles during various developmental processes including sex determination, gonadogenesis, neurogenesis, gliogenesis, eye development, ear formation, neural crest development, cardiogenesis, chondrogenesis, skeletogenesis, pituitary development, angiogenesis, and lymphopoiesis (Table 1). Literature data also revealed that mutations, dysfunction, and altered expression of SOX genes are linked to a wide spectrum of genetic disorders (Table 1) and different types of cancers (Table 2). In malignancies, SOX gene functions as oncogenes, tumor suppressors or both, depending on the cellular context and interacting partners (Grimm et al., 2020). It is interesting to point out that increased levels of some SOX TFs result in tumorigenesis in one organ, while their decreased expression results in tumorigenesis in another organ (Grimm et al., 2020). In addition, down-regulation of SOX9 gene expression is associated with inhibition of proliferation of glialoma cells and increased proliferation of melanoma cells (Olbronski et al., 2020).

It has been shown that numerous SOX genes are expressed in brain tumors and exert different important roles in this type of cancer (Ferletta, 2011; Grimm et al., 2020). The roles of SOX genes in GBM, the most common, most aggressive, and deadliest brain tumor, have been extensively studied, and it has been revealed that numerous SOX TFs influence the initiation and progression of this type of tumor acting as oncogenes, tumor suppressors, or both, depending on the cellular context (Castillo and Sanchez-Cespedes, 2012; Thu et al., 2014; Bryukhovetskiy et al., 2020; Vieira de Castro et al., 2020).

Despite enormous data indicating the key roles of SOX genes in the regulation of NSCs proliferation and differentiation during embryonic and adult neurogenesis, their expression and function in neuroregeneration are largely unknown with a very limited number of publications focusing on this issue. Data from a recent study have demonstrated a reduction in the number of SOX2 positive NSCs in the hippocampus of AD patients, which correlated with the severity of the disease related to cognitive capacity (Briley et al., 2016). Another study has demonstrated a significant decrease in the number of cells expressing SOX1, SOX2, and SOX21 within the subgranular zone in the transgenic mouse model of AD compared to their non- transgenic counterparts (Zaletel et al., 2018).

### The Roles of MicroRNAs in Development and Diseases

The expression profiles of miRNAs are specific for the particular type of tissue and stage of cell differentiation playing important roles in development, including neurogenesis and synaptic plasticity, immune system development and response, regulation of various metabolic pathways (cholesterol and fat metabolism), adiogenesis, establishment of hematopoietic lineages and regulation of cardiac development and pathophysiology (Gomase and Parundeak, 2009). Besides the SOX genes, the emerging data also point to the association between the dysregulation of miRNAs and various pathologies. Abrerrant expression profiles of miRNAs have been detected in various diseases, including NDS, spinal cord injury, Duchenne muscular dystrophy, cardiovascular diseases, diabetic nephropathy, sepsis, premature ovarian failure, and cancers (Fu et al., 2019; Davey et al., 2021; Ghafouri-Fard et al., 2021; Lin and Hu, 2021; Xu et al., 2021).

miR-200 family members, miR-147 and miR-124, are linked with the NDS (Fu et al., 2019; Lin and Hu, 2021; Xu et al., 2021), while miR-204 is deregulated in cardiovascular and renal diseases (Liu et al., 2021). In cancers, like SOX genes, miRNAs may function as oncogenes, tumor suppressors, or both, depending on the cellular context (Gajda et al., 2021). Important roles of miRNAs, for example, miR-138, miR-204, miR-145, miR-335, miR-338 and...
miR-21, have been revealed in different cancers (Li et al., 2016; Yeh et al., 2019; Xu et al., 2020; Moghbeli, 2021; Nguyen et al., 2021; Ye et al., 2021). Accordingly, a comprehensive understanding of the roles of miRNAs is crucial for determining whether miRNAs-related pathways could be recognized as novel targets for these diseases.

**SOX and MicroRNAs Interplay during Neural Development**

The majority of data about the interplay between SOX8 group members and miRNAs in brain development came from the studies of SOX1 and Sox2 genes. For instance, it was revealed that SOX1 was a direct target of miR-184 in human NPCs. Over-expression of this miRNA reduced the expression of SOX1 and other neuron and astrocyte-specific genes and promoted the differentiation of oligodendrocytes (Afrang et al., 2019). The interplay of Sox2 and miRNAs presents an important regulatory network controlling the balance between cell proliferation and differentiation in the brain. It has been demonstrated that a negative feedback loop between Sox2 and miR-200 is important for neural differentiation of NSCs and NPCs in the murine midbrain/hindbrain region (Peng et al., 2012). The authors show that when miR-200 suppresses the expression of Sox2 in both NSCs and NPCs, these cells exit the cell cycle and enter toward neuronal differentiation (Peng et al., 2012). Further, increased expression of miR-145 is essential for proper neural differentiation of NSCs through direct regulation of Sox2 and Sox2–Lin28/let-7 signaling pathway (Morgado et al., 2016). Interestingly, the interplay between Sox2 and miR-145 was also shown in oligodendroglia. The authors demonstrated that SOX2 represses the expression of miR-145 and speculated that SOX2 might be involved in the regulation of terminal differentiation of oligodendrocytes through inhibition of this miRNA (Hoffmann et al., 2014). Another axis important for neural differentiation of NSCs is miR-21/Sox2 interplay, where miR-21 directly regulates Sox2 expression, while both factors show mutually exclusive expression patterns in the mouse brain (Sathyam et al., 2015). All presented results indicate that Sox2 gene is regulated by several miRNAs in NSCs, where the interplay between them directs neural cell fate determination as well as region-specific differentiation of mature neurons or glial cells (Figure 1).

There are a number of studies that are focused on how miRNAs regulate SOX genes expression in various cancer types, while to the best of our knowledge, there is only one study focused on the interplay between SOX3 genes and miRNAs during neural development. The results of this study demonstrated that Sox4 gene is expressed in OPCs. Down-regulation of its expression by miR-204 leads to oligodendrocyte differentiation and onset of myelination (Figure 1) (Wittstatt et al., 2020).

SOX5 and SOX6 genes that belong to the SOX2 group are also regulated by different miRNAs during neural development. SOX5 is directly regulated by miR-96 in 3D cultures of human NSCs, and both these factors show exclusive expression patterns (Stevanato and Sinden, 2014). It was also suggested that miR-96 is involved in controlling cell-cycle progression and axon length modulation through direct regulation of SOX5 gene expression (Stevanato and Sinden, 2014). In OPCs, Sox6 gene is a direct target of two miRNAs, miR-219 and miR-338 (Dugas et al., 2010; Zhao et al., 2010). These miRNAs further initiate oligodendrocyte differentiation and myelination through inhibition of not only the Sox6 gene expression (Figure 1), but also the expression of other TFs involved in the promotion of oligodendrocyte progenitor state, like...
platelet-derived growth factor receptor alpha, forkhead box J3, and zinc finger protein 238 (Dugas et al., 2010; Zhao et al., 2010). Due to the importance of these miRNAs in promoting myelination, it was suggested that miR-219 and miR-338 could be considered as promising targets for the treatment and enhancement of axonal remyelination after nerve injuries in CNS (Nguyen et al., 2020).

The members of SOX9 group, SOX9, and SOX10 genes, in particular, are involved in the differentiation of oligodendrocytes (Figure 1) (Stolt et al., 2002; Weider et al., 2013; Klum et al., 2018). Therefore, the majority of studies were focused on miRNAs and SOX family interplay during differentiation of OPCs toward mature/myelinating oligodendrocytes (Gokey et al., 2012; Reiprich et al., 2017; Wittstatt et al., 2020). It is important to point out that, by regulating miRNAs expression, SOX9 and SOX10 regulate the expression of Sox4 and Sox9, respectively. Sox9 regulates the expression of miR-204 in OPCs that further directly regulates Sox4 expression (Figure 1) (Wittstatt et al., 2020). Further, miR-338 and miR-335 inhibit the expression of Sox9 gene in OPCs and promote differentiation of oligodendrocytes (Figure 1) (Reiprich et al., 2017). On the other side, SOX10 regulates the expression of miR-338 and miR-335 that leads to suppression of Hes Family BHLH Transcription Factor 5 (Hes5) and Hes Family BHLH Transcription Factor 6 (Hes6) gene expression leading to terminal differentiation of oligodendrocytes (Gokey et al., 2012). By regulating the expression of these two miRNAs, SOX10 is indirectly involved in the regulation of Sox9 gene expression in OPCs (Figure 1) (Reiprich et al., 2017). The proper expression of Sox9 is essential for NSCs maintenance during both embryonic and adult neurogenesis (Cheng et al., 2009; Scott et al., 2010). Cheng and colleagues demonstrated that Sox9 is a target of miR-124 in the subventricular zone. Silencing the expression of miR-124 led to increased expression of Sox9 and decreased neurogenesis (Cheng et al., 2009). Based on the presented results, it might be concluded that the interplay between miRNAs and SOX family is important for cell fate determination, pointing to them as fine tuners essential for proper differentiation of oligodendrocytes in particular (Figure 1).

It is more than evident that the interplay between SOX family and miRNAs is crucial for different aspects of neural development. As previously suggested, various SOX family and miRNAs show a functional link in orchestrating cell fate decisions and differentiation (Stevanovic et al., 2021). Here we are focused on highlighting the interplay between SOX family and miRNAs during neural development, particularly in NSCs, NPCs, and OPCs (Figure 1). The interplay between SOX family and miRNAs is important for the regulation of self-renewal and proliferative capacity of NSCs and progenitors, thus influencing the cell fate of these cells (Figure 1). The fact that the interplay between miRNAs and SOX family (Figure 1) is included in generating various types of neural cells from a limited pool of NSCs during adult neurogenesis is striking. Most of the studies regarding how miRNAs regulate SOX expression are conducted in animal models. The enormous progress in pluripotent stem cells research enabled the comprehensive study of miRNAs and SOX family interplay in the human model systems. Keeping in mind that both SOX family and miRNAs are important for neural development, the interplay between them in NSCs and NPCs can be exploited to better understand nervous system development, facilitating the progress in developing novel and more effective strategies for the treatment of brain pathologies.

**The Interplay between SOX TFs and MicroRNAs in Brain Pathologies**

Since the altered expression of miRNAs and SOX TFs is detected in different brain disorders, we present the overview of the current literature data about their interplay in different brain pathologies. We are focused on experimentally validated interactions between SOX and miRNAs and their potential interplay in various brain pathologies.

**The Interplay between SOX TFs and MicroRNAs in Neurodegenerative Diseases**

Neurodegenerative diseases, as a large group of neurological disorders characterized by progressive loss of neuronal and glial cells, have enormous and growing social and economic implications (Macciotta et al., 2013). These incurable, debilitating, and age-dependent disorders are becoming increasingly prevalent, which is associated with an increase in the elderly population in recent years (Gitler et al., 2017).

Here we present data indicating that some SOX TFs represent potential miRNAs targets in NDs (Figure 2). We also pointed out that modulation of SOX genes expression by miRNAs might be considered as a future strategy for the clinical treatment of NDs.

Insight into the interplay between SOX genes and miRNAs and their effects on the transition from NSCs to differentiated neural cells during development can improve NDs treatments. By directly targeting SOX genes, miRNAs can influence NSCs fate decisions during CNS development. The interplay of SOX2 and miR-200 family members regulates the proper generation and survival of ventral neuronal populations, including dopaminergic neurons (Peng et al., 2012). Both miR-124 and miR-200, which regulate Sox2 gene expression in NSCs, are associated with the pathogenesis of AD (Fu et al., 2013; Han et al., 2019) (Figure 2). These miRNAs are involved in the regulation of amyloid-β peptide secretion, which is considered the major cause of AD (Fu et al., 2019; Han et al., 2019). The functional link between SOX2 and beta-amyloid precursor protein, a precursor of amyloid-β, has also been revealed (Zhao et al., 2015). Accordingly, it has been proposed that SOX2 might play an important role in AD (Zhao et al., 2015). We hypothesize that the interplay between miR-124, miR-200, and SOX2 might be considered a new therapeutic target for AD treatment (Figure 2). The interplay between Sox6 and miR-129-5p is also shown in AD, where Sox6 and miR-129-5p are involved in the regulation of nerve injury and inflammatory response in the transgenic rat model of AD (Zheng et al., 2017). Another miRNA involved in the regulation of Sox6 expression, miR-138, is involved in the promotion of amyloid-β production through different pathways (Boscher et al., 2020). However, the
interplay between Sox6 and miR-138 in AD is yet to be confirmed in future studies (Figure 2).

One of the earliest stages of AD pathology includes loss of myelin sheaths as a result of impaired repair of OPCs, implying oligodendrocytes as novel therapeutic targets for the prevention and treatment of AD (Cai and Xiao, 2016). Here we point out that SOX TFs and miRNAs serve as fine tuners essential in regulating the loss of dopaminergic neurons in amyotrophic lateral sclerosis (ALS). miR-124, which regulates Sox2 and Sox9 genes expression in NSCs, is associated with the pathogenesis of PD (Figure 2), and it was suggested to be involved in the suppression of the neurodegeneration process during the development of this disease (Han et al., 2019). Based on the detected reduction in plasma levels, it was proposed that miR-124 could serve as a potential diagnostic biomarker in PD (Angelopoulou et al., 2016). Intracerebral administration of nanoparticles containing miR-124 increased the number of migrating neural tubes, induced migration of neurons into the lesioned striatum, and improved motor symptoms in 6-hydroxydopamine mouse model of PD (Saravia et al., 2016). Besides the role of miR-124, there is increasing interest in the therapeutic potential of miR-200 family members. The expression of miR-200 was suggested as a potential therapeutic tool for treating NDs (Favaro et al., 2009; Amador-Arjona et al., 2015), future studies are needed to identify how the interplay between SOX2 and miR-200 could be exploited for improvement of this outcome.

Further, miR-200 family members that regulate Sox2 expression in NSCs are recognized as an effective indicator of the progression of PD (Fu et al., 2019). Since SOX2 is important for proper neuronal differentiation, future studies are needed to identify how the interplay between SOX2 and miR-200 contributes to PD pathology (Figure 2). Also, miR-204 is involved in the regulation of the apoptotic signaling pathway, which leads to the apoptosis of dopaminergic neurons, a hallmark of PD (Chiu et al., 2019), while SOX4, a direct target of this miRNA, is down-regulated in the brain of patients affected with this disease (Sablik, 2018). Future studies are needed to identify how the interplay between SOX4 and miR-204 is involved in the pathogenesis of PD (Figure 2).

In addition to AD and PD, some studies associated deregulated miR-124 expression with HD pathology (Han et al., 2019). Particularly, miR-124 injected into the brain promoted neuronal differentiation and neuron survival in the striatum and slowed down the progress of this disease (Liu et al., 2015). Since SOX2 is involved in regulating neuron morphology and axon formation, a high level of SOX2 expression is detected in developing and mature neurons (Diana et al., 2019). Literature data indicate that miRNAs serve as potential therapeutic targets for the prevention and treatment of HD (Atif and Hicks, 2019; Pinchi et al., 2020). For example, increased expression of miR-21, the most studied miRNA in TBI, was found to improve the neurological outcome through inhibiting apoptosis and angiogenesis (Ge et al., 2015). Furthermore, a significant increase in miR-21 in neurons and extracellular vesicles, detected after TBI, suggested its additional role in cell-cell communication and neuroinflammation (Harrison et al., 2016). On the other hand, a recent study demonstrated that the overexpression of miR-200 in reactive astrocytes improved the recovery in mice after TBI (Chen et al., 2019). SOX2 is a functional target of miR-21 in mouse NSCs (Sathyan et al., 2015), however, their interplay in neural restoration following TBI needs further investigation. Since SOX2 can bind to the regulatory regions of many genes that control proliferation, differentiation, and cytokine signaling (Garros-Regulez et al., 2016; Mercuro et al., 2019; Stevanovic et al., 2021), a possible modulation of its expression by miR-21 (Figure 2) should be evaluated for future therapeutic strategies.

Impaired miRNAs profiles which were detected following cerebral ischemic stroke provided evidence that modulation of their expression could be considered as a diagnostic and prognostic tool providing a basis for potential therapeutic strategy (Khoshaman et al., 2017). A recent study in rodents demonstrated that the overexpression of miR-184 is suggested as an ischemic stroke and that the over-expression of this miRNA alleviates brain damage (Yang et al., 2021). A potential interplay between miR-184 and SOX1, which is critical for oligodendroglia differentiation during development (Afrang et al., 2019), suggests the importance of this interplay in neuroregenerative processes that could be applied in future therapeutic strategies.

Astrocytes, one of the most abundant cell type in the brain, play a dual role in neuronal injury – protecting neurons and increasing the injured area by forming edema (Stary and Giffard, 2015; Zhou et al., 2020). Numerous data suggested astrocytes as an attractive cellular candidate for stroke therapy (Stary and Giffard, 2015). A recent study demonstrated a protective role of miR-145 in these cells following ischemia-induced injury (Zheng et al., 2017). A high level of SOX2 expression is detected in developing and reactive astrocytes (Bani-Yaghoub et al., 2006; Gotz et al., 2015) indicating an important role of this TF in cell homeostasis. Furthermore, results from a recent study demonstrated the roles of this TF in functional recovery upon ischemic stroke by axonal regeneration (Zhao et al., 2018). Taken together, the interplay between miR-145 and SOX2, which was demonstrated previously in NSCs (Hoffmann et al., 2014), and its possible effect on astrocyte and neuron recovery following stroke should be further investigated.

The possibility of expanding the pool of self-renewing NSCs or directing their cell fate towards certain neural phenotypes is a hallmark of regenerative medicine. Based on numerous data on the role of SOX2 in diverse cell processes during development as well as the effect of different miRNAs on their expression, we can speculate that SOX/miRNA interplay should be considered as a target in the future strategies for prevention and therapy of various impairments of brain structure and function.

The Interplay between SOX TFs and MicroRNAs in Glioblastoma

GBM represents a prototypic brain tumor for studying neural cancer stem cells (Diana et al., 2019). Literature data indicate that these cells can bind to glioma biomarkers and can be used for targeted therapy of GBM (Mondal and Kulshreshtha, 2021). Moreover, it has been shown that miRNAs have an important function during the conversion of neural stem cells into neural cancer stem cells (Diana et al., 2019).

Numerous studies have confirmed complex interactions between miRNAs and SOX-specific miRNAs in GBM. Multiple miRNAs inhibit the expression of their SOX targets; thus, miRNAs regulate the key features of GBM by acting as oncogenes or tumor suppressors. Figure 3 shows the miRNA-SOX axis in glioma stem cells (GSCs) associated with their stem-like characteristics. Detailed information about specific miRNAs, their targets and the GBM cell properties affected by down-regulation of SOX expression is presented in Table 3.

The Interplay between SOX TFs and MicroRNAs in Glioma Stem Cells

The roles of miRNAs in GSCs have been extensively investigated since they regulate tumor-related miRNAs, thus controlling the stem-like properties of GSCs. Numerous studies associated deregulated miRNAs expression with the development and progression of neural stem cell tumorigenicity (Besse et al., 2013) playing both oncogenic and tumor-suppressive roles in GBM (Esquela-Kerscher and Slack, 2006).
Among miRNAs listed in Table 3, several of them also play important roles in the maintenance of GSCs (Jeon et al., 2011; Yang et al., 2012; Rani et al., 2013; Ying et al., 2013; Sathyan et al., 2015; Lopez-Bertoni et al., 2016; Xu et al., 2016; Su et al., 2017; Tian et al., 2017; Xiong et al., 2018; Kim et al., 2019; Qian et al., 2019; Sabelstrom et al., 2019; Zhao et al., 2019; Guan et al., 2020; Jiang et al., 2020). By down-regulation of SOX targets, these miRNAs control cell processes essential for glioma progression, such as proliferation, migration, invasion, apoptosis, stemness, differentiation, and chemosensitivity (Jeon et al., 2011; Yang et al., 2012; Rani et al., 2013; Ying et al., 2013; Sathyan et al., 2015; Lopez-Bertoni et al., 2016; Xu et al., 2016; Su et al., 2017; Tian et al., 2017; Xiong et al., 2018; Kim et al., 2019; Qian et al., 2019; Sabelstrom et al., 2019; Zhao et al., 2019; Guan et al., 2020; Jiang et al., 2020). Schematic representation of miRNAs regulating SOXs in GSCs is given in Figure 4.

Besides the roles of miRNAs in regulating SOX expression in GSCs, SOX2 has a reciprocal activity, regulating the expression of selected miRNAs in GSCs. Lopez-Bertoni et al. showed that SOX2, together with OCT4, induces promoter hypermethylation and silencing of a subset of miRNAs (miR-124, miR-148a, miR-17, miR-200a, miR-217, miR-296-5p, and miR-30c) by direct transactivation of the DNMT (DNA methyltransferase) promoter and consequent global DNA methylation (Lopez-Bertoni et al., 2015). In the same study, the authors revealed that miR-148a, one of the miRNAs whose expression was down-regulated by SOX2 and OCT4, inhibits GBC cell stem-like properties and their tumor-propagating potential (Lopez-Bertoni et al., 2015). Another down-regulated miRNA, miR-296-5p, directly targets HMGA1 (High mobility group AT-hook 1), which is associated with histone H1 displacement from the SOX2 promoter and inhibition of SOX2 expression (Lopez-Bertoni et al., 2016). Presented miR-296-5p-HMGA1-SOX2 axis functions as a negative regulator of the GSC phenotype (Lopez-Bertoni et al., 2016). In the study of de la Rocha et al. (2020), forced expression of SOX2 increased the expression of ABC: ATP-binding cassette; DMC: demethoxycurcumin; EMT: epithelial-to-mesenchymal transition; GBM: glioblastoma; GSC: glioma stem cell.

### Table 3 | miRNAs and their SOX targets down-regulated in glioblastoma

| Target SOX gene | miRNA that downregulates SOX target expression | GBM cells properties affected by downregulation of SOX expression | Reference |
|-----------------|---------------------------------------------|-------------------------------------------------------------|----------|
| SOX2            | miR-126-3p                                  | Enhances TMZ sensitivity, inhibits cell viability, reduces colony-forming potential, and induces apoptosis | Luo et al., 2019 |
|                 | miR-145                                     | Enhances GSCs chemosensitivity to DMC, increases cell proliferation inhibition and cell apoptosis effects of DMC, increases sensitivity to TMZ and radiation, decreases the expression of drug resistance and antiapoptotic genes in GSCs, inhibits anchorage-independent growth, and induces cell cycle arrest | Yang et al., 2012 |
| SOX9            | miR-129                                     | Suppresses cell viability and migration of GSCs, suppresses glioma tumor growth in vivo | Xiong et al., 2018 |
|                 | miR-132                                     | Inhibits cell viability, migration, and invasion in glioma cells | Zhang et al., 2018 |
|                 | miR-21                                      | Decreases the self-renewal capacity of GSC lines promotes migration and invasion of glioma cells | Yue et al., 2017 |
| SOX3            | miR-296-5p                                  | Inhibits self-renewal capacity of GSCs in vitro, inhibits the growth of GSC-derived glioma xenografts in vivo | Lopez-Bertoni et al., 2016 |
| SOX4            | miR-340-5p                                  | Reduces mesenchymal traits, cell migration, invasion, and stemness in GBM, reduces tumorigenicity in GSCs and xenograft mice | Dong et al., 2017 |
|                 | miR-429                                     | Inhibits proliferation, induces apoptosis, and suppresses invasion of GBM cells | Jin et al., 2017 |
|                 | miR-490                                     | Suppresses telomere maintenance, induces DNA-damage response, induces senescence, and reduces stemness in GBM cells | Jou et al., 2011 |
| SOX5            | miR-34                                     | Reduces stemness in GSCs | Jou et al., 2011 |
|                 | miR-122                                     | Inhibits the proliferation, migration, and invasion of GSCs, while promoting GSCs apoptosis | Su et al., 2017 |
|                 | miR-194-5p                                  | Suppresses self-renewal, stem cell-associated phenotype and migration of glioma cells, and induces loss of invasion and tumorigenicity in vivo | Ying et al., 2013 |
| SOX7            | miR-29a                                     | Promotes GBM growth in vivo and invasion of GBM and GSC cell lines | Zhao et al., 2019 |
|                 | miR-133a                                    | Inhibits glioma proliferation, metastasis, and EMT | Liu et al., 2020 |
|                 | miR-400                                     | Suppresses telomere maintenance, induces DNA-damage response, induces senescence, and reduces stemness in GBM cells | Vincuere et al., 2020 |
| SOX5            | miR-181d-5p                                 | Impairs the integrity and increases the permeability of blood-tumor-barrier, decreases the expression of tight junction related proteins in glioma endothelial cells | Guo et al., 2017 |
| SOX7            | miR-16                                     | Inhibits the migration, motility, invasion, and colony formation ability of GBM cells and promotes GSCs differentiation | Tian et al., 2017 |
|                 | miR-195                                     | Reduced tumor growth | Liu et al., 2018 |
| SOX4            | miR-395                                     | Increases proliferation of GBM cells | Hao et al., 2016 |
|                 | miR-24                                     | Suppresses the proliferation ability of GBM cells | Xiuju et al., 2016 |
|                 | miR-616                                     | Promotes proliferation and inhibits apoptosis in glioma cells | Bai et al., 2017 |
|                 | miR-21                                      | Inhibits cell proliferation and metastasis in GBM and GSC cells | Gao et al., 2020 |
| SOX9            | miR-145                                     | Inhibits proliferation, adhesion and invasion of GBM and GSC cells | Rani et al., 2013 |
|                 | miR-105                                     | Inhibits proliferation and invasion, and promotes apoptosis of glioma cells, and suppresses glioma tumor growth in vivo | Liu et al., 2016 |
|                 | miR-497-5p                                  | Inhibits proliferation, migration, and invasion of GBM cells | Yan et al., 2016 |
|                 | miR-101                                     | Inhibits proliferation, migration, and invasion of glioma cells, suppresses the tumor growth in vivo | Liu et al., 2017 |
|                 | miR-613                                     | Suppresses the proliferation, colony formation, migration, and invasion of glioma cells, inhibits glioma growth in vivo | Sang et al., 2018 |
|                 | miR-30c                                     | Suppresses the proliferation, migration, and invasion of GBM cells and suppresses tumor growth in vivo | Liu et al., 2019 |
|                 | miR-605                                     | Suppresses the proliferation, migration, and invasion of GBM cell lines, impairs tumor growth in vivo | Jia et al., 2019 |
| SOX5            | miR-138-5p                                  | Triggers differentiation of stem-like GBM cells towards a neuronal phenotype, decreases tumorigenicity and resistance to drugs and radiation | Sabelstrom et al., 2019 |

ABC: ATP-binding cassette; DMC: demethoxycurcumin; EMT: epithelial-to-mesenchymal transition; GBM: glioblastoma; GSC: glioma stem cell; ID4: inhibitor of differentiation 4; TMZ: temozolomide.
miR-128b and miR-425-3p in GSCs. SOX2 controls the transcriptional activity of miR-425-5p by direct binding to the promoter of this miRNA (de la Rocha et al., 2020). The authors also revealed that miR-425-5p is involved in the regulation of the proliferation and apoptosis of GSCs (de la Rocha et al., 2020). Papagiannakopoulos et al. (2012) analyzed the tumor-suppressive role of miR-128 in genetically defined primary glioma-initiating NSCs (NSCs transformed with oncogenic EGFRvIII (Epidermal growth factor receptor variant III) and lacking tumor suppressor genes, p16/p19) and revealed that miR-128 induced repression of mitogenic signaling of glioma-initiating NSCs and enhance their differentiation. miR-128 promoted differentiation of glioma-initiating NSCs by down-regulation of Nestin and SOX2 expression (Papagiannakopoulos et al., 2012).

Lopez-Bertoni et al. (2020) also revealed that SOX2 induced activation of miR-486-5p through SOX2-binding sites within its putative promoter region. The resulting SOX2-miR-486-5p axis inhibits tumor suppressor pathways and promotes the stemness of GSCs (Lopez-Bertoni et al., 2020).

In addition, global expression analysis of miRNAs obtained by comparing GSCs and non-stem GBM cell cultures revealed a subset of miRNAs that correlated with SOX2 expression (Sana et al., 2018). Among all analyzed GSC samples, GSC cell cultures with the highest tumorigenic potential and pronounced multilineage differentiation showed up-regulation of the expression of a subset of nine miRNAs (miR-9-3p, miR-93-3p, miR-93-5p, miR-106b-5p, miR-124-3p, miR-153-3p, miR-301a-3p, miR-345-5p, and miR-652-3p) compared to their expression in non-stem cell cultures (Sana et al., 2018). The expression of these miRNAs is positively correlated with SOX2 expression, suggesting their association with the stem-like characteristics of GSCs (Sana et al., 2018).

### Contribution of SOX TFs in Inverse Regulation of MicroRNAs in Neurodegeneration and Cancer

Results from numerous epidemiological studies revealed an inverse correlation between certain NDS and cancers (Seo and Park, 2020). Neurodegeneration results in the premature death of postmitotic neurons, while cancer is characterized by enhanced resistance to cell death. However, the progression of these two chronic physiological ailments results from molecular mechanisms that are either complementary deregulated or share overlapping signaling pathways, including epigenetic and post-transcriptional modifications (Plun-Favreau et al., 2010; Seo and Park, 2020). Compared to other mammalian organs, the highest levels of miRNAs are detected in the brain. Moreover, a significant increase or decrease in miRNAs expression was detected during the early stages of nerve deterioration and oncogenesis, respectively. Thus, recent studies suggested that these two conditions may be regulated by common miRNAs pathways involved in proliferation, differentiation, and cell death (Plun-Favreau et al., 2010; Godlewski et al., 2019; Seo and Park, 2020). This review presents a possible interplay between SOX TFs and miRNAs in these shared regulatory networks. The increase of miR-9, which is involved in the regulation of NSCs proliferation and differentiation in adult neurogenesis, has been associated with PD, HD, and AD pathology (Godlewski et al., 2019). However, by decreasing the SOX2 expression, miR-34a also reduces the stemness in GSCs (Jiang et al., 2020). miR-124, the most abundant miRNA in adult neurogenesis, has been associated with PD, HD, and AD pathology (Godlewski et al., 2019). However, by decreasing the SOX2 expression, miR-34a also reduces the stemness in GSCs (Jiang et al., 2020). miR-124, the most abundant miRNA in adult neurogenesis, has been associated with PD, HD, and AD pathology (Godlewski et al., 2019). However, by decreasing the SOX2 expression, miR-34a also reduces the stemness in GSCs (Jiang et al., 2020). miR-124, the most abundant miRNA in adult neurogenesis, has been associated with PD, HD, and AD pathology (Godlewski et al., 2019). However, by decreasing the SOX2 expression, miR-34a also reduces the stemness in GSCs (Jiang et al., 2020). miR-124, the most abundant miRNA in adult neurogenesis, has been associated with PD, HD, and AD pathology (Godlewski et al., 2019). However, by decreasing the SOX2 expression, miR-34a also reduces the stemness in GSCs (Jiang et al., 2020). miR-124, the most abundant miRNA in adult neurogenesis, has been associated with PD, HD, and AD pathology (Godlewski et al., 2019). 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There is no doubt that further elucidation of this interplay will provide new avenues for developing novel and safe miRNA-based strategies for efficiently combatting brain pathologies.

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