Expert Reviews in Molecular Medicine

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MicroRNAs regulating SOX2 in cancer progression and therapy response

Sepideh Mirzaei[1], Hamidreza Saebfar[2], Mohammad Hossein Gholami[3], Farid Hashemi[4], Ali Zarrabi[5], Amirhossein Zabolian[6], Maliheh Entezari[7], Kiavash Hushmandi[8], Saeed Samarghandian[9], Amir Reza Aref[10,11], Milad Ashrafizadeh[12,6] and Haroon Khan[13]

[1]Department of Biology, Faculty of Science, Islamic Azad University, Science and Research Branch, Tehran, Iran; [2]Asu Vanda Gene Industrial Research Company, Tehran, Iran; [3]Faculty of Veterinary Medicine, Kazerun Branch, Islamic Azad University, Kazerun, Iran; [4]Department of Comparative Biosciences, Faculty of Veterinary Medicine, University of Tehran, Tehran, Iran; [5]Sabanci University Nanotechnology Research and Application Center (SUNUM), Tuzla 34956, Istanbul, Turkey; [6]Young Researchers and Elite Club, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran; [7]Farhikhtegan Medical Convergence Sciences Research Center, Farhikhtegan Hospital Tehran Medical Sciences, Islamic Azad University, Tehran, Iran; [8]Department of Food Hygiene and Quality Control, Division of Epidemiology, Faculty of Veterinary Medicine, University of Tehran, Tehran, Iran; [9]Noncommunicable Diseases Research Center, Neyshabur University of Medical Sciences, Neyshabur, Iran; [10]Belfer Center for Applied Cancer Science, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [11]Department of Translational Sciences, Xsphera Biosciences Inc., Boston, MA, USA; [12]Faculty of Engineering and Natural Sciences, Sabanci University, Orta Mahalle, Üniversite Caddesi No. 27, Orhanlı, Tuzla 34956 Istanbul, Turkey and [13]Department of Pharmacy, Abdul Wali Khan University, Mardan 23200, Pakistan

Abstract

The proliferation, metastasis and therapy response of tumour cells are tightly regulated by interaction among various signalling networks. The microRNAs (miRNAs) can bind to 3′-UTR of mRNA and down-regulate expression of target gene. The miRNAs target various molecular pathways in regulating biological events such as apoptosis, differentiation, angiogenesis and migration. The aberrant expression of miRNAs occurs in cancers and they have both tumour-suppressor and tumour-promoting functions. On the contrary, SOX proteins are capable of binding to DNA and regulating gene expression. SOX2 is a well-known member of SOX family that its overexpression in different cancers to ensure progression and stemness. The present review focuses on modulatory impact of miRNAs on SOX2 in affecting growth, migration and therapy response of cancers. The lncRNAs and circRNAs can function as upstream mediators of miRNA/SOX2 axis in cancers. In addition, NF-κB, TNF-α and SOX17 are among other molecular pathways regulating miRNA/SOX2 axis in cancer. Noteworthy, anti-cancer compounds including bufalin and ovatodiolide are suggested to regulate miRNA/SOX2 axis in cancers. The translation of current findings to clinical course can pave the way to effective treatment of cancer patients and improve their prognosis.

Review

Cite this article: Mirzaei S *et al* (2021). MicroRNAs regulating SOX2 in cancer progression and therapy response. *Expert Reviews in Molecular Medicine* **23**, e13, 1–18. https://doi.org/10.1017/erm.2021.15

Received: 21 April 2021
Revised: 14 July 2021
Accepted: 26 August 2021

Key words:
Anti-tumour compound; biological function; cancer; chemotherapy; LncRNA; microRNA; non-coding RNA; SOX; transcription factor

Abbreviations:
MiRNA: microRNA: ncRNAs: non-coding RNAs: lncRNAs: long non-coding RNAs: circRNAs: circular RNAs: mRNA: messenger RNA: SRY: sex determining region Y: HMG: high mobility group: SOX: SRY-related HMG box: NLSs: nuclear localisation signals: NES: nuclear export signal: MAD2L1: mitotic arrest deficient 2 like 1: SOCS1: suppressors of cytokine signalling 1: IPSCs: induced pluripotent stem cells: AEG: anophthalmia–oesophageal –genital: EMT: epithelial-to-mesenchymal transition: TM4SF1: transmembrane 4L six family member 1: BBB: blood–brain barrier: PTX: paclitaxel: ABC: ATP-binding cassette: ABCC1: ABC subfamily C member 1: CP: cisplatin: USP34: ubiquitin-specific protease 34: HDAC11: histone deacetylase 11: TBL1XR1: transcriptional regulator transducing (β)-like 1x-linked receptor 1: PDGF-A: platelet-derived growth factor-A: GSK-3β: glycogen synthase-3beta: EGF: epidermal growth factor: CCL-5: chemokine (C-C motif) ligand 5: MAP3K8: mitogen-activated protein kinase kinase kinase 8: IGF2: insulin-like growth factor 2: HMGA1: high mobility group A1: PI3 K: phosphatidylinositol 3-kinase: Akt: protein kinase-B: 5-FU: 5-flourouracil: COX-2: cyclooxygenase-2: DUSP2: dual-specificity phosphatase 2: ceRNA: competing endogenous RNA: HDGF: hepatoma-derived growth factor: PFN2: profilin 2: ZEB1: zinc-finger E homeobox-biding 1: PVT1: plasmacytoma variant translocation 1: mTOR: mammalian target of rapamycin: AC: *antrodia cinnamomea*: Ova: ovatodiolide: TNF-α: tumour necrosis factor-α: Il: interleukin: NF-κB: nuclear factor-kappaB: EWS: ewing sarcoma breakpoint region 7 gene: ID4: inhibitor of DNA binding factor 4: HOXA9: homeobox protein Hox-A9

Author for correspondence:
Amir Reza Aref, Haroon Khan,
E-mail: Amir_aref@hms.harvard.edu, haroonkhan@awkum.edu.pk

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Introduction

MicroRNAs

The expression of genes at the post-transcriptional level is regulated by microRNAs (miRNAs) and they are considered as single-stranded, short endogenous non-coding RNAs (ncRNAs) with the length of 19–24 nucleotides (Refs 1–4). Overall, there are three kinds of ncRNAs such as miRNAs, long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs) that regulate vital biological processes in cells such as proliferation, migration, differentiation and angiogenesis (Refs 5–8). In addition to regulating biological processes, miRNAs are involved in modulating metabolic pathways such as lipid, glucose and bone metabolism (Refs 9–11). Since aberrant expression of miRNAs occurs in different pathological conditions, particularly cancer, studies have focused on targeting these ncRNAs in disease therapy (Refs 12, 13). A tiny section of genome is formed by protein-coding genes, and it has been reported that miRNAs occupy 1–2% of all genome in different species such as mammals, worms and flies (Ref. 14). The regulation of genes by miRNAs is performed via affecting 3′-untranslated region (3′-UTR) in messenger RNA (mRNA), resulting in gene-expression inhibition (Ref. 15). Noteworthy, it has been shown that miRNAs can also induce gene expression (Ref. 16). Each miRNA can affect expression level of more than one gene (Ref. 17). By abnormal expression of miRNAs, a variety of downstream targets of a certain miRNA undergoes changes in expression that may be in favour of disease development (Refs 18–20). Consequently, experiments have focused on targeting miRNAs in cancer therapy and revealing their relationship with different downstream targets (Ref. 21).

SOX family

Sex determining region Y (SRY)-related high-mobility group (HMG) box (SOX) is a family of transcription factors with more than 20 members in vertebrates that are categorised from

SOXA to SOXH (Refs 22–27). Evolutionarily, SOX family members originate from duplication and divergence and were identified a century ago (Refs 28, 29). *SOX* genes contain a well-known and specific site, called HMG. It has been reported that HMG is vital for shuttling between nucleoplasm and cytoplasm, and for this purpose, HMG has two autonomous nuclear localisation signals (NLSs) (Ref. 30) and one leucine-rich nuclear export signal (NES) (Ref. 31). HMG is capable of binding to DNA in a sequence-specific manner (Ref. 32). A transcription factor is included in SOX family, if it has 50% or higher similarity to HMG domain of Sry (Ref. 33). The definitive origin of *SOX* genes is not certain. However, based on identification of SOX-like genes in unicellular choanoflagellate *Monosiga brevicollis*, it can be concluded that *SOX* genes might be transited from unicellular organisms to multicellular ones (Refs 34, 35). After their discovery, much attention was directed towards *SOX* proteins, and their function in cancer progression. It is believed that SOX proteins possess both tumour-promoting and tumour-suppressor functions in cancer, so that a certain *SOX* transcription factor may either induce or suppress cancer progression and viability (Refs 36–38). This has resulted in much complexity in understanding exact function of *SOX* proteins in cancer (Refs 39–43).

Throughout this paper, we reveal associations between miRNAs and SOX2, as a key member of SOX family in different cancers. This review is based on investigating regulatory impact of miRNAs on SOX2 in cancer, that is associated with cancer progression/inhibition. SOX2 is considered as a downstream target of miRNAs in cancer, and revealing their interaction can lead to tumour eradication.

MicroRNAs in oncology: an overview

MiRNAs are considered as master regulators of molecular pathways in cancers (Refs 44–49). MiRNA dysregulation is an obvious finding in cancer, and these short ncRNAs are reliable biomarkers for cancer detection and prognosis (Refs 50, 51). For instance, in breast cancer patients, miRNA-221 and miRNA-489 demonstrate upregulation and down-regulation in expression, respectively. The 3-year survival is high in groups with low expression of miRNA-221 and in groups with overexpression of miRNA-489 (Ref. 52). Noteworthy, the expression level of tumour-suppressor miRNAs undergoes down-regulation in cancers. The miRNA-449a and miRNA-145-5p as biomarkers, show a decrease in expression upon endometrial cancer pathogenesis (Ref. 53). Consequently, miRNAs are potential non-invasive prognostic factors in cancer (Ref. 54). The miRNAs are able to regulate growth rate of tumours (Ref. 55). The miRNA-30a-3p remarkably down-regulates mitotic arrest deficient 2 like 1 (MAD2L1) to trigger G0/G1 arrest in gastric tumour (Ref. 56). The miRNA-125 exerts a similar anti-tumour activity in colorectal cancer by down-regulating TAZ and disrupting cancer growth (Ref. 56). The response of cancer cells to apoptosis is also regulated by miRNAs. It has been reported that miRNA-922 diminishes sensitivity of gastric cancer cells to apoptosis via suppressors of cytokine signalling 1 (SOCS1) inhibition (Ref. 57). The metastasis of cancer cells is dually regulated by miRNAs in cancer (Ref. 58). The miRNA-624-5p and miRNA-194-5p can induce and suppress migration of tumours, respectively, by targeting signalling networks, including PTPRB and Crk (Refs 59, 60). Besides, miRNAs determine sensitivity rate of tumours to therapy (Refs 61, 62). Hence, understanding miRNA interaction with downstream targets can pave the way to cancer therapy (Refs 63–65).

SOX2: Structure, function and role in cancer

SOX2 is one of the most well-known members of SOX transcription factors that plays a vital function in reprogramming somatic cells to induced pluripotent stem cells (IPSCs) (Ref. 66). *SOX2* gene encodes a protein containing 317 amino acids and has been located on chromosome 3 at position of q26.3-27 (Ref. 67). The HMG domain of SOX2 is essential for its binding to DNA. Besides, HMG domain of SOX2 has a nuclear localisation and a nuclear export signal. SOX2 is involved in inducing/inhibiting expression of target genes via C-terminal transactivation domain capable of binding and recognising promoter of target gene (Ref. 68). The SOX2 is a vital factor for development and its abnormal expression results in emergence of developmental disorders including anophthalmia–esophageal–genital (AEG) syndrome that is due to heterozygous mutation of SOX2 and subsequent anomalies in development of ectodermal and endodermal tissues (Ref. 69). The SOXB1 group has three members including SOX1, SOX2 and SOX3 (Ref. 70). The contribution of SOX2 in stem cell maintenance is more confirmed by presence of a pluripotency regulatory network that is formed among SOX2, Oct-4 and Nanog (Refs 71–73).

The SOX2 function in tumours has been confirmed in various experiments (Ref. 74). The accumulation of genetic alterations in cells leads to cell cycle changes that are in factor of tumour development. SOX2 gene amplification is an obvious finding in cancer that is due to multiplication of 3q26.3 gene locus (Refs 75, 76). The SOX2 amplification has been observed in different tumours such as lung cancer, glioblastoma and squamous cell carcinoma (Refs 75, 77–79). The SOX2 can also be utilised as a prognostic factor in clinical course. In 14 studies on 2077 colorectal cancer patients, SOX2 overexpression has a positive correlation with tumour stage, distant invasion and unfavourable prognosis (Ref. 80). In respect to the role of SOX2 in cancer metastasis, its down-regulation is of importance in minimising migration of cancer cells. MTA3 can function as upstream regulator of SOX2, suppressing its expression and preventing cancer metastasis (Ref. 81). In contrast, transmembrane 4 L six family member 1 (TM4SF1) induces SOX2 expression via upregulating Wnt expression, leading to metastasis and epithelial-to-mesenchymal transition (EMT) stimulation in colorectal tumour (Ref. 82).

In breast cancer cells, SOX2 overexpression increases brain metastasis via elevating cell adhesion to brain microvascular endothelial cells, transendothelial migration and blood–brain barrier (BBB) invasion, whereas SOX2 down-regulation prevents brain metastasis of breast cancer cells (Ref. 82). In addition to metastasis, SOX2 is involved in cancer growth and viability. Down-regulating SOX2 impairs proliferation of cancer cells and reduces their survival (Refs 83, 84). Based on involvement of SOX2 in cancer growth and invasion, it can be concluded that this transcription factor participates in cancer chemoresistance (Refs 85, 86). Newly published experiments have confirmed this statement. SOX2 can provide intrinsic resistance of melanoma cells to paclitaxel (PTX) by enhancing activity and expression of ATP-binding cassette (ABC) subfamily C member 1 (ABCC1) (Ref. 87). The ubiquitin-specific protease 34 (USP34) is a deubiquitinase that can induce cisplatin (CP) resistance in laryngeal carcinoma cells by upregulating SOX2 expression and promoting cancer growth and survival (Ref. 88). The SOX2 down-regulation by histone deacetylase 11 (HDAC11) inhibitors impairs self-renewal capability and enhances chemosensitivity (Ref. 89). Table 1 provides a summary of SOX2 role in proliferation, invasion and chemoresistance of different cancers.

MicroRNAs and SOX2

In previous sections, it was found that miRNAs and SOX2 are two key players in cancer, that dysregulation in their expression can lead to development of cancer. Proliferation, metastasis and therapy response are modulated by SOX2 and miRNAs (Refs 101–

https://doi.org/10.1017/erm.2021.15 Published online by Cambridge University Press

104). The next parts will describe interaction between miRNA and SOX2, and its impact on cancer malignancy are provided to shed some light on their relationship.

Cancer metastasis

First of all, migratory capacity of tumours is under modulation by miRNAs (Refs 105, 106). The miRNAs can dually suppress/induce migration of cancers. A number of factors such as Wnt, STAT3 and EMT are affected by miRNAs (Refs 107–109). As it was mentioned earlier, SOX2 can positively affect migration of cancer cells (Ref. 110). Therefore, tumour-suppressor miRNAs should inhibit SOX2 expression in preventing cancer invasion. The miRNA-590-5p can reduce expression of SOX2 in decreasing stem cell population and impairing breast cancer metastasis. Down-regulation of SOX2 by miRNAs is conducted via binding to 3′-UTR (Ref. 111). The tumours show low expression of miRNAs with anti-tumour activity. Enhancing miRNA-145-5p expression disrupts progression and distant migration of breast tumour via SOX2 down-regulation. Furthermore, miRNA-145-5p overexpression provides favourable prognosis of breast tumour (Ref. 112). In increasing migration of cancer cells, SOX2 can affect EMT mechanism. SOX2 overexpression by transcriptional regulator transducin (β)-like 1 X-linked receptor 1 (TBL1XR1) stimulates EMT-mediated invasion in gastric cancer cells, and is associated with chemoresistance (Ref. 108). The SOX2 down-regulation significantly diminishes cancer metastasis via EMT inhibition (Ref. 113). These studies demonstrate modulatory effect of SOX2 on EMT in cancer cells. Noteworthy, SOX2/EMT axis can be modulated by miRNAs. The miRNA-590-5p reduces SOX2 expression to inhibit EMT via enhancing E-cadherin expression and decreasing vimentin, SNAI1 and SNAI2 expressions (Ref. 114).

Bcl-w, a tumour-promoting factor with overexpression in cancers, has a close association with metastasis (Refs 115, 116). In glioblastoma multiforme, Bcl-w promotes cancer invasion by inducing SOX2 expression. For this purpose, Bcl-w interacts with platelet-derived growth factor-A (PDGF-A) to provide SOX2 upregulation. However, this axis is disrupted by anti-tumour activity of miRNA-340-5p. This ncRNA can down-regulate SOX2 and Bcl-w expression levels that are in favour of inhibiting their interaction. Then, migration and mesenchymal features of glioblastoma cells undergo impairment (Ref. 117). Consequently, when expression levels of such tumour-suppressor miRNAs diminishes, an increase occurs in tumour migration by SOX2 upregulation (Ref. 118).

The exact function of miRNA-638 in tumour is not certain. It has been reported that miRNA-638 acts as a survival mechanism in inducing malignant behaviour of oesophageal cancer cells via autophagy stimulation (Ref. 119). However, there are studies demonstrating tumour-suppressor role of miRNA-638. The miRNA-638 down-regulation through methylation promotes progression of endometrial carcinoma cells (Ref. 120). Furthermore, it reduces EZH2 expression in triggering apoptotic cell death and autophagy in liver tumour (Ref. 121). In non-small cell lung tumour, miRNA-638 exerts an anti-tumour activity via regulating SOX2 expression. Enhancing miRNA-638 expression effectively suppresses lung cancer progression and metastasis via SOX2 down-regulation and subsequent inhibition of EMT (Ref. 122).

It seems that angiogenesis can be affected by miRNA/SOX2 axis in cancer. The angiogenesis induction can be mediated by molecular pathways such as VEGF to increase tumour progression and metastasis (Ref. 123). Since SOX2 upregulation stimulates angiogenesis in tumour, its targeting can provide novel therapeutics (Refs 124, 125). In colorectal tumour cells, miRNA-450a-5p shows a decrease in expression upon cancer progression. This miRNA suppresses colorectal cancer progression by SOX2 inhibition via binding to 3′-UTR. SOX2 overexpression promotes stemness and angiogenesis of colorectal cancer cells, and also, reduces VE-cadherin expression. These impacts are in favour of cancer invasion, and SOX2 inhibition by miRNA-450a-5p significantly suppresses malignant behaviour of colorectal cancer cells (Ref. 126).

Cancer proliferation

Table 1 obviously demonstrates contribution of SOX2 in cancer proliferation and viability. Therefore, the next critical step can be revealing interaction of miRNAs and SOX2 in cancer proliferation to target them, both pharmacologically and genetically, in future studies. In this section, a discussion of miRNA and SOX2 is provided in various cancers.

It seems that for promoting cancer growth and viability by SOX2 upregulation, upstream mediators should be regulated by miRNAs. The Wnt/β-catenin axis is an oncogene factor that can enhance tumour proliferation upon nuclear translocation of β-catenin. Glycogen synthase kinase-3β (GSK-3β) inhibits Wnt signalling by phosphorylating β-catenin, and preventing its nuclear translocation (Refs 127, 128). The activation of Wnt signalling pathway significantly increases viability and malignancy of cancer cells via SOX2 overexpression that is of importance for their stemness (Refs 129, 130). In prostate cancer, miRNA-1301-3p acts as a tumour-promoting factor and increases stem cell expansion via stimulating Wnt signalling. In this way, miRNA-1301-3p reduces SFRP1 and GSK-3β expression levels to induce nuclear translocation of β-catenin. Then, overexpression of SOX2 occurs by miRNA-1301-3p/Wnt axis to promote stem cell expansion of prostate cancer (Ref. 131). For activating SOX2 expression and increasing stem cell population, coordination among molecular pathways is necessary. It has been reported that epidermal growth factor (EGF) preserves stem cell population in cervical cancer via inducing PI3 K signalling and subsequent upregulation of SOX2. The miRNA-181a-2-3p shows a decrease in expression in cervical cancer cells. By restoring miRNA-181a-2-3p expression, SOX2 down-regulation occurs due to EGF inhibition. Hence, a coordination between miRNA-181a-2-3p and EGF/PI3 K/SOX2 is vital in which miRNA down-regulation leads to final upregulation of SOX2 in increasing cancer progression (Ref. 132). In addition, miRNAs cooperate in modulating SOX2 expression and CSC features. It has been reported that simultaneous upregulation of miRNA-21 and down-regulation of miRNA-145 are essential in SOX2 overexpression and maintaining CSC features and cancer proliferation (Ref. 133). In contrast, tumour-suppressor miRNAs such as miRNA-15a suppress stemness and growth of cancer cells via SOX2 inhibition (Ref. 134). These studies clearly demonstrate that miRNA and SOX2 interaction is of interest in regulating growth and proliferation of different cancers (Ref. 135).

The self-renewal capacity of cancer cells mainly depends on SOX2 expression. The miRNA-27b can suppress self-renewal capability of colorectal cancer stem cells *in vitro* via down-regulating SOX2 expression (Ref. 136). One of the complexities related to miRNAs is that their exact role is not certain, and they may exert various functions, both tumour-promoting and tumour-suppressor roles in cancers. For instance, miRNA-589-5p negatively affects growth and migration of prostate tumours. The decreased expression of miRNA-589-5p occurs in prostate tumour and elevating its expression disrupts cancer growth and invasion via chemokine (C-C motif) ligand 5 (CCL-5) inhibition (Ref. 137). However, another study emphasises on tumour-promoting activity of miRNA-589-5p that is mediated via

https://doi.org/10.1017/erm.2021.15 Published online by Cambridge University Press

Table 1. Potential role of SOX2 in cancer proliferation, metastasis and chemoresistance

Tumour	Study design	Cell line/Animal model	SOX2 expression	Remarks	Refs
Lung cancer	*In vitro*	HCC827 and H1975 cells	Down-regulation	SOX2 inhibition by TGF-β Triggering EMT Inducing resistance to tyrosine kinase inhibitors	(Ref. 90)
Lung cancer	*In vitro* *In vivo*	A549 cells Xenograft tumours	Down-regulation	Ciclesonide reduces SOX2 expression in inhibiting cancer progression Reducing cancer stem cell formation	(Ref. 91)
Breast cancer	*In vivo*	Xenografts model	Down-regulation	SOX2 overexpression promotes cancer stem cell phenotype Iadademstate reduces SOX2 expression	(Ref. 92)
Esophageal cancer	*In vitro* *In vivo*	KYSE cells	Upregulation	Stabilising SOX2 and enhancing its expression Promoting cancer growth	(Ref. 93)
Colorectal cancer	*In vitro* *In vivo*	CRC cells Subcutaneous xenograft models	Down-regulation	Disrupting cancer proliferation Suppressing drug resistance Vitamin D receptor reduces SOX2 expression	(Ref. 74)
Cervical cancer	*In vitro* *In vivo*	SiHa, HeLa, C33A, CaSki and HT-3 cells Tumour xenograft	Upregulation	Enhancing cancer cell proliferation Increasing cancer stem cell features NF-YA binds to SOX2 promoter in elevating its expression	(Ref. 94)
Prostate cancer	*In vitro* *In vivo*	LNcap, C4-2, PC3, DU145, and 293 T cells Xenograft tumour model	Upregulation	Preserving cancer stemness Enhancing cancer progression Inducing Akt and MAPK/ERK signalling pathways	(Ref. 95)
Bladder cancer	*In vitro*	T24 T and U5637 cells	Down-regulation	Inhibition of bladder cancer migration by compound ChIA-F Down-regulating SOX2 expression	(Ref. 96)
Bladder cancer	*In vitro*	T24 and 5637 cell lines	Upregulation	Enhanced spheroid formation by SOX2 Triggering IGF2 expression Elevating cancer growth	(Ref. 97)
Ewing sarcoma	*In vitro* *In vivo*	A673 and RD-ES cells Xenograft model	Upregulation	Enhancing proliferation and survival of cancer cells Elevating G1/S progression Stimulating PI3 K/Akt axis	(Ref. 98)
Ewing sarcoma	*In vitro*	Human paediatric mesenchymal stem cells	Upregulation	Increased expression Participating in carcinogenesis Involving in cell differentiation of Ewing sarcoma family tumours	(Ref. 99)
Pediatric sarcoma	*In vivo*	Immunodeficient mice	Upregulation	Providing tumorigenesis Involving in tumour initiation and growth	(Ref. 100)

stimulating STAT3 signalling and triggering chemoresistance (Ref. 138). In hepatocellular carcinoma, miRNA-589-5p exerts a tumour-suppressor role via affecting SOX2 expression. In this way, miRNA-589-5p decreases mitogen-activated protein kinase kinase kinase 8 (MAP3K8) expression at mRNA level to inhibit SOX2 expression. This axis prevents carcinogenesis and tumour spheroid formation capacity in hepatocellular carcinoma (Ref. 139). As a hint, it should be noted that SOX2 can also modulate miRNA expression in ensuring cancer development (Refs 140, 141).

It has been reported that miRNA and SOX2 interaction can be utilised for predicting progression of cancer cells. In prostate cancer, miRNA-34b demonstrates a reduction in expression that mediates progression of this life-threatening disease by enhancing stemness through SOX2 overexpression (Ref. 142). SOX2 not only promotes stemness of cancer cells, but also provides their uncontrolled proliferation and tumour sphere formation. Consequently, when SOX2 down-regulation occurs by tumour-suppressor miRNAs such as miRNA-451, their viability and growth demonstrate a significant decrease (Ref. 143). In clinical studies, relationship between miRNA and SOX2 determines prognosis. The miRNA-1181 has low expression in prostate cancer patients that mediates undesirable prognosis and low survival through promoting stem cell-like phenotypes via SOX2 overexpression (Ref. 144). These studies are in agreement with positive correlation of SOX2 with cancer stemness and proliferation, and its regulation by miRNAs.

Insulin-like growth factor 2 (IGF2) is a tumour-promoting molecule in tumours including hepatocellular carcinoma (Ref. 145). It has been reported that IGF2 upregulation enhances sphere-forming activity of cancer cells and is associated with carcinogenesis *in vivo* (Ref. 146). The IGF2 transcription can be epigenetically regulated, since IGF2 overexpression occurs due to impairment in DNA methylation of IGF2 promoter (Ref. 147). In hepatocellular carcinoma, down-regulation of miRNA-100 and miRNA-125b paves the way for IGF2 overexpression and increasing CSC properties via SOX2 upregulation (Ref. 148). Restoring expression of miRNA-125b and miRNA-100 can reduce SOX2 expression via suppressing IGF2. One of the signalling pathways in cancer progression is Wnt/β-catenin (Ref. 149). The stimulation of Wnt signalling by SOX2 leads to tumour progression (Refs 150, 151). In breast cancer stem cells, the

https://doi.org/10.1017/erm.2021.15 Published online by Cambridge University Press

interaction between SOX2 and β-catenin ensures their self-renewal capability. It has been reported that miRNA-208a can upregulate expression of SOX2 to induce β-catenin and promote self-renewal capacity (Ref. 152). These studies demonstrate that miRNAs can target other molecular pathways such as IGF2 in affecting SOX2 expression in cancer. Furthermore, miRNAs can target SOX2 in affecting molecular pathways required for cancer progression. These kinds of interactions promote complexity of signalling networks.

One of the interesting interactions in cancer is observed between EMT and SOX2. SOX2 elevates tumour migration via EMT stimulation, and in turn, EMT enhances aggressive behaviour of tumours via SOX2 induction (Refs 153, 154). These dual associations are of importance for increasing cancer progression. A recent experiment has demonstrated that SOX2 and EMT interaction can be affected by miRNA-147. The miRNA-147 has low expression in colon tumour and increasing its expression can dually suppress proliferation (SOX2 inhibition) and metastasis (EMT inhibition). The miRNA-147 down-regulation enhances invasion of colon tumour via EMT stimulation. Subsequently, EMT promotes proliferation via SOX2 upregulation (Ref. 155). The expression level of miRNAs can be affected in a methylation-dependent manner. For instance, down-regulation of miRNA-296-5p occurs in glioblastoma stem cells via DNA methylation. Then, high mobility group A1 (HMGA1) enhances SOX2 expression to enhance stemness of cancer cells (Ref. 156). The miRNAs with anti-tumour activity, significantly diminish expression level of SOX2 in impairing cancer proliferation (Ref. 157).

Cancer chemo- and radio-therapy

In respect to the role of SOX2 in increasing cancer proliferation and metastasis, it can be concluded that SOX2 may have a close relationship with resistance of cancer cells to therapy, since an increase in growth, viability and migration provides condition for obtaining resistance (Refs 158–161). Experiments have confirmed involvement of SOX2 in stimulating chemo- and radio-resistance. In case of drug resistance, SOX2 can stimulate Wnt5a/β-catenin signalling pathway (Ref. 162). Reducing SOX2 expression and its destabilisation, for instance via inhibiting phosphatidylinositol 3-kinase (PI3 K)/protein kinase B (Akt) axis is of importance in reversing resistance of lymphoma cells to therapy (Ref. 85). In triggering radioresistance, SOX2 promotes expression of Hedgehog signalling by occupying HHAT promoter (Ref. 163). Studies have examined association between miRNAs and SOX2, and its relationship with chemo- and radio-therapy response is discussed in this section. Noteworthy, SOX2 can provide resistance of tumours to immunotherapy via suppressing STAT3 signalling and inducing immune evasion (Ref. 85). However, there is no study about relationship between miRNA/SOX axis and response to immunotherapy that can be considered in future experiments.

CP is an anti-tumour agent capable of stimulating cell death and DNA damage in cancer cells (Ref. 164). A variety of factors have been recognised to be involved in triggering CP resistance, and SOX2 is one of them. In lung cancer, a significant decrease occurs in expression of hsa-miRNA-340-5p that subsequently, mediates overexpression of SOX2, and emergence of CP resistance (Ref. 165). By restoring expression of tumour-suppressor miRNAs such as miRNA-450b-5p, expression level of SOX2 undergoes down-regulation. Then, sphere-forming capacity and stemness of cancer cells decrease. This is in favour of 5-fluorouracil (5-FU) chemo-sensitivity, reducing cell viability, inducing DNA damage and increasing apoptosis via caspase-3 upregulation (Ref. 166). The factors that can regulate CSC properties of cancer cells such as TMED3 are affected by miRNAs in reversing chemoresistance. For instance, miRNA-876-3p down-regulates expression of TMED3 in gastric cancer cells that mediates a decrease in SOX2 expression and enhancing CP sensitivity (Ref. 167).

PTX is another chemotherapeutic agent with anti-tumour activity against various tumours including breast tumour, glioblastoma, lung cancer and cervical cancer (Ref. 168). Upregulation of SOX2 leads to PTX resistance via PI3 K/Akt induction (Refs 169, 170). In breast cancer cells and tissues, miRNA-145-5p demonstrates a decrease in expression, leading to tumour cell growth and metastasis, as well as PTX chemo-resistance. Enhancing miRNA-145-5p is associated with PTX sensitivity of breast tumour via SOX2 inhibition, and impairing their growth and migration (Ref. 171). A same story occurs for miRNA-200c-3p in PTX-resistant breast tumour cells (MCF-7). The miRNA-200c-3p down-regulation increases breast tumour progression via SOX2 overexpression that is in favour of PTX resistance (Ref. 172). Consequently, identification of miRNAs with regulatory effect on SOX2 can be of importance in increasing efficacy of cancer chemotherapy (Ref. 173).

The miRNA-106a function in chemotherapy has not been completely understood. Although studies demonstrate that miRNA-106a has low expression in chemo-resistant-tumour cells and elevating its expression is correlated with chemosensitivity (Refs 174, 175), a recent study demonstrated miRNA-106a function in providing drug resistance via JAK2/STAT3 axis induction (Ref. 176). In colorectal cancer cells, miRNA-106a follows a unique pathway in triggering 5-FU resistance. In this way, miRNA-106a enhances expression of cyclooxygenase-2 (COX-2) via dual-specificity phosphatase 2 (DUSP2) inhibition. Then, stemness of cancer cells increases due to SOX2 overexpression, leading to emergence of 5-FU resistance (Ref. 177).

In case of radioresistance, miRNAs can target SOX2 as a stem cell factor. The miRNA-106b is a driver of different cancers, promoting both proliferation and metastasis, and can target various molecular pathways such as PTEN and FAT4 (Refs 178–180). In colorectal cancer cells, miRNA-106b mediates chemoresistance via increasing colony sphere formation and upregulation of stemness factors such as SOX2 (Ref. 181). Although a few studies have investigated regulation of SOX2 by miRNAs in radiotherapy response, based on involvement of SOX2 in cancer progression and malignancy, this interaction should be more examined in revealing molecular pathways that are responsible for radioresistance of cancer cells (Fig. 1 and Table 2).

Upstream mediators

Long non-coding RNAs

The epigenetic regulation of human pathophysiology is performed by lncRNAs and it seems that lncRNAs contribute to carcinogenesis (Refs 210–212). These kinds of ncRNAs have more than 200 nucleotides in length and lack protein-coding capacity. For years, lncRNAs were considered as transcription noise, but further experiments revealed role of these factors in cancer progression/inhibition (Refs 213, 214). LncRNAs have both pro-survival and pro-death functions. For instance, lncRNA LINC00511 shows high expression level in breast tumour. Overexpression of this lncRNA provides unfavourable prognosis. In order to increase tumorigenesis and stemness of breast tumour cells, lncRNA LINC00511 diminishes miRNA-185-3p expression by acting as ceRNA. Then, E2F1 as a down-stream target undergoes activation that further, promotes stem cell features of breast tumour via SOX2 upregulation (Ref. 215). Noteworthy, SOX2 not only enhances metastasis and growth of cancer cells, but also increases CSC properties (Ref. 216). In lung cancer cells, lncRNA ROS elevates growth and metastasis by activating p53,

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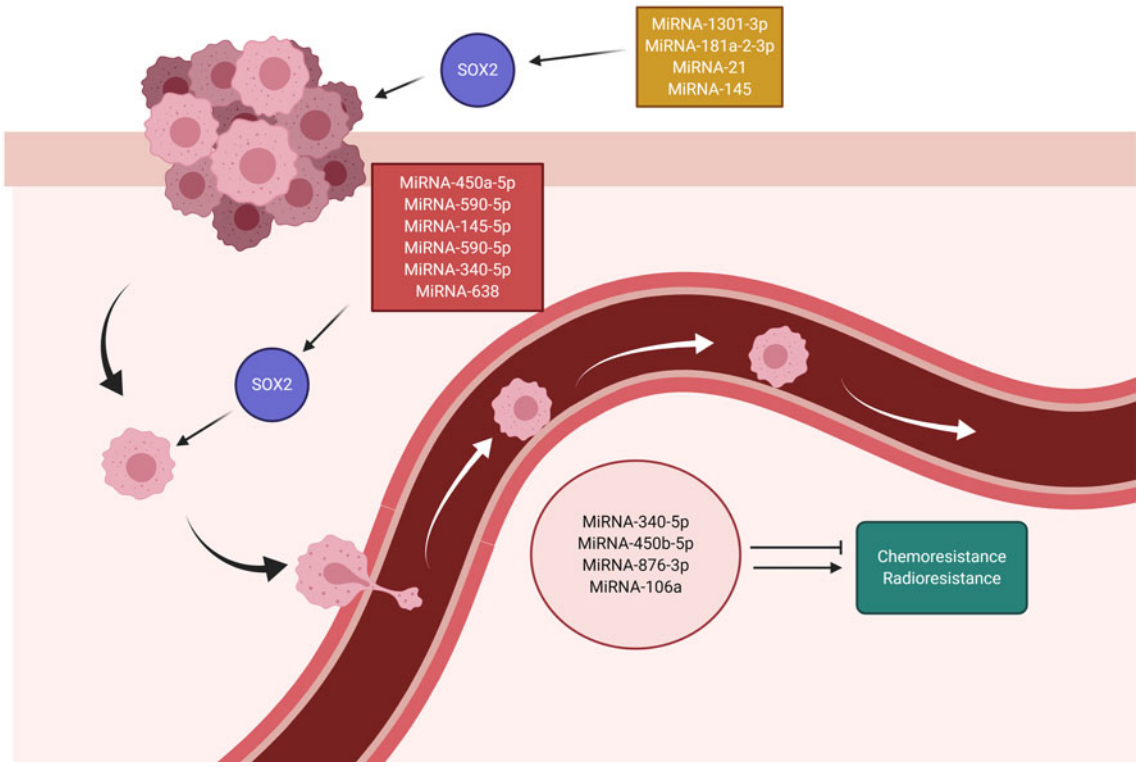


Fig. 1. MiRNAs in regulating proliferation, metastasis and therapy response of cancer cells. MiRNAs can induce SOX2 in increasing stemness, proliferation and migration of cancer cells to distant sites. Identification of such pathways and their targeting are of importance in effective cancer therapy. MiRNA, microRNA.

subsequent decrease in miRNA-145 expression, and promoting SOX2 expression. Furthermore, this axis enhances CSC properties of lung cancer cells (Ref. 217).

LncRNA FOXD2-AS1 is a driver of cancer development increasing migration via miRNA-25-3p down-regulation (Ref. 218). Furthermore, FOXD2-AS1 induces hepatoma-derived growth factor (HDGF) via miRNA-760 down-regulation to increase tumour progression (Ref. 219). The lncRNA FOXD2-AS1 affects different miRNAs in cancers. In breast cancer cells, lncRNA FOXD2-AS1 increases expression of profilin 2 (PFN2) via inhibiting miRNA-150-5p expression. Consequently, condition is provided for promoting breast cancer malignancy via SOX2 upregulation, as a stem cell factor (Ref. 220). It appears that there is a close association between SOX2, as stem cell factor, and metastatic factors such as EMT. These factors can positively affect expression of each other in promoting cancer progression. Hence, revealing their relationship can be of importance for targeting a novel signalling network for disrupting cancer proliferation and metastasis.

The EMT is induced by increasing vimentin and N-cadherin levels, and reducing E-cadherin (Refs 221, 222). The zinc-finger E homeobox-binding 1 (ZEB1) is an inducer of EMT in enhancing cancer metastasis and invasion (Refs 223, 224). In pancreatic cancer cells, lncRNA linc-DYNC2H1-4 diminishes miRNA-145 expression through sponging. Then, activation of ZEB1 occurs that not only promotes cancer metastasis via EMT, but also enhances cancer progression via SOX2 upregulation (Ref. 225). In previous sections, it was shown that SOX2 can also affect miRNAs in cancer. The SOX2/miRNA axis can also be affected by lncRNAs. In this way, lncRNA ES1 increases proliferation and cell cycle progression of breast tumour. Furthermore, ES1 participates in increasing breast cancer metastasis via EMT induction. These tumorigenesis impacts are mediated via inducing Oct-4/SOX2 axis, and increasing expression of miRNA-302, since silencing ES1 down-regulates expressions of SOX2 and its downstream target miRNA-302 (Ref. 226).

LncRNA ATB mediates miRNA-141-3p down-regulation to elevate colorectal tumour progression (Ref. 227). Furthermore, lncRNA ATB can provide ignorance of tumours towards apoptosis via miRNA-200c inhibition (Ref. 228). These studies demonstrate modulatory effects of ATB on cancer proliferation and migration via targeting miRNAs. In endometrial cancer cells and tissues, lncRNA ATB demonstrates upregulation to increase tumour differentiation. This lncRNA reduces miRNA-126 to induce PIK3R2/SOX2 axis, resulting in proliferation, apoptosis inhibition (caspase-3 down-regulation) and cell cycle progression (Ref. 229). LncRNA Plasmacytoma Variant Translocation 1 (PVT1) enhances cancer stem cell-like features of nasopharyngeal cancer via miRNA-1207 down-regulation and subsequent upregulation of SOX2 in promoting viability and proliferation (Fig. 2 and Table 3) (Ref. 230).

Compounds targeting miRNA/SOX2 axis

Anti-cancer agents can affect miRNA/SOX2 axis in cancer therapy. This impact can be beneficial in limiting cancer progression. However, the results are not always in line with cancer inhibition. Vitamin C is considered as a well-known anti-cancer agent in tumour treatment with efficacy of potentiating immunotherapy (Ref. 239). Furthermore, vitamin C restricts progression of cancer cells and enhances their sensitivity to cancer chemotherapy (Refs 239, 240). However, administration of vitamin C exerts carcinogenesis effect. Vitamin C stimulates reprogramming of breast cancer cells, and enhances expression of miRNA-302-367 members. This restores proliferative and metastatic capabilities of breast cancer cells via EMT induction and SOX2 overexpression (Ref. 241).

Bufalin is a cardiotonic steroid derived from ChanSu, a toad venom (Ref. 242). Bufalin has demonstrated anti-tumour activity

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Table 2. MiRNAs as modulators of SOX2 in affecting growth, migration and therapy response of cancer cells

MiRNA	Cancer type	Effect on SOX2	Signalling network	Remarks	Refs
MiRNA-126	Hepatocellular carcinoma	Inhibition	–	Suppressing proliferation and viability Triggering apoptosis and cell cycle arrest	(Ref. 182)
MiRNA-590-3p	Hepatocellular carcinoma	Inhibition	–	Reducing self-renewal and self-maintenance capacities of cancer cells	(Ref. 183)
MiRNA-130b	Hepatocellular carcinoma	Inhibition	–	Inhibiting migratory ability SOX2 down-regulation	(Ref. 184)
MiRNA-31	Head and neck squamous cell carcinoma	Inhibition	ARID1A/SOX2	Down-regulating ARID1A expression SOX2 inhibition Enhancing stemness properties	(Ref. 185)
MiRNA-340	Triple-negative breast cancer	Inhibition	–	Blocking breast cancer metastasis via SOX2 down-regulation	(Ref. 186)
MiRNA-708	Breast cancer	Inhibition	–	Suppressing cancer metastasis Down-regulating SOX2/Oct-4 axis	(Ref. 187)
MiRNA-638	Breast cancer	Inhibition	E2F2/SOX2	Decreasing E2F2 levels, and reducing SOX2 expression Suppressing proliferation, metastasis and self-renewal capacities	(Ref. 188)
MiRNA-484	Breast cancer	Inhibition	–	Inhibiting stemness and migration Enhancing sensitivity to tamoxifen chemotherapy SOX2 down-regulation	(Ref. 189)
MiRNA-340 MiRNA-429	Breast cancer Lung cancer	Inhibition	IL-4/SOX2	Inhibiting IL-4/SOX2 axis Radiation exposure reduces expression of miRNAs in inducing IL-4/SOX2 axis and promoting cancer malignancy	(Ref. 190)
MiRNA-296-5p	Glioblastoma	Inhibition	HMGA1/SOX2	SOX2 inhibition via HMGA1 down-regulation Suppressing stemness and tumour sphere formation capacities	(Ref. 156)
MiRNA-302/367	Glioblastoma	Inhibition	–	Suppressing carcinogenesis and malignant cell transformation via SOX2 down-regulation	(Ref. 191)
MiRNA-378	Glioblastoma	Induction	–	Enhancing self-renewal capacity via SOX2 overexpression	(Ref. 192)
MiRNA-130b	Glioblastoma	Induction	Hippo/SOX2	Suppressing Hippo signalling Increasing expressions of YAP and TAX SOX2 overexpression and promoting stem cell-like features	(Ref. 193)
MiRNA-21	Glioblastoma	Inhibition	–	Reverse relationship between miRNA-21 and SOX2 Patients with low miRNA-21 expression and high SOX2 expression possess high overall survival	(Ref. 194)
MiRNA-490	Glioblastoma	Inhibition	–	Inducing DNA damage Inhibiting telomere maintenance Down-regulating SOX2 expression	(Ref. 195)
MiRNA-149	Glioma	Inhibition	CDK6/SOX2	Disrupting cancer proliferation Enhancing temozolomide sensitivity Suppressing CDK6/SOX2 axis	(Ref. 196)
MiRNA-638	Gastric cancer	Inhibition	–	Reducing SOX2 expression Inducing apoptosis and cell cycle arrest Impairing metastasis	(Ref. 197)
MiRNA-638	Colorectal carcinoma cells	Inhibition	–	Inhibiting metastasis and mesenchymal phenotype of cancer cells via SOX2 down-regulation	(Ref. 198)
MiRNA-429	Colorectal cancer	Inhibition	–	Reducing SOX2 expression by binding to its 3′-UTR Increasing cancer cell survival Inhibiting apoptosis in cancer cells	(Ref. 199)
MiRNA-34a	Osteosarcoma	Inhibition	PAI-1/SOX2	MiRNA-34a reduces PAI-1 expression to inhibit SOX2 expression New therapeutic target for affecting differentiation of cancer cells	(Ref. 200)
MiRNA-410	Non-small cell lung cancer	Induction	GSK-3β/β-catenin	Promoting stemness of cancer cells Triggering Wnt/β-catenin signalling via GSK-3β down-regulation Enhancing SOX2 overexpression	(Ref. 201)

(*Continued*)

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Table 2. (*Continued.*)

MiRNA	Cancer type	Effect on SOX2	Signalling network	Remarks	Refs
MiRNA-145	Laryngeal squamous cell carcinoma	Inhibition	–	Suppressing cancer cell proliferation and metastasis Inducing apoptosis and cell cycle arrest Reducing SOX2 expression	(Ref. 202)
MiRNA-145	Laryngeal carcinoma	Inhibition	–	Inhibiting stem cells features via SOX2 down-regulation	(Ref. 203)
MiRNA-146a	Bladder cancer	Inhibition	COX2/PEG2/ lett7/SOX2	Reducing SOX2 expression via COX2 down-regulation Potential as a biomarker	(Ref. 204)
MiRNA-34c	Nasopharyngeal carcinoma	Inhibition	–	Impairing progression via SOX2 down-regulation Increasing cisplatin sensitivity of cancer cells	(Ref. 205)
MiRNA-181c-5p	Cervical cancer	Inhibition	GSKIP/SOX2	Reducing mRNA level of GSKIP Inhibition SOX2 expression Inducing apoptosis and proliferation inhibition	(Ref. 204)
MiRNA-101	Liver cancer	Inhibition	ANXA2/ERK/ SOX2	Suppressing metastasis and tumorigenesis Inhibition ANXA2/ERK axis Down-regulating SOX2 expression	(Ref. 206)
MiRNA-340-5p	Melanoma	Inhibition	–	Down-regulation of miRNA-340-5p in hypoxic condition and increased SOX2 expression	(Ref. 207)
MiRNA-148a	Oesophageal squamous cell carcinoma	Inhibition	–	Suppressing stemness via SOX2 down-regulation	(Ref. 208)
MiRNA-146a	Oral cancer	Inhibition	–	Suppressing aggressive behaviour via SOX2 down-regulation	(Ref. 209)

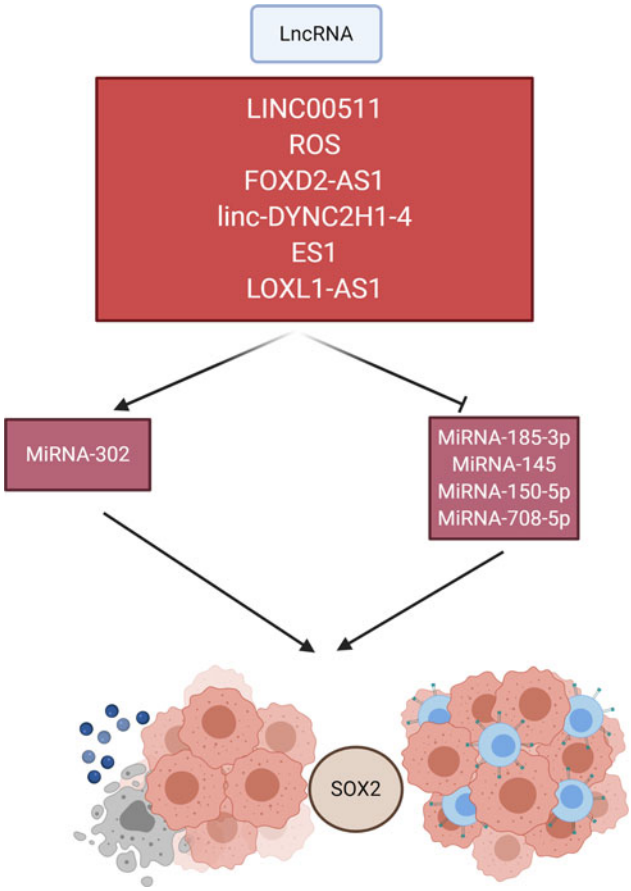


Fig. 2. LncRNAs as potential regulators of miRNA/SOX2 axis in cancer. LncRNA, long non-coding RNA; miRNA, microRNA.

against different cancers by targeting molecular pathways. Bufalin induces apoptosis and proliferation inhibition via Axl down-regulation in lung cancer (Ref. 243). The PI3 K/Akt and mammalian target of rapamycin (mTOR)/HIF-1α are other molecular pathways down-regulated by bufalin in cancer therapy (Refs 244, 245). In glioma cells, bufalin significantly promotes

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Table 3. LncRNAs as upstream mediators of miRNA/SOX2 axis in cancer

LncRNA	Signalling network	Effect on SOX2	Remarks	Refs
LOXL1-AS1	MiRNA-708-5p/USF1/SOX2	Induction	Overexpression of LOXL1-AS1 in gastric cancer cells and tissues Negative association with prognosis Enhancing proliferation and metastasis MiRNA-708-5p inhibition via sponging USF1 upregulation and subsequent induction of SOX2	(Ref. 231)
LINC00337	MiRNA-145/KLF5/SOX2	Induction	Reducing miRNA-145 expression via sponging KLF5 upregulation and enhancing tumorigenesis via SOX2 overexpression	(Ref. 232)
SNHG15	MiRNA-627/SOX2	Induction	MiRNA-627 inhibition in promoting SOX2 expression Triggering temozolomide resistance	(Ref. 233)
DANCR	MiRNA-216a-5p/SOX2	Induction	Association of DANCR with poor prognosis Enhancing cell proliferation and invasion *in vitro* and *in vivo* Reducing miRNA-216a-5p expression and increasing SOX2 expression	(Ref. 234)
DANCR	MiRNA-874-3p/SOX2	Induction	TUFT1 stimulates DANCR expression Reducing miRNA-874-3p expression by acting as ceRNA SOX2 overexpression and EMT induction in breast cancer cells	(Ref. 235)
PCAT-1	CD133/SOX2	Induction	Triggering chemoresistance and tumour growth Activating CD133/SOX2 axis	(Ref. 236)
SNHG3	MiRNA-3619-5p/ARL2	Induction	Inducing cisplatin resistance Increasing stem cell-like properties Down-regulating miRNA-3619-5p via sponging Upregulating ARL2 expression Subsequent overexpression of SOX2	(Ref. 237)
SNHG20	MiRNA-197/LIN28	Induction	Reducing miRNA-197 expression and subsequent activation of LIN28 Enhancing growth, tumour-sphere capacity and viability via SOX2 overexpression	(Ref. 212)
HOTTIP	MiRNA-148a-3p/Wnt1	Induction	Accelerating stemness and clonogenicity Reducing miRNA-148a-3p expression Inducing Wnt1 signalling Promoting SOX2 expression as a stemness factor	(Ref. 238)

expression of miRNA-203 as a tumour-suppressing factor. Then, the way is paved for suppressing CSC features of glioma cells via SOX2 overexpression (Ref. 246). Therefore, anti-tumour compounds may possess epigenetic regulatory effects that are of importance in cancer therapy.

Antrodia cinnamomea (*AC*) is a photophobic fungus with parasitic behaviour that develops in the inner wall of *Cinnamomum kanehirai* (Ref. 247). It has been reported that bioactive compounds present in AC possess anti-tumour activity against colon and oral cancers via triggering apoptosis (Refs 248, 249). A recently published study has shown potential of AC in enhancing sensitivity of colon cancer cells to 5-FU chemotherapy. In this way, AC enhances expression of miRNA-142-3p that has anti-tumour activity against colon cancer cells. Then, a decrease occurs in viability, proliferation, stemness and colony formation via SOX2 down-regulation (Ref. 250).

Ovatodiolide (Ova) is a natural diterpenoid derived from *Anisomeles indica* with anti-tumour activity against a wide variety of cancers. Ova administration is of importance in suppressing clonogenicity and chemoresistance via inhibiting miRNA-21/STAT3/β-catenin (Ref. 251). It can induce apoptosis in cervical cancer cells via NF-κB down-regulation (Ref. 252). Furthermore, Ova stimulates cell cycle arrest in prostate cancer cells via inhibiting Ras/Raf axis (Ref. 253). Ova administration enhances expression of miRNA-122 to inhibit stemness, cancer cell viability and resistance to imatinib therapy. The ability of cancer cells in forming spheres decreases and apoptosis induction occurs via enhancing Bax/Bcl-2 ratio. Furthermore, Ova reduces SOX2 expression in disrupting stemness of chronic myeloid leukaemia stem cells (Ref. 254). Although anti-tumour compounds have potentiality in suppressing cancer progression via affecting miRNA-SOX2 axis, they also have some drawbacks. Poor bioavailability and presence of biological barriers in cancer cells reduce efficacy of anti-tumour compounds. For overcoming these challenges, nanoformulations have been designed for delivery of anti-tumour agents (Refs 159, 255, 256). Dendrosomes significantly increase bioavailability of curcumin in glioblastoma therapy. Dendrosomal curcumin promotes miRNA-145 expression to suppress glioblastoma stemness via SOX2 down-regulation (Ref. 257). Therefore, application of anti-tumour compounds as modulators of miRNA/SOX2 axis is of interest in cancer therapy (Refs 258, 259).

Other molecular pathways

One of the interesting points is regulation of miRNA/SOX2 axis by other kinds of SOX family members such as SOX17. The SOX17 increases sensitivity of oesophageal cancer cells to chemotherapy and radiotherapy via inducing DNA damage and preventing DNA repair (Ref. 260). SOX2 overexpression induces cell cycle arrest in breast cancer cells via down-regulating Cyclin A2, Cyclin B1 and Cyclin D1 (Ref. 261). SOX2 down-regulation increases cancer progression and is associated with poor prognosis (Ref. 262). In colorectal cancer cells, SOX17 enhances expression of miRNA-371-5p as a tumour-suppressing factor. Then, this miRNA reduces SOX2 expression to decrease stemness of cancer cells (Ref. 263). This study demonstrates how a SOX transcription factor affects miRNAs in targeting SOX2 in cancer.

One of the hallmarks of cancer is chronic inflammation. Increasing evidence demonstrates involvement of inflammation in promoting cancer progression. Tumour necrosis factor-α (TNF-α) is a pro-inflammatory cytokine that enhances cancer

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metastasis via interacting with interleukin-33 (IL-33) (Ref. 264). Furthermore, TNF-α enhances NF-κB expression to promote breast cancer proliferation (Ref. 265). Interestingly, TNF-α can affect SOX2 expression via targeting miRNAs. In osteosarcoma cancer stem cells, TNF-α increases miRNA-155 as a tumour-promoting factor and generates a positive feedback loop. The TNF-α/miRNA-155 axis participates in obtaining CSC feature of osteosarcoma cells via SOX2 upregulation (Ref. 266). NF-κB can also increase miRNA-155 expression in promoting CSC feature via SOX2 upregulation (Ref. 267). In addition to proliferation, apoptosis is affected by miRNA/OX2 axis. For instance, in osteosarcoma, ewing sarcoma breakpoint region 1 gene (EWS) reduces expression level of tumour-suppressor factor miRNA-199a-5p to induce SOX2 expression. Then, proliferation rate of cancer cells increases and they obtain resistance to apoptosis (Ref. 268). That is why SOX2 overexpression is in favour of chemoresistance, since chemotherapeutic agents are not able to induce apoptosis in cancer cells. Such association has been explored in action of inhibitor of DNA binding factor 4 (ID4). Paracrine signalling of breast cancer cells stimulates ID4 expression in tumour-associated macrophages to promote invasive behaviour of cancer cells (Ref. 269). ID4 can trigger chemoresistance of breast cancer cells via enhancing activity of drug transporters (Ref. 265). In glioma cells, miRNA-9 suppresses SOX2 expression to induce chemoresistance and cancer stemness. ID4 as an upstream mediator, provides miRNA-9 down-regulation to induce SOX2 expression, resulting in overexpression of ABCC3 and ABCC6 as drug transporters involved in chemoresistance (Ref. 270).

In previous sections, it was mentioned that lncRNAs can regulate miRNA/SOX2 expression in cancers. Noteworthy, it seems that circRNAs are other regulators of miRNA/SOX2 in cancer. CircRNAs play a key role in development and progression of cancer (Ref. 271). They possess some distinct features including high stability, presence of covalently closed continuous loop, lack of 5′ to 3′ polarity and polyadenylated tail (Ref. 272). The hsa_circ_0103809 has demonstrated a tumour-promoting role in hepatocellular carcinoma capable of enhancing cancer proliferation and metastasis as well as inhibiting apoptosis. The hsa_circ_0103809 reduces expression of miRNA-490-5p to upregulate SOX2 expression, leading to cancer growth, viability and invasion (Ref. 273). Response of cancer cells to CP chemotherapy is regulated by circRNAs and their effect on miRNA/SOX2 axis. As a tumour-promoting factor, circRNA CDR1as enhances expression of homeobox protein Hox-A9 (HOXA9) via miRNA-641 down-regulation, leading to CP resistance and malignancy of non-small cell lung cancer cells via SOX2 overexpression (Fig. 3) (Ref. 274).

MiRNAs, SOX2 and tumour microenvironment

Tumour microenvironment (TME) has two major sections including extracellular matrix (ECM) and stromal cells (Refs 275, 276). In ECM, there are chemokines, pro-inflammatory factors, matrix metalloproteinases (MMPs), and stromal cells consist of cancer cells, CSC, pericytes, endothelial cells, cancer-associated fibroblasts (CAFs) and immune cells (Ref. 277). The metabolism in TME is completely competing among the cells (Ref. 278). The vasculature condition of TME is poor that provides some challenges for providing enough energy and also, removing waste materials. Therefore, a competition occurs among cancer cells that require high amount of energy for division, and immune cells that need energy for providing anti-tumour activity (Refs 279, 280). TME remarkably participates in cancer progression and it is one of the important targets in cancer therapy (Refs 277, 281, 282).

Recent years, much attention has been directed towards role of hypoxia in cancer. Hypoxia is capable of regulating proliferation, migration, survival and apoptosis in cancer development (Refs 283, 284). Upon hypoxia, activation of HIF-1α occurs that subsequently, translocates to nucleus, affecting expression level of genes containing hypoxia-responsive elements (HREs) (Ref. 285). In addition to HIF-1α, other molecular pathways such as NF-κB, STAT3 and mTOR activated (Refs 286–288). Importantly, there are interactions between SOX2 and hypoxia in cancer. It has been reported that SOX2 expression undergoes upregulation in hypoxic condition in a time-dependent manner. Then, SOX2 activates HIF-1α signalling to increase breast cancer metastasis (Ref. 289). Hypoxia-mediated SOX2 overexpression also enhances colony formation capacity of cancer cells. The SOX2 upregulation is vital for cellular functions of hypoxia in cancer (Ref. 290).

It has been reported that SOX2 is vital for lung metastasis of breast cancer cells. Further investigation reveals that SOX2 affects tumour-associated macrophages (TAMs) in providing cancer metastasis. In this case, SOX2 recruits TAMs to induce STAT3 and NF-κB signalling pathways, resulting in lung metastasis of breast cancer cells. TAMs rescue compromised lung metastasis caused by SOX2 inhibition, showing that TAM activation is vital for metastasis induction by SOX2 (Ref. 291). By providing acidic microenvironment for colorectal cancer cells, a decrease occurs in proliferation and drug sensitivity enhances due to transcriptional suppression of SOX2 (Ref. 292). Similarly, miRNAs are key players in TME and can dually inhibit/increase cancer progression via affecting TME and its components. For instance, miRNA-149 impairs cancer migration and invasion via suppressing M2 macrophage infiltration in TME (Ref. 293). MiRNA-216a inhibits interaction of cancer cells with CAFs to suppress breast cancer progression (Ref. 294). The studies highlight the fact that SOX2 and miRNAs can affect TME components, such interaction was mentioned about SOX2 and recruiting macrophages.

Noteworthy, a few of the experiments have shown the miRNA/SOX2 signalling pathway in TME of cancer cells. The miRNA-21-5p undergoes upregulation in glioblastoma and it is associated with chemoresistance. The miRNA-21-5p diminishes M2 polarisation of macrophages. In drug-resistant-glioblastoma cells, SOX2 shows an increase in expression and although this study has shown the role of miRNA-21-5p in TME and affecting cancer progression, there is no examination of their interaction (Ref. 295). Another experiment clearly investigates the role of miRNA/SOX2 axis in immunosuppression. In this way, lncRNA prostate cancer-associated transcript-1 (PCAT-1) induces CAF/myofibroblast secretion in TME by providing fibroblast differentiation via activating CD133/SOX2 axis. This is a consequence of upregulating expression levels of miRNA-182 and miRNA-217 as immunosuppressor factors (Ref. 236). Platelet-derived growth factor-A (PDGF-A) is a tumour-promoting factor in TME that undergoes upregulation by SOX2. The miRNA-340-5 can suppress progression of glioblastoma cells via down-regulating SOX2 and subsequent inhibition of mesenchymal features (Ref. 117). Overall, SOX2 and miRNA interaction occurs in TME, and their expression (both SOX2 and miRNA) is regulated by TME not cancer cells (Ref. 233), and future experiments can focus on identification of more miRNAs regulating SOX2 and developing novel therapeutics for its targeting in the near future. Figure 4 represents miRNA/SOX2 axis and related molecular pathways in different cancers.

Concluding remarks

In the present review, a comprehensive discussion of miRNAs and SOX2 interaction was provided to shed some light on their

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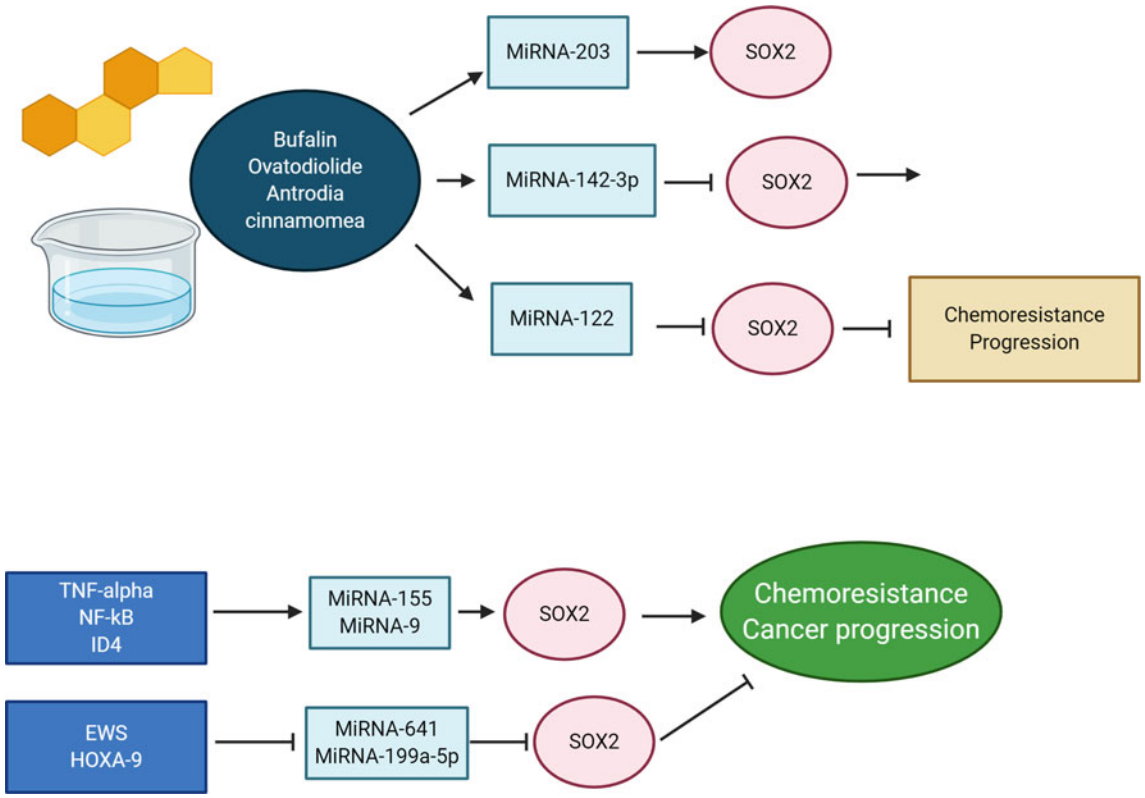


Fig. 3. Anti-tumour compounds and other upstream mediators of miRNA/SOX2 axis in cancer. MiRNA, microRNA; TNF, tumour necrosis factor; NF-kB, nuclear factor-kappaB; EWS, ewing sarcoma breakpoint region 1 gene; HOXA-9, homeobox protein Hox-A9; ID4, inhibitor of DNA binding factor 4.

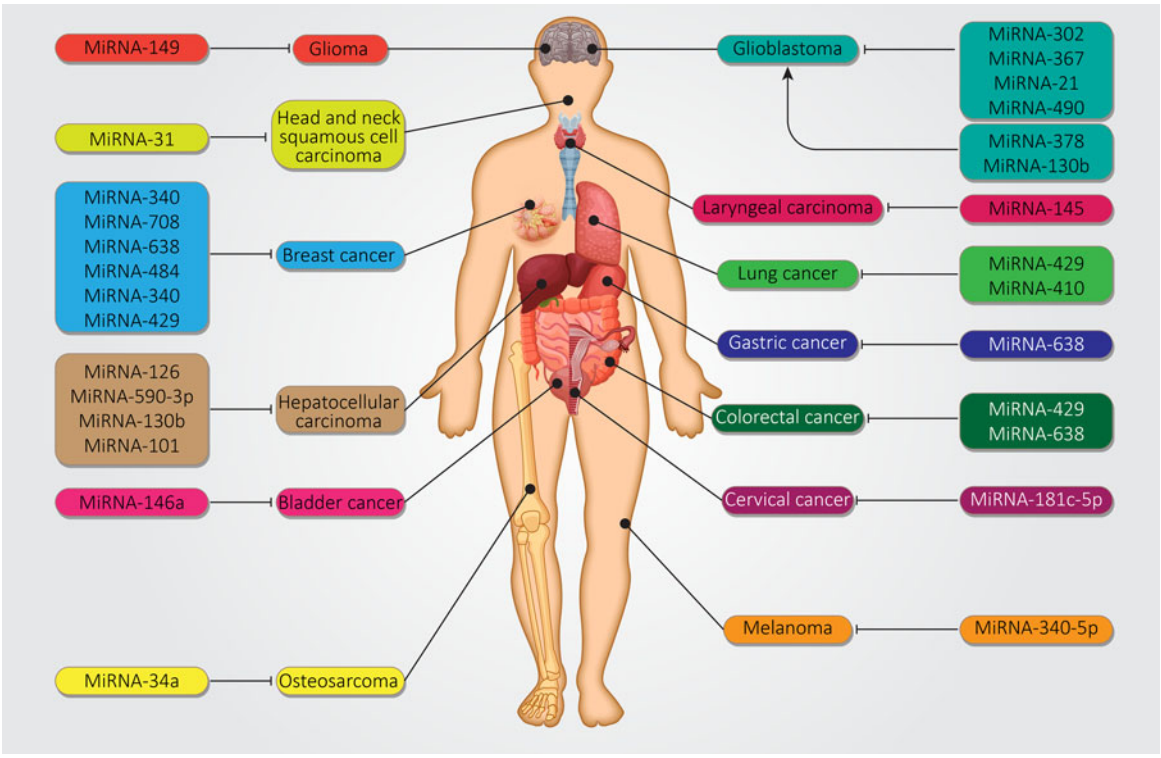


Fig. 4. Regulation of SOX2 by miRNAs in different cancers.

relationship and paves the way for developing novel therapeutic targets in cancer therapy, as a life-threatening disease. Metastasis of cancer cells is tightly regulated by miRNA-SOX2 axis. The interesting point is that SOX2 as a stemness factor, can induce EMT in enhancing metastasis of cancer cells. The miRNA-590-5p, −340-5p, −638 and −450a-5p are among miRNAs that regulate SOX2 in inducing/suppressing cancer metastasis. The most important action of SOX2 can be explored

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in cancer proliferation and viability. SOX2 is downstream target of tumour-promoting factors such as Wnt in enhancing stemness and growth of cancer cells. The miRNA-1301-3p, −181a-2-3p, −145, −27b and −589-5p can regulate SOX2 in affecting survival and stemness of cancer cells.

As it was mentioned previously, SOX2 plays a significant role in developing resistance of cancer cells to radiotherapy and chemotherapy. This phenomenon occurs as a result of increased cancer proliferation and invasion upon SOX2 upregulation. SOX2 overexpression stimulates resistance to CP, PTX and 5-FU chemotherapy. The miRNAs can either inhibit or induce chemoresistance via regulating SOX2 expression.

It seems that there are upstream mediators capable of regulating miRNA/SOX2 axis in cancer cells. LncRNAs are the most important regulators of miRNA/SOX2 axis that can affect SOX2 expression by reducing miRNA expression via acting as a ceRNA. Anti-tumour agents such as bufalin, AC and Ova can diminish SOX2 expression in suppressing cancer progression. Other molecular pathways such as circRNA, ID4, SOX17, NF-κB and TNF-α can regulate miRNA-SOX2 axis in cancer cells. However, more studies are needed to reveal miRNAs and SOX2 interaction in cancers.

Although a wide variety of experiments have been performed in the field of cancer therapy, cancer is still an increasing challenge to public health (Refs 296–300). This is due to the fact that clinical translation of current findings has been ignored. This review discussed SOX2 and miRNA interaction as the key player in the progression of different cancers. The *in vitro* and *in vivo* studies have confirmed this notion. However, there is no clinical study showing the role of miRNA and SOX2 interaction in cancer patients and its association with survival and prognosis. Noteworthy, there are studies evaluating SOX2 expression in cancers. For instance, SOX2 overexpression occurs in nuclei of lung cancer cells and it can be considered as a biomarker for non-small cell lung cancer diagnosis and therapy (Ref. 301). Furthermore, its upregulation enhances migration of liver cancer cells and is associated with poor survival of liver cancer patients (Ref. 302). The findings of present review can be used for cancer diagnosis and determining prognosis, as well as developing novel therapeutics for targeting miRNA and SOX2 interaction. Future studies will shed more light on this signalling network. Another issue is related to expression difference in cancer cells and tissues. An experiment conducted by Kanopka and colleagues demonstrates differences between mRNA expression of Fas and Rac in gastrointestinal cells and tissues (Ref. 303). The next experiments can demonstrate if the expression level of miRNA/SOX2 is various in cancer cells and tissues or not. Such investigation is of importance for further application of miRNA/SOX2 axis in cancer diagnosis and prognosis.

Data

Not applicable.

Acknowledgements. The graphical abstract and figures 1–3 were drawn by Biorender software (biorender.com/).

Authors' contributions. M.A, H.K and M.N participated in the design of outline and concept. A.Z (Ali.Zarrabi) performed software works. M.A, H.S, M.E, S.M, MH.G, F.H, A.Z (Amirhossein.Zabolian), K.H, S.S and AR.A prepared the first draft.

Financial support. No funding.

Conflict of interest. The authors have declared no conflict of interest.

Ethical standards. Not applicable.

Consent for publication. Not applicable.

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