Seminars in Cancer Biology 92 (2023) 74–83

Contents lists available at ScienceDirect

Seminars in Cancer Biology

journal homepage: www.elsevier.com/locate/semcancer

Epigenetic programing of cancer stemness by transcription factors-non-coding RNAs interactions

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ARTICLE INFO

Keywords:
Cancer stem cells
NF-κB
STAT-3
Non-coding RNAs
MiRNAs
LncRNAs

ABSTRACT

Cancer 'stemness' is fundamental to cancer existence. It defines the ability of cancer cells to indefinitely perpetuate as well as differentiate. Cancer stem cell populations within a growing tumor also help evade the inhibitory effects of chemo- as well as radiation-therapies, in addition to playing an important role in cancer metastases. NF-κB and STAT-3 are representative transcription factors (TFs) that have long been associated with cancer stemness, thus presenting as attractive targets for cancer therapy. The growing interest in non-coding RNAs (ncRNAs) in the recent years has provided further insight into the mechanisms by which TFs influence cancer stem cell characteristics. There is evidence for a direct regulation of TFs by ncRNAs, such as, microRNAs (miRNAs), long non-coding RNAs (lncRNAs) as well as circular RNAs (circRNAs), and vice versa. Additionally, the TF-ncRNAs regulations are often indirect, involving ncRNA-target genes or the sponging of other ncRNA species by individual ncRNAs. The information is rapidly evolving and this review provides a comprehensive review of TF-ncRNAs interactions with implications on cancer stemness and in response to therapies. Such knowledge will help uncover the many levels of tight regulations that control cancer stemness, providing novel opportunities and targets for therapy in the process.

1. Introduction

Stem cells produce cells that differentiate into different types [1]. There are multiple traits associated with stem cells which include maintaining homeostasis in the microenvironment, production of specialized daughter cells, self-renewal, multipotency, genome repair, and changes in cell cycle [1–4]. All of these characteristics are integral in maintaining cell number in different tissues, and so nearly all organs have stem cells to maintain the organization of cells within those organs.

Similar to regular stem cells, human cancers also have associated stem cells, the 'cancer stem cells, CSCs'. Cancer stem cells facilitate cancer progression by aiding metastasis, clonogenicity, growth, proliferation, homing and therapy resistance [1,5–7]. Additionally, cancer stem cells manipulate neighboring tissues within the tumor microenvironment to contribute to cancer survival and progression [8]. They achieve this by evading the immune system, and manipulating the neighboring tissue into supplying nutrients to the tumor [1]. Cancer stemness is the main reason behind the heterogeneity in the tumor population, which provides for higher survival capability of the tumor and the increased ability to resist stress and therapies (chemotherapy as well as radiotherapy). There are many factors contributing to the acquisition of stemness in cancer, and these include the deregulation of transcription factors (TFs) and the noncoding RNAs (ncRNAs).

TFs are a group of proteins that bind to genes in order to modulate their expression [9]. They usually bind to the 5′ region of the genes that are to be regulated. TFs lead to changes in cell behavior by affecting transcription and thereby affecting protein synthesis. There are many families of TFs that interact with DNA, and these include: zinc finger, basic protein-leucine zipper, helix-turn-helix, helix-loop-helix, and β-sheet motifs [10]. The change in gene expression can lead to many

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https://doi.org/10.1016/j.semcancer.2023.04.005
Received 30 January 2023; Received in revised form 30 March 2023; Accepted 9 April 2023
Available online 11 April 2023

different outcomes, ranging from regulation of inflammation to dictating the cell phenotype. Activation of TFs can potentially be initiated at different levels; through the binding of a ligand on a cell membrane receptor or in the nucleus, and could involve kinase signaling pathways. The activity of TFs is known to be affected by acetylation, nitration, phosphorylation etc. [11–14]. Deregulation of TFs plays a major role in cancer cell survival and progression, and is observed in a myriad of cancers [14,15]. This deregulation includes the deletion, amplification, or mutation that leads to either an acquisition or loss of function [15]. Pro-tumor signal transduction has been observed to modify TFs affecting cell differentiation. For example, in PML (promyelocytic leukemia), the TF RARA is deregulated which blocks the differentiation of myeloid cells [15]. Thus, the deregulation of TFs can affect cancer stemness, in turn affecting the cancer progression.

Epigenetics is the study of changes in the cellular function that are stable. Epigenetic changes are reversible and do not involve any changes in the DNA sequence [16]. Some well characterized epigenetic events include DNA methylation, histone modifications and the regulation through ncRNAs [17]. Among these epigenetic events, deregulation of ncRNAs can also contribute to cancer cell progression through the modulation of stemness [18]. As well established over many years, ncRNAs are a group of RNA sequences that do not code for proteins [18]. For a long time, they were considered genomic junk [19] but now they are known to be involved in the epigenetic regulation of genes. There are classified into short ncRNAs, such as microRNAs (miRNAs) which are ~ 22 nucleotides long, and long non-coding RNAs (lncRNAs) that span more than 200 nucleotides. In addition to these linear RNAs, circular-RNAs (circRNAs) are another class of ncRNAs. The epigenetic regulation of genes by the ncRNA family leads to changes in cell function and behavior [20]. In cancer, the aberrant expression of ncRNAs contributes to cancer phenotypes such as stemness [21,22]. Many ncRNAs are either suppressed or overexpressed in order to manipulate the gene expression to favor the stemness in cancer cells [23].

2. Deregulation of transcription factors in cancer stemness

TFs have been known to be aberrantly expressed in cancer [24]. There are families of TFs that can give cancer stem cell like qualities upon their deregulation, and we will provide an overview of a few of them here. TEAD (transcriptional enhanced associate domain) TFs regulate development, regeneration, proliferation, and more functions in healthy cells [24]. In cancer, however, the overexpression of TEAD TFs facilitates EMT (epithelial-to-mesenchymal transition) and metastasis [24]. In leukemia, there is deregulated expression of TFs that are in charge of hematopoiesis or the differentiation of blood cells [25]. The expression of TF GATA-1 in red blood cells and megakaryocytes (bone marrow cells) affects their differentiation [25]. Mutations in GATA-1 that lead to its inhibition are significantly associated with the acquisition of AMKL (acute megakaryoblastic leukemia) in children with down syndrome [25]. Other TFs that are associated with the cancer pathogenesis are c-Myc, Oct4, Sox2, Nanog, Klf4, PU.1, CCAAT enhancer-binding protein alpha (coded by the CEBPA gene), Runt-related transcription factor 1 (coded by AML1/ RUNX1) etc. A number of these TFs, such as c-Myc, Oct4, Sox2, Nanog and Klf4, are known to a play a role in acquisition of cancer stemness.

TF deregulation not only causes stemness but could give the cells a more aggressive phenotype. TFs have varied effects on cancer phenotype and aggression. The FOXO family of TFs play roles in differentiation, cell cycle arrest, DNA damage repair and senescence [26]. Downregulation of family members, such as, FOXO3 and FOXM1 contributes to stemness and chemoresistance [26]. Additionally, overexpressed FOXO1, FOXQ1, FOXF2 and FOXC2 have been shown to induce EMT in cancers, with FOXO1 having an additional ability to stimulate angiogenesis and metastasis.

Among the many TFs that have been investigated with considerable detail in human cancers, the two that clearly stand out are NF-κB and STAT-3. We, therefore, focus on these TFs for their role in determining cancer stem cell phenotype, to showcase, in particular, their regulation by ncRNAs as the underlying mechanism.

2.1. NF-κB

The Nuclear Factor Kappa B (NF-κB) family is made up of proteins that control the rate at which transcription occurs within a wide scope of biological processes [27]. The NF-κB regulatory network is evident in a wide range of biological processes and therefore, complications associated with therapeutic treatments, specifically of chronic conditions, remain a challenge [28]. In mammals, the NF-κB member protein monomers (p65/RelA, RelB, cRel, p50, and p52) are regulated by canonical and the non-canonical NEMO (NF-κB essential modulator)-dependent pathway [29]. The receptors work as messengers when they transfer the signals to cell nucleus and induce gene expression. In tumorigenesis, the pathways are uncontrolled and thus, facilitate cancer growth and development. The NF-κB signaling pathway is directly involved in the development and progression of various human cancers [30–32]. Dysregulated NF-κB signaling connects chronic inflammation and tumorigenesis [32].

2.2. STAT3

STAT3 belongs to the family that has several family members, including STAT1, STAT2, STAT4, STAT5 (STAT5B and STAT5A) and STAT6, which are vital transducers in growth factors and cytokines. STAT3 is estimated to be over-expressed and/or activated in more than 70% of all solid and hematological tumors [33,34]. STAT3 plays an important role in gene expression and is associated with cell differentiation, immune response, growth, apoptosis, and proliferation [35]. STAT3 impacts the immune system's inflammation by responding to injured or infected regions. Abnormal activation of STAT3 protein could lead to harmful cell transformation, which is associated with the development of tumors.

3. Deregulation of non-coding RNAs in cancer stemness

An emerging area of research interest in recent years is the one which aims to better understand the role of ncRNAs in cancer stemness. With the realization that cancer stemness controls so many different aspects of cancer progression, the interest in its regulation is understandable. Among the many ncRNAs, the three that have generated considerable interest are miRNAs, lncRNAs and circRNAs.

3.1. miRNAs

miRNAs are the short non-coding RNAs that are approximately 22 nucleotides in length. The deregulation of miRNAs has been studied in cancer for many years and it is now well established that their deregulation is associated with different stages of cancer progression. Given the volumes of literature on the involvement of miRNAs in cancer pathogenesis [36–45], it is impossible to provide an impartial and brief overview. Thus, we will keep the introduction focused on cancer stemness. While some miRNAs are known to be oncogenic, others are tumor-suppressive. In breast cancer, oncogenic miRNAs miR-181 and miR-155 are deregulated and they contribute to self-renewal [46]. This leads to higher proliferation, expansion of breast cancer cells, invasion and migration, which are properties associated with cancer stemness. In hepatocellular carcinoma, the tumor suppressor miR-206 and miR-192–5p are downregulated, which leads to dedifferentiation and the expansion of cancer cells, among other properties related to stemness [47]. A few other notable miRNAs that contribute to stemness are miR-125, miR-125b, miR-194, miR-217, miR-494, miR-500a-3p, miR-613 [47]. Moreover, the miRNA families let-7 and miR-34 have shown tumor suppressing functions, and since they are involved in

differentiation, it is suggested that they contribute to stemness [46]. miR-21, miR-221, miR-17–5p etc. are other miRNAs that are aberrantly upregulated and are involved in self-renewal and promotion of EMT [48,49]. miRNAs are known to affect cellular signaling pathways such as Notch signaling, wnt signaling and hedgehog signaling [50–53] that are known to correlate with stem cell characteristics [54–56], which provides a mechanistic insight into how miRNAs might potentially affect cancer stem cell phenotype. EMT is another mechanism very closely associated with cancer stem cells and many miRNAs are now known to influence this process thus impacting cancer stem cells in the process [46,57–61].

3.2. lncRNAs

lncRNAs (long non-coding RNAs) are relatively longer non-coding RNAs that are longer than 200 nucleotides in length. Compared to miRNAs, these molecules have been a little less characterized but over the last several years, the interest in these non-coding RNAs in the regulation of cancer pathogenesis has increased exponentially. Similar to miRNAs, now there is a plethora of literature detailing such role of lncRNAs [62–65]. LncRNAs have also been linked to cancer stem cells. A few lncRNAs that have been shown to regulate cancer stem cells include, MALAT1, DILC, MUF, lncTCF7, HAND2-AS1, HOTAIR, DLX6-AS1, PKMYT1AR, PDK1, TUG1 etc. [47,66–68].

3.3. circRNAs

CircRNAs (circular RNAs) are another type of non-coding RNAs that are gaining interest. As suggested by their name, they are ‘closed’ loop RNA molecules which makes them distinct from the regular linear RNA molecules. Because of their closed structure, circRNAs do not have exposed 5′ or 3′ ends thus making them resistant to action of exonucleases resulting in a rather stable structure to the extent that they can even be more abundant that the linear RNAs [69]. Their role in etiology of many different and diverse diseases is emerging [70–79] and their role in pathophysiology of different human cancers is relatively better understood [80–89]. Similar to miRNAs and lncRNAs, a role of circRNAs in stemness has been proposed [90,91].

4. Non-coding RNAs affecting TFs-mediated cancer stemness

While there is evidence for role of non-coding RNAs, miRNAs, lncRNAs and circRNAs, in cancer stemness, as briefly outlined in preceding section, we provide here a discussion of specific studies that have evidenced an action of these non-coding RNAs in the cancer stemness mediated by the TFs that are the focus of this review i.e. NF-κB and STAT-3.

4.1. miRNA targeting of TFs

Data is constantly emerging providing evidence supporting a connection between miRNAs and TFs in the regulation of stemness in different cancers. Some studies have provided a more direct targeting of TFs by miRNAs while others have provided an indirect effect, and yet others are a little more complicated. Like for example, the study in NSCLC (non-small cell lung cancer) that found up-regulation of miR-324–5p by TF c-Myc [92]. miR-324–5p targets and suppresses CUEDC2 which then plays a role in cancer stemness through regulation of NF-κB. Thus, this study reported TFs both up- and down-stream of a miRNA.

4.1.1. Evidence supporting direct miRNA-TF interactions

As a proof of direct interaction between TF and miRNAs (Table 1), a study, that looked at the effects of ATO (arsenic trioxide) on hepatic CSCs and the resulting chemoresistance, reported that ATO activates miR-148a which then directly targets NF-κB [93]. With the known positive correlation between NF-κB and CSCs, suppression of NF-κB by ATO-activated miR-148a provides the mechanism of miRNA-mediated NF-κB regulation. miRNAs that have been reported to target NF-κB leading to modulation of CSC characteristics include miR-708 in CLL (chronic lymphocytic leukemia) [94] and breast cancer [95]. Similar to NF-κB, TF STAT3 is also targeted by miRNAs, for example, by let-7e and miR-125a [96] and miR-671–5p [97] in gliomas, miR-665 in colorectal cancer [98], miR-29 in hepatoblastoma [99] and miR-142–3p [100] and

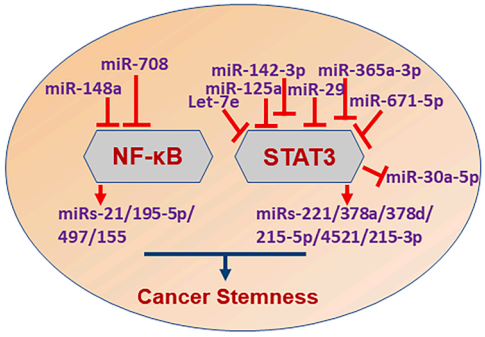

Fig. 1. TF-miRNA interactions. A number of miRNAs target and inhibit TFs NF-κB and STAT-3. Conversely, NF-κB and STAT-3 have also been reported to modulate the expression of several miRNAs. These TF-miRNA interactions have been demonstrated to affect cancer cells’ stemness.

Table 1
Direct regulation of TFs by miRNAs or vice versa.

miRNA	TF	Interaction Hierarchy	Cancer Model	Observation	Reference
miR-21	NF-κB	TF → miR	Gastric	NF-κB-miR-21 axis regulates gastric CSCs	[103,104]
mir-29	STAT3	miR → TF	Hepatoblastoma	Mediates circRNA effects	[99]
miR-30a-5p	STAT3	TF → miR	Colorectal	Determines overall survival	[109]
miR-142–3p	STAT3	miR → TF	Breast	Suppresses malignancy	[100]
miR-148a	NF-κB	miR → TF	Liver	ATO suppresses CSCs and resulting chemoresistance	[93]
miR-155	NF-κB	TF → miR	Liver	NF-κB mediates arsenite-induced liver cancer through miR-155	[106]
			NSCLC	NF-κB-miR-155 axis plays a role in TKI-resistance	[105]
miR-195–5p	NF-κB	TF → miR	Colon	NF-κB-regulation of miRNA regulates CSCs	[102]
miR-221	STAT3	TF → miR	Breast	STAT3 promotes biogenesis of miR-221 microvesicles	[107]
miR-365a-3p	STAT3	miR → TF	Breast	Mediates circRNA effects	[101]
miR-378a-3p miR-378d	STAT3	TF → miR	Breast	STAT3 induces miRNA enrichment	[108]
miR-497–5p	NF-κB	TF → miR	Colon	NF-κB-regulation of miRNA regulates CSCs	[102]
miR-665	STAT3	miR → TF	Colon	miRNA mediates lncRNA-regulation of STAT3	[98]
miR-671–5p	STAT3	miR → TF	Glioma	Regulates radio-resistance	[97]
miR-708	NF-κB	miR → TF	Breast	miRNA-TF interaction affects tumor growth and metastasis	[95]
			CLL	NF-κB suppressor miR-708 is epigenetically silenced in CLL	[94]

CLL: Chronic Lymphocytic Leukemia, CSC: Cancer Stem Cell, NSCLC: Non-Small Cell Lung Cancer, TF: Transcription Factor, TKI: Tyrosine Kinase Inhibitor

miR-365a-3p [101] in breast cancer (Fig. 1).

In colon cancer cells, NF-κB was reported to negatively affect the expression of miR-195–5p and miR-497–5p [102] and as relevant to colon cancer stem cells, ectopic expression of these miRNAs could attenuate NF-κB effects on colon cancer CSCs and, moreover, the effects were observed in vitro as well as in vivo. This study identified MCM2 as the miRNA target that could reverse the effects of miRNAs on CSC characteristics. A few other miRNAs have also been reported to be regulated by NF-κB, such as, miR-21 in gastric cancer [103,104], and miR-155 in NSCLC [105] and liver cancer [106] (Fig. 1).

Additionally, STAT3 has also been reported to directly affect expression of a few miRNAs (Fig. 1). Like for example, STAT3 is involved in the regulation and expression of oncogenic miR-221 in CAFs (cancer-associated fibroblasts) which gets transported out of CAFs via microvesicles in the tumor microenvironment [107]. Elevated STAT3 in breast cancer stem cells binds to the promoters of miR-378a-3p and miR-378d with a direct and positive effect on their expression [108]. STAT3 also upregulates miR-215–5p, miR-4521 and miR-215–3p, and downregulates miR-30a-5p in colorectal cancer where downregulation of miR-30a-5p, in particular, affects overall survival of patients [109] (Fig. 1). (Fig. 2).

4.1.2. Evidence supporting indirect miRNA-TF interactions

The physiological signaling cascades are complex and often the regulation is indirect that involves intermediate molecules/factors. Although there are reports on a direct interaction between non-coding RNAs and TFs, as discussed above, there are several reports on an indirect regulation as well (Table 2). For example, in glioma CSCs, miR-18a has oncogenic effect and it suppresses RORA (retinoic acid receptor-related orphan receptor A) and thus RORA is downregulated in gliomas [110]. RORA overexpression inactivates NF-κB in glioma CSCs, thus completing the loop facilitating an indirect relationship between miRNA miR-18a and the TF NF-κB. A recent study in breast cancer found that miR-765 targets tumor suppressor TRG16 (Transformation-Related Gene 16 Protein) and that, as expected, TRG16 is downregulated in breast cancer tissues, compared to normal tissues [111]. Ectopic expression of TRG16 resulted in inhibition of stem cell characteristics as evidenced by reduced expression of several stem cell markers such as CD44, Nanog, aldehyde dehydrogenase etc. as well as reduced number of mammospheres. TRG16 was directed targeted by miR-765 and it, in turn could suppress NF-κB.

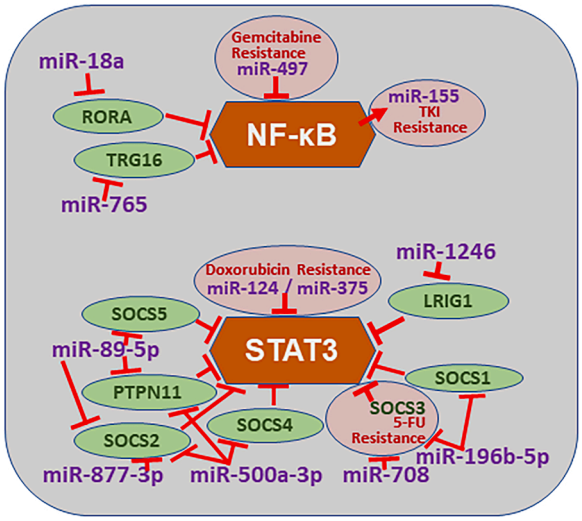

Fig. 2. Indirect miRNA-TF interactions and drug resistance. In addition to the direct targeting, miRNAs affect TFs indirectly as well. miRNAs target and inhibit tumor suppressors (in green) that are, in turn, known inhibitors of either NF-κB or STAT-3. Additionally, miRNA-TF interactions also play a role in determining response to several chemotherapies, such as gemcitabine, TKI (tyrosine kinase inhibitors), doxorubicin and 5-FU. LRIG1: Leucine Rich Repeats And Immunoglobulin Like Domains 1, PTPN11: Protein Tyrosine Phosphatase Non-Receptor Type 11, RORA: Retinoic acid Receptor-related Orphan receptor A, SOCS1: Suppressor Of Cytokine Signaling 1, SOCS2: Suppressor Of Cytokine Signaling 2, SOCS3: Suppressor Of Cytokine Signaling 3, SOCS4: Suppressor Of Cytokine Signaling 4, SOCS5: Suppressor Of Cytokine Signaling 5, TRG16: Transformation-Related Gene 16 Protein.

TF STAT3′s regulation by miR-185–5p involves upregulation of HOXB5 [112]. STAT's regulation by miR-877–3p has been shown to have SOCS2 as an intermediate [113]. The study aimed at understanding the induction of CSC by cytokine GM-CSF which involved activated STAT3 signaling and the acquisition of CSC characteristics and drug resistance. On the other hand, SOCS1 and SOCS3 mediate the modulation of STAT3 by miR-196b-5p [114] and just SOCS3 mediates the regulation of STAT3 by miR-708 in colorectal cancer [115]. In HCC (hepatocellular carcinoma), miR-500a-3p regulates stemness and STAT3 activation through SOCS2, SOCS4 and PTPN11 [116]. miR-500a-3p is elevated in HCC patients and these high levels correlate with higher spheroid formation ability in vitro through a mechanism involving STAT3 activation. In HCC, another miRNA, miR-589–5p, has also been shown to exhibit similar activity [117]. Similar to miR-500a-3p, miR-589–5p targeted SOCS2 and PTPN11 but, additionally, it also targeted SOCS5 and PTPN1, leading to STAT3 activation and the maintenance of stemness, as measured by increased spheroid formation ability and the increased CD133-positive side-populations [117]. Targeting of STAT3 by miR-1246 through regulation of LRIG1 has been reported in acute myeloid leukemia cells [118].

4.1.3. Effects on drug resistance

An important characteristic of CSCs is their ability to enable resistance against therapies [119–121]. While TFs as well as miRNAs have been individually correlated with such resistance, some interesting studies have provided a mechanistic link between miRNAs and the TFs in imparting resistance against therapies (Table 3). For example, resistance against TKIs (tyrosine kinase inhibitors), the pharmacologic anticancer agents that disrupt protein tyrosine kinases-mediated signaling in cancer cells [122], involves CSCs [123,124]. In a work that looked at gefitinib resistance, FOXO3a was reported to influence EGFR mutation-independent EGFR-TKI sensitivity [105]. FOXO3a correlated negatively with the resistance against gefitinib. Its suppression, therefore, induced resistance against gefitinib along with increased CSC characteristics. TF NF-κB suppressed the expression of FOXO3a through its regulation of miR-155 both in vitro as well as in vivo.

A recent study has indicated a role of miR-497 in gemcitabine resistance of pancreatic CSCs [125]. This study found NF-κB as a direct target of miR-497 which explains the detailed observations that NF-κB was high in CSCs especially playing role in resistance against gemcitabine, while at the same time, miR-497 was downregulated. Additionally, inhibition of miR-497 increased gemcitabine resistance while its overexpression inhibited resistance as well as metastasis of pancreatic CSCs.

Within the breast cancer tumor microenvironment, signaling involving STAT3 can help produce miR-221 in CAFs that gets transported by microvesicles and reaches the breast tumor cells leading to establishment of CSC niches that are marked by induced resistance against hormonal therapy [107]. Various chemotherapies can also induce expression of certain miRNAs that are then packaged in exosomes and transported within the tumor microenvironment to the neighboring cells so as to enable them escape the chemotherapy-induced cytotoxic effects. This is exactly what was shown in a study where doxorubicin and paclitaxel cycles resulted in enrichment of miR-378a-3p and miR-378d in exosomes through a STAT3-dependent mechanism in the host cells [108]. Once transported to neighboring cells, the miRNAs induced stemness by activating wnt and NOTCH signaling pathways.

The extracellular vesicles (EVs)-mediated transfer of miR-30b-3p can induce temozolomide resistance in gliomas [126]. This work reported

Table 2
Indirect regulation of TFs leading to modulation of Cancer Cells' Stemness.

miRNA	Cancer Model	miRNA target	TF Involved	Effect on TF	Reference
miR-18a	Glioma	RORA	NF-κB	RORA inhibits NF-κB signaling	[110]
miR-185–5p	Glioma	HOXB5	STAT3	Mediates circRNA effects	[112]
miR-196b-5p	Colorectal	SOCS1/SOCS3	STAT3	SOCSs target STAT3	[114]
miR-324–5p	NSCLC	CUEDC2	NF-κB	CUEDC2 downregulation activates NF-κB	[92]
miR-500a-3p	HCC	SOCS2, SOCS4, PTPN11	STAT3	Promotes spheroid formation through STAT3 activation	[116]
miR-589–5p	HCC	SOCS2, SOCS5, PTPN1, PTPN11	STAT3	Promotes stemness and tumorigenicity	[117]
miR-708	Colorectal	SOCS3	STAT3	Mediates lncRNA effects	[115]
miR-765	Breast	TRG16	NF-κB	TRG16 negatively regulates NF-κB	[111]
miR-877–3p	Gastric	SOCS2	STAT3	Involved in cytokine-induced CSCs	[113]
miR-1246	AML	LRIG1	STAT3	Exosomal transfer induces stemness	[118]

CSC: Cancer Stem Cell, CUEDC2: CUE domain-containing 2, HOXB5: Homeo Box B5, LRIG1: Leucine Rich Repeats And Immunoglobulin Like Domains 1, PTPN1: Protein Tyrosine Phosphatase Non-Receptor Type 1, PTPN11: Protein Tyrosine Phosphatase Non-Receptor Type 11, RORA: Retinoic acid Receptor-related Orphan receptor A, SOCS1: Suppressor Of Cytokine Signaling 1, SOCS2: Suppressor Of Cytokine Signaling 2, SOCS3: Suppressor Of Cytokine Signaling 3, SOCS4: Suppressor Of Cytokine Signaling 4, SOCS5: Suppressor Of Cytokine Signaling 5, TF: Transcription Factor, TRG16: Transformation-Related Gene 16 Protein

Table 3
miRNA-TF interactions leading to drug resistance.

miRNA	TF	CSC modulation Effects	Cancer Type	Reference
miR-30a-5p	STAT3	Affects response to regorafenib	Colorectal	[109]
miR-30b-3p	STAT3	Induces temozolomide resistance	Glioma	[126]
miR-92	STAT3	Modulates paclitaxel response	Ovarian	[127]
miR-124	STAT3	Reverses doxorubicin resistance	Breast	[128]
miR-148a	NF-κB	Negatively regulates chemoresistance	Liver	[93]
miR-155	NF-κB	Regulates resistance against TKI gefitinib	NSCLC	[105]
miR-196b-5p	STAT3	Promotes stemness and 5-FU resistance	Colorectal	[114]
miR-221	STAT3	Determines CSC niche and promotes hormonal therapy resistance	Breast	[107]
miR-375	STAT3	Inhibits Adriamycin resistance	Breast	[129]
miR-378a-3p and miR-378d	STAT3	Induce stemness in neighboring cells after exosomal transfer	Breast	[108]
miR-497	NF-κB	Inhibits gemcitabine resistance	Pancreatic	[125]
miR-589–5p	STAT3	Induces doxorubicin resistance	HCC	[117]
miR-590–5p	STAT3	Induces docetaxel resistance	Prostate	[130]

5-FU: Fluorouracil, CSC: Cancer Stem Cell, HCC: Hepatocellular Carcinoma; NSCLC: Non-Small Cell Lung Cancer, TF: Transcription Factor, TKI: Tyrosine Kinase Inhibitor

that EVs derived from gliomas CSCs can induce temozolomide resistance in glioma cells by transporting miR-30b-3p through EVs within the tumor microenvironment. The EVs were produced under hypoxic conditions and the miRNA levels were induced by STAT3. In ovarian cancer, targeting STAT3 synergistically improves response to paclitaxel through reduced CSCs and regulation of miR-92a [127].

In colorectal cells, particularly in the context of sensitivity to 5-FU, a role of miR-196b-5p in CSC phenotype and modulation of STAT3 has been reported [114]. This study first established an oncogenic effect of miR-196b-5p as the miRNA was upregulated in tumor specimens from colorectal cancer patients. Further, these higher expressions of miR-196b-5p correlated with CSC phenotype as silencing of miRNA led to decrease in spheroids formation ability, a surrogate for CSC characteristic. In terms of drug sensitivity, higher miR-196b-5p levels correlated with reduced response to 5-FU while silencing of miR-196b-5p induced 5-FU-mediated apoptosis. As a mechanism, it was shown that miR-196b-5p targets SOCS1 and SOCS3 which are negative regulators of STAT3 [114]. Also, in colorectal cancer, STAT3 is upregulated while the miRNA it inhibits, miR-30a-5p, is downregulated in tumorspheres, which indicates the TF-miRNA's involvement in stemness [109]. Further, STAT3-miR-30a-5p axis modulated response to regorafenib-mediated apoptosis in tumorspheres.

In HCC, a role of miR-589–5p in determining response to doxorubicin has been reported [117]. This miRNA is elevated in HCC and is responsible for stemness as evidenced by its support for spheroid forming ability and the CSC marker CD133 bearing side-populations. Further, HCC cells with higher miR-589–5p are significantly more resistant to doxorubicin-induced apoptosis. This induced resistance against chemotherapy is mediated by targeting of its target genes by miR-589–5p resulting in constitutive activation of STAT3 signaling and the maintenance of stemness [117]. Another miRNA, miR-124 has been implicated in doxorubicin resistance, but in breast cancer [128]. The study compared doxorubicin-resistant MCF-7 breast cancer cells with the native MCF-7 cells and found elevated STAT3, thus relating STAT3 with doxorubicin resistance. miR-124, on the other hand, was downregulated in resistant cells and it could restore sensitivity to doxorubicin by targeting STAT3 [128]. In breast cancer cells, miR-375 inhibits resistance against adriamycin by targeting JAK2/STAT3 and thereby reducing stemness [129].

The docetaxel resistance in prostate cancer is affected by lncRNA HOTAIR that sponges miR-590–5p and induces STAT3 in the process [130]. The mechanism involves an indirect action of miR on STAT3 and involves a direct action of miR-590–5p on upstream factor IL-10. Tumors with elevated HOTAIR levels are marked by increased growth rate. All these lines of evidence, as discussed above in this section, are indicative of miRNA-TF axis that serves to modulate sensitivity/resistance to various chemotherapies.

4.1.4. *Effects on radio-resistance*

Not just chemoresistance, a role of miRNAs as well as TFs in radio-resistance i.e. resistance against radiation therapy has also been suggested by many studies [131–133]. In NSCLC, such role of miRNAs, miR-15a/miR-16 in radio-resistance has been suggested [134]. miR-15a/miR-16 were linked to improved radiation-sensitivity and the mechanism was determined to be a negative correlation between these miRs and NF-κB signaling.

In a study focused on glioblastoma radio-resistance, a rather complex relationship between TF NF-κB and miR-103a was suggested that also involved another transcription factor, YY1 [135]. It was proposed that radio-resistance involves activation of NF-κB which activates YY1. YY1 was found to target and suppress miR-103a. So, whereas both TFs, NF-κB and YY1 were elevated in radio-resistance, miR-103a was suppressed. As a proof of this mechanism, restoration of miR-103a expression attenuated radio-resistance [135]. Again, in glioma, a role of miR-671–5p in radio-resistance has also been suggested [97]. This miRNA modulates

radio-sensitivity of glioma cells by targeting STAT3 as well as MSI1 (Musashi-1), a RNA binding protein that induces radio-resistance. While MSI1 and STAT3 positively correlate with radio-resistance, miR-671–5p has opposite effects.

4.2. The lncRNA-miRNA-TF axis

One of the primary mechanism by which the lncRNAs exert their biological effects is through sequestration/sponging of miRNAs [65,136,137]. It is therefore not surprising that the mechanism is evident even when TFs and CSC characteristics are involved. This section provides an overview of studies that have linked lncRNAs with miRNAs and TFs, NF-κB and STAT-3 (Table 4).

In gastric cancer, lncRNA ASB16-AS1 (ASB16 antisense RNA 1) is oncogenic and therefore elevated in gastric cancer patients with positive correlation with CSC characteristics [138]. It sponges miR-3918 and miR-4676, thus leading to activation of their target gene TRIM37 (tripartite motif containing 37) and also the TF NF-κB in the process that ultimately leads to cisplatin resistance. In triple negative breast cancers (TNBCs) that lack a validated target for therapy, lncRNA HLA-F-AS1 (HLA-F antisense RNA 1) is significantly upregulated and it promotes stemness along with cell proliferation [139]. This lncRNA inhibits cell cycle arrest an apoptosis; and induces in vivo tumor growth. As an interesting mechanism, STAT3 transcriptionally induces this lncRNA and thus plays an important role in its upregulation in TNBCs. Once elevated, HLA-F-AS1 sponges miR-541–3p and de-represses TRABD (TraB domain containing).

lncRNA GAS5 (growth arrest-specific transcript 5) is a lncRNA that reduces glioma cells' proliferation and invasion, as well as impairs stemness and growth of glioma stem cells [96]. This lncRNA's biological effects are mediated by its action on miRNAs let-7e and miR-125a that work to block STAT3 signaling. Modulation of STAT3 is also involved in the action of BCAR4 (Breast cancer anti-estrogen resistance 4) in colorectal cancers wherein, based on its higher expression, it supports proliferation of ALDH-positive cells, that are reminiscent of CSCs [98]. Reduced expression of lncRNA BCAR4 leads to diminished CSC population. The study identified miR-665 as the miRNA sponged by BCAR4 and miR-665 was shown to target STAT3 [98]. In colorectal cancer, tumor suppressor lncRNA Meg3 sponges the oncogenic miR-708 which then indirectly regulates STAT3 through its target SOCS3 [115].

Glioma stem cells are facilitated by lncRNA LINC00115 and it sponges miR-200 s that target ZEB1 [140]. miR-200 s represent tumor suppressive miRs that are inversely related with onset of EMT [141–144] and they target the mesenchymal factor ZEB1; their sponging by LINC00115 ensures induction of EMT, a phenomenon that is connected to cancer stemness [145]. This also involves activation of STAT3, and the silencing of stem cells marker EZH2 reverses LINC00115 effects [140].

Prostate cancer is managed by androgen deprivation therapy. However, it often relapses and the stem cells are known to play an important role in this relapse. In a lncRNA-focused study [130], role of lncRNA HOTAIR was suggested in the maintenance of prostate CSCs. HOTAIR sponged miR-590–5p which in turn targeted IL-10, a molecule that is upstream of STAT3 and regulates STAT3 expression. In a later study, HOTAIR was reported upregulated in pancreatic CSCs wherein it targeted miR-34a [146]. Silencing of HOTAIR or the ectopic expression of its target miR-34a suppressed CSC characteristics and reduced cell migration / invasion by targeting STAT3 signaling pathway.

4.3. CircRNAs-miRNA-TF axis

Even the circular RNAs are now known to influence CSC characteristics [23], and such regulation can involve TFs as well as miRNAs. For example, based on the higher expression of circRNA ciRS-7 in tumor samples derived from esophageal squamous cell carcinoma patients, the biological implication of this elevated ciRS-7 was studied in vitro [147]. It was found that this circRNA targets miR-7 and promotes cancer cells' migration and invasion. miR-7 could reverse these effects. Further CSC marker KLF-4 (Kruppel-like factor-4), being the direct gene target of miR-7, was elevated in cells with high ciRS-7 thus directly correlating this circRNA with CSCs. The involvement of TF NF-κB was suggested by an experiment wherein the NF-κB inhibitor BAY 11–7082 was used and it reversed ciRS-7 effects on cell invasion. ciRS-7 also increased the phosphorylation of IKK-α, thus directly impacting NF-κB activation [147].

TF STAT3 has also been reported to interact with circRNAs. It was shown to induce circRNA Circ_0000915 that sponged miR-890 to modulate propranolol sensitivity [148]. Recently, STAT3 signaling has also been implicated in gastric CSC characteristics mediated by circRNA circFCHO2 [149]. This circRNA is elevated in gastric cancer patients and associates with poor outcome. Its silencing reduces cell proliferation, invasion and angiogenesis through de-repression of miR-194–5p. However, when circFCHO2 levels are elevated, such as in gastric cancer patients, miR-194–5p is sponged, which leads to induced activation of STAT3 pathway. Circ_0043800 sponges miR-29a/b/c-3p in hepatoblastoma cells thereby inducing STAT3 and promoting tumor growth through induced stem cell characteristics [99]. circATP5B is elevated in glioma CSCs wherein it sponges miR-185–5p that targets STAT3

Table 4
Interactions between lncRNA/circRNA, miRNAs and TFS, NF-κB and STAT-3.

lncRNA / circRNA	miRNA affected	TF	Cancer Type	Biological Effect	Reference
ASB16-AS1 (lncRNA)	miR-3918 and miR-4676	NF-κB	Gastric	Induces cisplatin resistance	[138]
BCAR4	miR-665	STAT3	Colorectal	Promotes tumorigenicity	[98]
ciRS-7 (circRNA)	miR-7	NF-κB	ESCC	Induces invasion	[147]
Circ_0000915 (circRNA)	miR-890	STAT3	-	Propranolol sensitivity	[148]
Circ_0043800	miR-29a/b/c-3p	STAT3	Hepatoblastoma	Induces tumor growth	[99]
circATP5B	miR-185–5p	STAT3	Glioma	Induces proliferation	[112]
circFCHO2	miR-194–5p	STAT3	Gastric	Induces tumor growth	[149]
circNOLC1	miR-365a-3p	STAT3	Breast	Affects EMT and stemness	[101]
GAS5	Let-7e/miR-125a	STAT3	Glioma	Impacts stemness	[96]
HLA-F-AS1	miR-541–3p	STAT3	Breast	Promotes stemness	[139]
HOTAIR	miR-590–5p	STAT3	Prostate	Regulates chemoresistance	[130]
	miR-34a	STAT3	Pancreatic	Induces stemness	[146]
LINC00115	miR-200 s	STAT3	Glioma	Induces EMT	[140]
Meg3	miR-708	STAT3	Colorectal	Regulates tumorigenesis	[115]

ASB16-AS1: ASB16 antisense RNA 1, BCAR4: Breast cancer anti-estrogen resistance 4, EMT: Epithelial-to-Mesenchymal Transition, ESCC: Esophageal Squamous Cell Carcinoma, GAS5: Growth Arrest-Specific transcript 5, HLA-F-AS1: HLA-F antisense RNA 1, HOTAIR: HOX Transcript Antisense RNA, Meg3: Maternally Expressed 3, TF: Transcription Factor, TRABD: TraB Domain containing

activating HOXB5 [112]. Similarly, circNOLC1 (circular RNA nucleolar and coiled-body phosphoprotein 1) is elevated in breast cancer tissues where it induces stemness and EMT [101]. It sponges miR-365a-3p which then targets STAT3 and thus levels of stemness and EMT-associated circNOLC1 correlate directly with those of STAT3.

5. Conclusions and future perspectives

The role that cancer stem cells play in cancer pathophysiology and progression is irrefutable. NF-κB and STAT3 are two well studied TFs that have been investigated in multiple cancers for their role in inducing stemness that is fundamental to clinically relevant challenges such as resistance to therapies and metastases. As an added layer of mechanism, ncRNAs have been extensively studied for their role in regulation of NF-κB and STAT3 resulting in the modulation of CSC characteristics. It is therefore no brainer that non-coding RNAs can possibly be targeted for possible cancer therapy- just like miR-326 was loaded into super-paramagnetic iron oxide nanoparticles and transfected in vitro resulting in suppressed cell proliferation [150], as would be expected with overexpression of a tumor suppressor miRNA. Interestingly, it was shown that miR-326 effects were partially due to reduced STAT3 signaling and suppressed CSC phenotype. Though performed in an in vitro setting, this work is indicative of a right approach which ultimately has to be tested in vivo and in clinical settings. An interesting tool that can possibly help achieve this goal are the exosomes. Exosomes are being extensively studied for their multi-faceted roles in cancer pathophysiology [151]. In addition to their diverse cargo, they can also transport miRNAs such as miR-21 and miR-155 [152] that can influence CSC characteristics of recipient cells. In terms of the two specific TFs discussed in this article, STAT3 signaling is involved in biogenesis of CAFs-released microvesicles that transport oncogenic miR-221 [107]. Thus, there is evidence for a direct connection between NF-κB/STAT3 and exosomes as well as the miRNA cargo impacting CSC phenotype in recipient cells. The finer details to master the manufacturing of exosomes with desired cargo and fine-tuning the delivery methods will go a long way in exploiting exosomes for cancer therapy. Additionally, ncRNAs levels can potentially be exploited as diagnostic and or prognostic biomarkers, especially for the CSCs characteristics of tumor cells, with implications in better management of cancer recurrence.

Funding source

No funding to report.

CRediT authorship contribution statement

Aamir Ahmad: Conceptualization, Supervision, Writing – original draft, Writing – review & editing. **Reem Khaled M.E. Alsayed:** Writing – original draft. **Khalid Sultan A.M.Sheikhan:** Writing – original draft. **Majid Ali Alam:** Writing – review & editing. **Jorg Buddenkotte:** Writing – review & editing. **Martin Steinhoff:** Writing – review & editing. **Shahab Uddin:** Writing – review & editing.

Declaration of Competing Interest

None of the authors have any conflict of interest to report.

Data Availability

No data was used for the research described in the article.

Acknowledgment

Open Access funding for this article has been provided by the Qatar National Library.

References

[1] P.M. Aponte, A. Caicedo, Stemness in cancer: stem cells, cancer stem cells, and their microenvironment, Stem Cells Int. 2017 (2017) 5619472.
[2] S. He, D. Nakada, S.J. Morrison, Mechanisms of stem cell self-renewal, Annu Rev. Cell Dev. Biol. 25 (2009) 377–406.
[3] U. Weissbein, N. Benvenisty, U. Ben-David, Quality control: genome maintenance in pluripotent stem cells, J. Cell Biol. 204 (2) (2014) 153–163.
[4] L. Liu, W. Michowski, A. Kolodziejczyk, P. Sicinski, The cell cycle in stem cell proliferation, pluripotency and differentiation, Nat. Cell Biol. 21 (9) (2019) 1060–1067.
[5] G. Sher, T. Masoodi, K. Patil, S. Akhtar, S. Kuttikrishnan, A. Ahmad, S. Uddin, Dysregulated FOXM1 signaling in the regulation of cancer stem cells, Semin Cancer Biol. 86 (Pt 3) (2022) 107–121.
[6] R.A. Eid, M. Alaa Edeen, E.M. Shedid, A.S.S. Kamal, M.M. Warda, F. Mamdouh, S. A. Khedr, M.A. Soltan, H.W. Jeon, M.S.A. Zaki, B. Kim, Targeting cancer stem cells as the key driver of carcinogenesis and therapeutic resistance, Int. J. Mol. Sci. 24 (2) (2023).
[7] A.R. Safa, Drug and apoptosis resistance in cancer stem cells: a puzzle with many pieces, Cancer Drug Resist 5 (4) (2022) 850–872.
[8] A. Ahmad, Tumor microenvironment and immune surveillance, Microenviron Microecol Res. 4 (1) (2022) 6.
[9] G. Wang, F. Wang, Q. Huang, Y. Li, Y. Liu, Y. Wang, Understanding transcription factor regulation by integrating gene expression and DNase I hypersensitive sites, Biomed. Res. Int. 2015 (2015), 757530.
[10] K. Struhl, Helix-turn-helix, zinc-finger, and leucine-zipper motifs for eukaryotic transcriptional regulatory proteins, Trends Biochem. Sci. 14 (4) (1989) 137–140.
[11] D. Thiagarajan, S. Vedantham, R. Ananthakrishnan, A.M. Schmidt, R. Ramasamy, Mechanisms of transcription factor acetylation and consequences in hearts, Biochim. Biophys. Acta 1862 (12) (2016) 2221–2231.
[12] J.M. Park, S.H. Jo, M.Y. Kim, T.H. Kim, Y.H. Ahn, Role of transcription factor acetylation in the regulation of metabolic homeostasis, Protein Cell 6 (11) (2015) 804–813.
[13] Y. Li, D. Liu, Y. Liu, E. Li, H. Wang, K. Liu, J. Qi, Protein nitration promotes inducible nitric oxide synthase transcription mediated by NF-κB in high glucose-stimulated human lens epithelial cells, Mol. Cell Endocrinol. 370 (1–2) (2013) 78–86.
[14] B. Mayr, M. Montminy, Transcriptional regulation by the phosphorylation-dependent factor CREB, Nat. Rev. Mol. Cell Biol. 2 (8) (2001) 599–609.
[15] A.S. Bhagwat, C.R. Vakoc, Targeting transcription factors in cancer, Trends Cancer 1 (1) (2015) 53–65.
[16] M. Farhan, M.F. Ullah, M. Faisal, A.A. Farooqi, U.Y. Sabitaliyevich, B. Biersack, A. Ahmad, Differential methylation and acetylation as the epigenetic basis of Resveratrol's anticancer activity, Medicine 6 (1) (2019).
[17] A. Ahmad, S. Azim, H. Zubair, M.A. Khan, S. Singh, J.E. Carter, R.P. Rocconi, A. P. Singh, Epigenetic basis of cancer health disparities: looking beyond genetic differences, Biochim. Biophys. Acta Rev. Cancer 1868 (1) (2017) 16–28.
[18] J. Naipauer, M.E. García Solá, D. Salyakina, S. Rosario, S. Williams, O. Coso, M. C. Abba, E.A. Mesri, E. Lacunza, A. Non-Coding, RNA Network Involved in KSHV Tumorigenesis, Front. Oncol. 11 (2021), 687629.
[19] A. Ahmad, Non-coding RNAs: a tale of junk turning into treasure, Noncoding RNA Res. 1 (1) (2016) 1–2.
[20] S. Kumar, E.A. Gonzalez, P. Rameshwar, J.P. Etchegaray, Non-coding RNAs as mediators of epigenetic changes in malignancies, Cancers 12 (12) (2020).
[21] X. Yang, D. Cao, W. Ma, S. Gao, G. Wen, J. Zhong, Wnt signaling in triple-negative breast cancers: Its roles in molecular subtyping and cancer cell stemness and its crosstalk with non-coding RNAs, Life Sci. 300 (2022), 120565.
[22] J.A. Gutierrez-Cruz, V. Maldonado, J. Melendez-Zajgla, Regulation of the cancer stem phenotype by long non-coding RNAs, Cells 11 (15) (2022).
[23] H.M. Chao, T.W. Wang, E. Chern, S.H. Hsu, Regulatory RNAs, microRNA, long-non coding RNA and circular RNA roles in colorectal cancer stem cells, World J. Gastrointest. Oncol. 14 (4) (2022) 748–764.
[24] H.D. Huh, D.H. Kim, H.S. Jeong, H.W. Park, Regulation of TEAD transcription factors in cancer biology, Cells 8 (6) (2019).
[25] Y. Shima, I. Kitabayashi, Deregulated transcription factors in leukemia, Int. J. Hematol. 94 (2) (2011) 134–141.
[26] Y. Jiramongkol, E.W. Lam, FOXO transcription factor family in cancer and metastasis, Cancer Metastas Rev. 39 (3) (2020) 681–709.
[27] X. Dolcet, D. Llobet, J. Pallares, X. Matias-Guiu, NF-kB in development and progression of human cancer, Virchows Arch. 446 (5) (2005) 475–482.
[28] T. Lawrence, The nuclear factor NF-kappaB pathway in inflammation, Cold Spring Harb. Perspect. Biol. 1 (6) (2009) a001651.
[29] S. Mitchell, J. Vargas, A. Hoffmann, Signaling via the NFκB system, Wiley Inter. Rev. Syst. Biol. Med. 8 (3) (2016) 227–241.
[30] Y. Xia, S. Shen, I.M. Verma, NF-κB, an active player in human cancers, Cancer Immunol. Res. 2 (9) (2014) 823–830.
[31] S. Kuttikrishnan, K.S. Prabhu, A.H. Al Sharie, Y.O. Al, Zu'bi, F.Q. Alali, N. H. Oberlies, A. Ahmad, T. El-Elimat, S. Uddin, Natural resorcylic acid lactones: a chemical biology approach for anticancer activity, Drug Discov. Today 27 (2) (2022) 547–557.
[32] L. Xia, S. Tan, Y. Zhou, J. Lin, H. Wang, L. Oyang, Y. Tian, L. Liu, M. Su, H. Wang, D. Cao, Q. Liao, Role of the NFκB-signaling pathway in cancer, Onco Targets Ther. 11 (2018) 2063–2073.
[33] L. Arora, A.P. Kumar, F. Arfuso, W.J. Chng, G. Sethi, The role of signal transducer and activator of transcription 3 (STAT3) and its targeted inhibition in hematological malignancies, Cancers 10 (9) (2018).

[34] K. Al Zaid Siddiquee, J. Turkson, STAT3 as a target for inducing apoptosis in solid and hematological tumors, Cell Res. 18 (2) (2008) 254–267.
[35] H.Q. Wang, Q.W. Man, F.Y. Huo, X. Gao, H. Lin, S.R. Li, J. Wang, F.C. Su, L. Cai, Y. Shi, B. Liu, L.L. Bu, STAT3 pathway in cancers: past, present, and future, 2020, MedComm 3 (2) (2022), e124.
[36] S. Mishra, T. Yadav, V. Rani, Exploring miRNA based approaches in cancer diagnostics and therapeutics, Crit. Rev. Oncol. Hematol. 98 (2016) 12–23.
[37] A. Ahmad, Epigenetic regulation of immunosuppressive tumor-associated macrophages through dysregulated microRNAs, Semin. Cell Dev. Biol. 124 (2022) 26–33.
[38] G. Pepe, L. Parca, L. Viviani, G. Ausiello, M. Helmer-Citterich, Variation in the co-expression profile highlights a loss of miRNA-mRNA regulation in multiple cancer types, Noncoding RNA Res. 7 (2) (2022) 98–105.
[39] M.A. Abbas, I.E.T. El Sayed, A.M. Kamel Abdu-Allah, A. Kalam, A.G. Al-Sehemi, O.A. Al-Hartomy, M. Salah, A. El-Rahman, Expression of MiRNA-29b and MiRNA-31 and their diagnostic and prognostic values in Egyptian females with breast cancer, Noncoding RNA Res. 7 (4) (2022) 248–257.
[40] Y.S. Lee, A. Dutta, MicroRNAs in cancer, Annu Rev. Pathol. 4 (2009) 199–227.
[41] A. Ahmad, Y. Li, B. Bao, D. Kong, F.H. Sarkar, Epigenetic regulation of miRNA-cancer stem cells nexus by nutraceuticals, Mol. Nutr. Food Res. 58 (1) (2014) 79–86.
[42] B. He, Z. Zhao, Q. Cai, Y. Zhang, P. Zhang, S. Shi, H. Xie, X. Peng, W. Yin, Y. Tao, X. Wang, miRNA-based biomarkers, therapies, and resistance in Cancer, Int. J. Biol. Sci. 16 (14) (2020) 2628–2647.
[43] S. Ahmad, S. Manzoor, S. Siddiqui, N. Mariappan, I. Zafar, A. Ahmad, A. Ahmad, Epigenetic underpinnings of inflammation: Connecting the dots between pulmonary diseases, lung cancer and COVID-19, Semin Cancer Biol. 83 (2022) 384–398.
[44] M. Hill, N. Tran, miRNA interplay: mechanisms and consequences in cancer, Dis. Model Mech. 14 (4) (2021).
[45] A.A. Farooqi, S. Tabassum, A. Ahmad, MicroRNA-34a: a versatile regulator of myriads of targets in different cancers, Int. J. Mol. Sci. 18 (10) (2017).
[46] A.Q. Khan, E.I. Ahmed, N.R. Elareer, K. Junejo, M. Steinhoff, S. Uddin, Role of miRNA-regulated cancer stem cells in the pathogenesis of human malignancies, Cells 8 (8) (2019).
[47] S. Ghafouri-Fard, M. Hajiesmaeili, H. Shoorei, Z. Bahroudi, M. Taheri, G. Sharifi, The Impact of lncRNAs and miRNAs in regulation of function of cancer stem cells and progression of cancer, Front. Cell Dev. Biol. 9 (2021), 696820.
[48] C. Farace, A. Pisano, C. Griñan-Lison, G. Solinas, G. Jiménez, M. Serra, E. Carrillo, F. Scognamillo, F. Attene, A. Montella, J.A. Marchal, R. Madeddu, Deregulation of cancer-stem-cell-associated miRNAs in tissues and sera of colorectal cancer patients, Oncotarget 11 (2) (2020) 116–130.
[49] Z.T. Dai, Y. Xiang, Y.Y. Duan, J. Wang, J.P. Li, H.M. Zhang, C. Cheng, Q. Wang, T. C. Zhang, X.H. Liao, MiR-17-5p and MKL-1 modulate stem cell characteristics of gastric cancer cells, Int. J. Biol. Sci. 17 (9) (2021) 2278–2293.
[50] M. Majidinia, S.G. Darband, M. Kaviani, S.M. Nabavi, R. Jahanban-Esfahlan, B. Yousefi, Cross-regulation between Notch signaling pathway and miRNA machinery in cancer, DNA Repair 67 (2018) 30–41.
[51] M. Jafarzadeh, B.M. Soltani, MiRNA-Wnt signaling regulatory network in colorectal cancer, J. Biochem. Mol. Toxicol. 35 (10) (2021), e22883.
[52] Y. Katoh, M. Katoh, Hedgehog signaling, epithelial-to-mesenchymal transition and miRNA (review), Int. J. Mol. Med. 22 (3) (2008) 271–275.
[53] A.A. Farooqi, C.W. Shu, H.W. Huang, H.R. Wang, Y.T. Chang, S. Fayyaz, S. F. Yuan, J.Y. Tang, H.W. Chang, TRAIL, Wnt, Sonic Hedgehog, TGFβ, and miRNA signalings are potential targets for oral cancer therapy, Int. J. Mol. Sci. 18 (7) (2017).
[54] A. Bigas, C. Porcheri, Notch and stem cells, Adv. Exp. Med. Biol. 1066 (2018) 235–263.
[55] T. Reya, H. Clevers, Wnt signalling in stem cells and cancer, Nature 434 (7035) (2005) 843–850.
[56] I.S. Shimada, Y. Kato, Ciliary signaling in stem cells in health and disease: hedgehog pathway and beyond, Semin Cell Dev. Biol. 129 (2022) 115–125.
[57] G. Pan, Y. Liu, L. Shang, F. Zhou, S. Yang, EMT-associated microRNAs and their roles in cancer stemness and drug resistance, Cancer Commun. 41 (3) (2021) 199–217.
[58] B. Dong, S. Li, S. Zhu, M. Yi, S. Luo, K. Wu, MiRNA-mediated EMT and CSCs in cancer chemoresistance, Exp. Hematol. Oncol. 10 (1) (2021) 12.
[59] Z. Wang, Y. Li, A. Ahmad, A.S. Azmi, D. Kong, S. Banerjee, F.H. Sarkar, Targeting miRNAs involved in cancer stem cell and EMT regulation: an emerging concept in overcoming drug resistance, Drug Resist Updat (4–5) (2010) 109–118.
[60] B. Bao, A.S. Azmi, Y. Li, A. Ahmad, S. Ali, S. Banerjee, D. Kong, F.H. Sarkar, Targeting CSCs in tumor microenvironment: the potential role of ROS-associated miRNAs in tumor aggressiveness, Curr. Stem Cell Res. Ther. 9 (1) (2014) 22–35.
[61] S. Kotiyal, S. Bhattacharya, Breast cancer stem cells, EMT and therapeutic targets, Biochem. Biophys. Res. Commun. 453 (1) (2014) 112–116.
[62] W. Lin, Q. Zhou, C.Q. Wang, L. Zhu, C. Bi, S. Zhang, X. Wang, H. Jin, LncRNAs regulate metabolism in cancer, Int. J. Biol. Sci. 16 (7) (2020) 1194–1206.
[63] S. Ghafouri-Fard, S. Dashti, M. Taheri, M.D. Omrani, TINCR: An lncRNA with dual functions in the carcinogenesis process, Noncoding RNA Res. 5 (3) (2020) 109–115.
[64] W.X. Peng, P. Koirala, Y.Y. Mo, LncRNA-mediated regulation of cell signaling in cancer, Oncogene 36 (41) (2017) 5661–5667.
[65] K. Li, T. Yao, Z. Wang, lncRNA-mediated ceRNA network in bladder cancer, Noncoding RNA Res. 8 (2) (2023) 135–145.
[66] Y. He, X. Jiang, L. Duan, Q. Xiong, Y. Yuan, P. Liu, L. Jiang, Q. Shen, S. Zhao, C. Yang, Y. Chen, LncRNA PKMYT1AR promotes cancer stem cell maintenance in non-small cell lung cancer via activating Wnt signaling pathway, Mol. Cancer 20 (1) (2021) 156.
[67] F. Peng, J.H. Wang, W.J. Fan, Y.T. Meng, M.M. Li, T.T. Li, B. Cui, H.F. Wang, Y. Zhao, F. An, T. Guo, X.F. Liu, L. Zhang, L. Lv, D.K. Lv, L.Z. Xu, J.J. Xie, W. X. Lin, E.W. Lam, J. Xu, Q. Liu, Glycolysis gatekeeper PDK1 reprograms breast cancer stem cells under hypoxia, Oncogene 37 (8) (2018) 1062–1074.
[68] Y. Cao, W. Chai, Y. Wang, D. Tang, D. Shao, H. Song, J. Long, lncRNA TUG1 inhibits the cancer stem cell-like properties of temozolomide-resistant glioma cells by interacting with EZH2, Mol. Med. Rep. 24 (1) (2021).
[69] W.R. Jeck, J.A. Sorrentino, K. Wang, M.K. Slevin, C.E. Burd, J. Liu, W.F. Marzluff, N.E. Sharpless, Circular RNAs are abundant, conserved, and associated with ALU repeats, RNA 19 (2) (2013) 141–157.
[70] C.P.C. Gomes, A. Salgado-Somoza, E.E. Creemers, C. Dieterich, M. Lustrek, Y. Devaux, Circular RNAs in the cardiovascular system, Noncoding RNA Res. 3 (1) (2018) 1–11.
[71] Z. Zhang, Y. Huang, A. Guo, L. Yang, Research progress of circular RNA molecules in aging and age-related diseases, Ageing Res Rev. 87 (2023), 101913.
[72] J. Liao, Q. Zhang, J. Huang, H. He, J. Lei, Y. Shen, J. Wang, Y. Xiao, The emerging role of circular RNAs in Parkinson's disease, Front. Neurosci. 17 (2023) 1137363.
[73] L.M. Holdt, A. Kohlmaier, D. Teupser, Molecular functions and specific roles of circRNAs in the cardiovascular system, Noncoding RNA Res. 3 (2) (2018) 75–98.
[74] S. Sekar, W.S. Liang, Circular RNA expression and function in the brain, Noncoding RNA Res. 4 (1) (2019) 23–29.
[75] J. Wen, J. Liu, L. Wan, F. Wang, Long noncoding RNA/circular RNA regulates competitive endogenous RNA networks in rheumatoid arthritis: molecular mechanisms and traditional Chinese medicine therapeutic significances, Ann. Med. 55 (1) (2023) 973–989.
[76] H. Liang, Q. Liu, The role of non-coding RNA in lupus nephritis, Hum. Cell (2023).
[77] J. Li, Y. Han, S. Wang, X. Wu, J. Cao, T. Sun, Circular RNAs: biogenesis, biological functions, and roles in myocardial infarction, Int J. Mol. Sci. 24 (4) (2023).
[78] S. Liao, X. Lin, C. Mo, Integrated analysis of circRNA-miRNA-mRNA regulatory network identifies potential diagnostic biomarkers in diabetic foot ulcer, Noncoding RNA Res. 5 (3) (2020) 116–124.
[79] C. Siracusa, J. Sabatino, I. Leo, C. Eyileten, M. Postula, S. De Rosa, Circular RNAs in ischemic stroke: biological role and experimental models, Biomolecules 13 (2) (2023).
[80] A. Szczepaniak, A. Bronisz, J. Godlewski, Circular RNAs-new kids on the block in cancer pathophysiology and management, Cells 12 (4) (2023).
[81] A. Beilerli, S. Begliarzade, A. Sufianov, T. Ilyasova, Y. Liang, O. Beylerli, Circulating ciRS-7 as a potential non-invasive biomarker for epithelial ovarian cancer: an investigative study, Noncoding RNA Res. 7 (3) (2022) 197–204.
[82] A.A. Farooqi, K. Gulnara, A.A. Mukhanbetzhanovna, U. Datkhayev, A. Z. Kussainov, A. Adylova, Regulation of RUNX proteins by long non-coding RNAs and circular RNAs in different cancers, Noncoding RNA Res. 6 (2) (2021) 100–106.
[83] L. Zhang, X. Wang, W. Zhao, J. Liu, Overview of m(6)A and circRNAs in human cancers, J. Cancer Res Clin. Oncol. (2023).
[84] A. Dawoud, Z. Ihab Zakaria, H. Hisham Rashwan, M. Braoudaki, R.A. Youness, Circular RNAs: new layer of complexity evading breast cancer heterogeneity, Noncoding RNA Res. 8 (1) (2023) 60–74.
[85] A. Sufianov, S. Begliarzade, A. Beilerli, Y. Liang, T. Ilyasova, O. Beylerli, Circular RNAs as biomarkers for lung cancer, Noncoding RNA Res. 8 (1) (2023) 83–88.
[86] L. Guan, Q. Hao, F. Shi, B. Gao, M. Wang, X. Zhou, T. Han, W. Ren, Regulation of the tumor immune microenvironment by cancer-derived circular RNAs, Cell Death Dis. 14 (2) (2023) 132.
[87] Z.H. Zhang, Y. Wang, Y. Zhang, S.F. Zheng, T. Feng, X. Tian, M. Abudurexiti, Z. D. Wang, W.K. Zhu, J.Q. Su, H.L. Zhang, G.H. Shi, Z.L. Wang, D.L. Cao, D.W. Ye, The function and mechanisms of action of circular RNAs in urologic cancer, Mol. Cancer 22 (1) (2023) 61.
[88] A. Sufianov, S. Begliarzade, V. Kudriashov, A. Beilerli, T. Ilyasova, Y. Liang, O. Beylerli, The role of circular RNAs in the pathophysiology of oral squamous cell carcinoma, Noncoding RNA Res. 8 (1) (2023) 109–114.
[89] A. Beilerli, I. Gareev, O. Beylerli, G. Yang, V. Pavlov, G. Aliev, A. Ahmad, Circular RNAs as biomarkers and therapeutic targets in cancer, Semin Cancer Biol. 83 (2022) 242–252.
[90] H.J. Lu, J. Li, G. Yang, C.J. Yi, D. Zhang, F. Yu, Z. Ma, Circular RNAs in stem cells: from basic research to clinical implications, Biosci. Rep. 42 (1) (2022).
[91] F.A. Lagunas-Rangel, Circular RNAs and their participation in stemness of cancer, Med. Oncol. 37 (5) (2020) 42.
[92] D. Ghatak, A. Datta, T. Roychowdhury, S. Chattopadhyay, S. Roychoudhury, MicroRNA-324-5p-CUEDC2 axis mediates gain-of-function mutant p53-driven cancer stemness, Mol. Cancer Res 19 (10) (2021) 1635–1650.
[93] Y. Wang, F. Jiang, K. Jiao, L. Ju, Q. Liu, Y. Li, L. Miao, Z. Li, De-methylation of miR-148a by arsenic trioxide enhances sensitivity to chemotherapy via inhibiting the NF-κB pathway and CSC like properties, Exp. Cell Res. 386 (2) (2020), 111739.
[94] C. Baer, C.C. Oakes, A.S. Ruppert, R. Claus, S.Z. Kim-Wanner, D. Mertens, T. Zenz, S. Stilgenbauer, J.C. Byrd, C. Plass, Epigenetic silencing of miR-708 enhances NF-κB signaling in chronic lymphocytic leukemia, Int. J. Cancer 137 (6) (2015) 1352–1361.
[95] K.J. Senthil Kumar, M. Gokila Vani, H.W. Hsieh, C.C. Lin, J.W. Liao, P.J. Chueh, S. Y. Wang, MicroRNA-708 activation by glucocorticoid receptor agonists regulate breast cancer tumorigenesis and metastasis via downregulation of NF-κB signaling, Carcinogenesis 40 (2) (2019) 335–348.

[96] S. Wu, K. Ren, J. Zhao, J. Li, B. Jia, X. Wu, Y. Dou, X. Fei, Y. Huan, X. He, T. Wang, W. Lv, L. Wang, Y. Wang, J. Zhao, Z. Fei, S. Li, LncRNA GAS5 represses stemness and malignancy of gliomas via elevating the SPACA6-miR-125a/let-7e Axis, Front. Oncol. 12 (2022), 803652.
[97] J.C. Lin, C.Y. Kuo, J.T. Tsai, W.H. Liu, miR-671-5p inhibition by MSI1 promotes glioblastoma tumorigenesis via radioresistance, tumor motility and cancer stem-like cell properties, Biomedicines 10 (1) (2021).
[98] S. Ouyang, X. Zhou, Z. Chen, M. Wang, X. Zheng, M. Xie, LncRNA BCAR4, targeting to miR-665/STAT3 signaling, maintains cancer stem cells stemness and promotes tumorigenicity in colorectal cancer, Cancer Cell Int. 19 (2019) 72.
[99] Y. Liu, J. Song, Y. Liu, Z. Zhou, X. Wang, Transcription activation of circ-STAT3 induced by Gli2 promotes the progression of hepatoblastoma via acting as a sponge for miR-29a/b/c-3p to upregulate STAT3/Gli2, J. Exp. Clin. Cancer Res. 39 (1) (2020) 101.
[100] B. Mansoori, P.H.G. Duijf, A. Mohammadi, E. Safarzadeh, H.J. Ditzel, M. F. Gjerstorff, W.C. Cho, B. Baradaran, MiR-142-3p targets HMGA2 and suppresses breast cancer malignancy, Life Sci. 276 (2021), 119431.
[101] Y.P. Liu, J.Y. Heng, X.Y. Zhao, E.Y. Li, The inhibition of circular RNA circNOLC1 by propofol/STAT3 attenuates breast cancer stem cells function via miR-365a-3p/STAT3 signaling, J. Transl. Med. 19 (1) (2021) 467.
[102] L. Wang, J. Guo, J. Zhou, D. Wang, X. Kang, L. Zhou, NF-κB maintains the stemness of colon cancer cells by downregulating miR-195-5p/497-5p and upregulating MCM2, J. Exp. Clin. Cancer Res. 39 (1) (2020) 225.
[103] S.J. Ni, L.Q. Zhao, X.F. Wang, Z.H. Wu, R.X. Hua, C.H. Wan, J.Y. Zhang, X. W. Zhang, M.Z. Huang, L. Gan, H.L. Sun, G.P. Dimri, W.J. Guo, CBX7 regulates stem cell-like properties of gastric cancer cells via p16 and AKT-NF-κB-miR-21 pathways, J. Hematol. Oncol. 11 (1) (2018) 17.
[104] X. Wang, C. Wang, X. Zhang, R. Hua, L. Gan, M. Huang, L. Zhao, S. Ni, W. Guo, Bmi-1 regulates stem cell-like properties of gastric cancer cells via modulating miRNAs, J. Hematol. Oncol. 9 (1) (2016) 90.
[105] C.F. Chiu, Y.W. Chang, K.T. Kuo, Y.S. Shen, C.Y. Liu, Y.H. Yu, C.C. Cheng, K. Y. Lee, F.C. Chen, M.K. Hsu, T.C. Kuo, J.T. Ma, J.L. Su, NF-κB-driven suppression of FOXO3a contributes to EGFR mutation-independent gefitinib resistance, Proc. Natl. Acad. Sci. USA 113 (18) (2016) E2526–E2535.
[106] C. Chen, F. Luo, Q. Yang, D. Wang, P. Yang, J. Xue, X. Dai, X. Liu, H. Xu, J. Lu, A. Zhang, Q. Liu, NF-κB-regulated miR-155, via repression of QKI, contributes to the acquisition of CSC-like phenotype during the neoplastic transformation of hepatic cells induced by arsenite, Mol. Carcinog. 57 (4) (2018) 483–493.
[107] P. Sansone, M. Berishaj, V.K. Rajasekhar, C. Ceccarelli, Q. Chang, A. Strillacci, C. Savini, L. Shapiro, R.L. Bowman, C. Mastroleo, S. De Carolis, L. Daly, A. Benito-Martin, F. Perna, N. Fabbri, J.H. Healey, E. Spisni, M. Cricca, D. Lyden, M. Bonafé, J. Bromberg, Evolution of cancer stem-like cells in endocrine-resistant metastatic breast cancers is mediated by stromal microvesicles, Cancer Res. 77 (8) (2017) 1927–1941.
[108] Q. Yang, S. Zhao, Z. Shi, L. Cao, J. Liu, T. Pan, D. Zhou, J. Zhang, Chemotherapy-elicited exosomal miR-378a-3p and miR-378d promote breast cancer stemness and chemoresistance via the activation of EZH2/STAT3 signaling, J. Exp. Clin. Cancer Res. 40 (1) (2021) 120.
[109] C.C. Cheng, B.L. Yang, W.C. Chen, A.S. Ho, Z.L. Sie, H.C. Lin, C.C. Chang, STAT3 mediated miR-30a-5p inhibition enhances proliferation and inhibits apoptosis in colorectal cancer cells, Int. J. Mol. Sci. 21 (19) (2020).
[110] Y. Jiang, J. Zhou, J. Zhao, D. Hou, H. Zhang, L. Li, D. Zou, J. Hu, Y. Zhang, Z. Jing, MiR-18a-downregulated RORA inhibits the proliferation and tumorigenesis of glioma using the TNF-α-mediated NF-κB signaling pathway, EBioMedicine 52 (2020), 102651.
[111] F. Chi, X. Jin, L. Chen, G. He, S. Han, TRG16, targeted by miR-765, inhibits breast cancer stem cell-like properties via regulating the NF-κB pathway, Mol. Cell Biochem. 477 (12) (2022) 2801–2816.
[112] J. Zhao, Y. Jiang, H. Zhang, J. Zhou, L. Chen, H. Li, J. Xu, G. Zhang, Z. Jing, The SRSF1/circATP5B/miR-185-5p/HOXB5 feedback loop regulates the proliferation of glioma stem cells via the IL6-mediated JAK2/STAT3 signaling pathway, J. Exp. Clin. Cancer Res. 40 (1) (2021) 134.
[113] X. Xiang, H.Z. Ma, Y.Q. Chen, D.Z. Zhang, S.X. Ma, H.J. Wang, D.M. Liu, Y. Yuan, H. Cai, GM-CSF-miRNA-Jak2/Stat3 signaling mediates chemotherapy-induced cancer cell stemness in gastric cancer, Front. Pharm. 13 (2022), 855351.
[114] D. Ren, B. Lin, X. Zhang, Y. Peng, Z. Ye, Y. Ma, Y. Liang, L. Cao, X. Li, R. Li, L. Sun, Q. Liu, J. Wu, K. Zhou, J. Zeng, Maintenance of cancer stemness by miR-196b-5p contributes to chemoresistance of colorectal cancer cells via activating STAT3 signaling pathway, Oncotarget 8 (30) (2017) 49807–49823.
[115] S. Zhang, W.W. Ji, W. Wei, L.X. Zhan, X. Huang, Long noncoding RNA Meg3 sponges miR-708 to inhibit intestinal tumorigenesis via SOCS3-repressed cancer stem cells growth, Cell Death Dis. 13 (1) (2021) 25.
[116] C. Jiang, J. Long, B. Liu, M. Xu, W. Wang, X. Xie, X. Wang, M. Kuang, miR-500a-3p promotes cancer stem cells properties via STAT3 pathway in human hepatocellular carcinoma, J. Exp. Clin. Cancer Res. 36 (1) (2017) 99.
[117] J. Long, C. Jiang, B. Liu, Q. Dai, R. Hua, C. Chen, B. Zhang, H. Li, Maintenance of stemness by miR-589-5p in hepatocellular carcinoma cells promotes chemoresistance via STAT3 signaling, Cancer Lett. 423 (2018) 113–126.
[118] L. Chen, Z. Guo, Y. Zhou, J. Ni, J. Zhu, X. Fan, X. Chen, Y. Liu, Z. Li, H. Zhou, microRNA-1246-containing extracellular vesicles from acute myeloid leukemia cells promote the survival of leukemia stem cells via the LRIG1-meditated STAT3 pathway, Aging 13 (10) (2021) 13644–13662.
[119] H. Qayoom, N.A. Wani, B. Alshehri, M.A. Mir, An insight into the cancer stem cell survival pathways involved in chemoresistance in triple-negative breast cancer, Future Oncol. 17 (31) (2021) 4185–4206.
[120] L.T.H. Phi, I.N. Sari, Y.G. Yang, S.H. Lee, N. Jun, K.S. Kim, Y.K. Lee, H.Y. Kwon, Cancer stem cells (CSCs) in drug resistance and their therapeutic implications in cancer treatment, Stem Cells Int. 2018 (2018) 5416923.
[121] T.B. Steinbichler, J. Dudás, S. Skvortsov, U. Ganswindt, H. Riechelmann, I. I. Skvortsova, Therapy resistance mediated by cancer stem cells, Semin Cancer Biol. 53 (2018) 156–167.
[122] L. Huang, S. Jiang, Y. Shi, Tyrosine kinase inhibitors for solid tumors in the past 20 years (2001-2020), J. Hematol. Oncol. 13 (1) (2020) 143.
[123] K.F. Man, S. Ma, Mechanisms of resistance to tyrosine kinase inhibitors in liver cancer stem cells and potential therapeutic approaches, Essays Biochem 66 (4) (2022) 371–386.
[124] R. Suresh, S. Ali, A. Ahmad, P.A. Philip, F.H. Sarkar, The role of cancer stem cells in recurrent and drug-resistant lung cancer, Adv. Exp. Med Biol. 890 (2016) 57–74.
[125] Q. Yu, Z. Xiu, Y. Jian, J. Zhou, X. Chen, X. Chen, C. Chen, H. Chen, S. Yang, L. Yin, W. Zeng, microRNA-497 prevents pancreatic cancer stem cell gemcitabine resistance, migration, and invasion by directly targeting nuclear factor kappa B 1, Aging 14 (14) (2022) 5908–5924.
[126] J. Yin, X. Ge, Z. Shi, C. Yu, C. Lu, Y. Wei, A. Zeng, X. Wang, W. Yan, J. Zhang, Y. You, Extracellular vesicles derived from hypoxic glioma stem-like cells confer temozolomide resistance on glioblastoma by delivering miR-30b-3p, Theranostics 11 (4) (2021) 1763–1779.
[127] M.W. Chen, S.T. Yang, M.H. Chien, K.T. Hua, C.J. Wu, S.M. Hsiao, H. Lin, M. Hsiao, J.L. Su, L.H. Wei, The STAT3-miRNA-92-Wnt signaling pathway regulates spheroid formation and malignant progression in ovarian cancer, Cancer Res. 77 (8) (2017) 1955–1967.
[128] C. Liu, H. Xing, C. Guo, Z. Yang, Y. Wang, Y. Wang, MiR-124 reversed the doxorubicin resistance of breast cancer stem cells through STAT3/HIF-1 signaling pathways, Cell Cycle 18 (18) (2019) 2215–2227.
[129] Q. Zhao, Y. Liu, T. Wang, Y. Yang, H. Ni, H. Liu, Q. Guo, T. Xi, L. Zheng, MiR-375 inhibits the stemness of breast cancer cells by blocking the JAK2/STAT3 signaling, Eur. J. Pharm. 884 (2020), 173359.
[130] N. Wang, Y. Jiang, S. Lv, H. Wen, D. Wu, Q. Wei, Q. Dang, HOTAIR expands the population of prostatic cancer stem-like cells and causes Docetaxel resistance via activating STAT3 signaling, Aging 12 (13) (2020) 12771–12782.
[131] L. Darvish, M.T. Bahreyni Toossi, H. Azimian, M. Shakeri, E. Dolat, A. Ahmadizad Firouzjaei, S. Rezaie, A. Amraee, S.H. Aghaee-Bakhtiari, The role of microRNA-induced apoptosis in diverse radioresistant cancers, Cell Signal. 104 (2023), 110580.
[132] J. Guo, K. Jin, T. Tang, H.M. Liu, Y.A. Xie, A new biomarker to enhance the radiosensitivity of hepatocellular cancer: miRNAs, Future Oncol. 18 (28) (2022) 3217–3228.
[133] M. Bai, X. Ma, X. Li, X. Wang, Q. Mei, X. Li, Z. Wu, W. Han, The accomplices Of NF-kappaB lead to radioresistance, Curr. Protein Pept. Sci. 16 (4) (2015) 279–294.
[134] F. Lan, X. Yue, G. Ren, H. Li, L. Ping, Y. Wang, T. Xia, miR-15a/16 enhances radiation sensitivity of non-small cell lung cancer cells by targeting the TLR1/NF-κB signaling pathway, Int. J. Radiat. Oncol. Biol. Phys. 91 (1) (2015) 73–81.
[135] J. Gu, N. Mu, B. Jia, Q. Guo, L. Pan, M. Zhu, W. Zhang, K. Zhang, W. Li, M. Li, L. Wei, X. Xue, Y. Zhang, W. Zhang, Targeting radiation-tolerant persister cells as a strategy for inhibiting radioresistance and recurrence in glioblastoma, Neuro Oncol. 24 (7) (2022) 1056–1070.
[136] M.I. Khan, A. Ahmad, LncRNA SNHG6 sponges miR-101 and induces tamoxifen resistance in breast cancer cells through induction of EMT, Front. Oncol. 12 (2022) 1015428.
[137] S. Rajakumar, S. Jamespaulraj, Y. Shah, P. Kejamurthy, M.K. Jaganathan, G. Mahalingam, K.T. Ramya, Devi, Long non-coding RNAs: an overview on miRNA sponging and its co-regulation in lung cancer, Mol. Biol. Rep. (2022).
[138] T. Fu, K. Ji, L. Jin, J. Zhang, X. Wu, X. Ji, B. Fan, Z. Jia, A. Wang, J. Liu, Z. Bu, J. Ji, ASB16-AS1 up-regulated and phosphorylated TRIM37 to activate NF-κB pathway and promote proliferation, stemness, and cisplatin resistance of gastric cancer, Gastric Cancer 24 (1) (2021) 45–59.
[139] D. Wu, H. Jia, Z. Zhang, S. Li, STAT3-induced HLA-F-AS1 promotes cell proliferation and stemness characteristics in triple negative breast cancer cells by upregulating TRABD, Bioorg. Chem. 109 (2021), 104722.
[140] J. Tang, B. Yu, Y. Li, W. Zhang, A.A. Alvarez, B. Hu, S.Y. Cheng, H. Feng, TGF-β-activated lncRNA LINC00115 is a critical regulator of glioma stem-like cell tumorigenicity, EMBO Rep. 20 (12) (2019), e48170.
[141] A. Ahmad, A. Aboukameel, D. Kong, Z. Wang, S. Sethi, W. Chen, F.H. Sarkar, A. Raz, Phosphoglucose isomerase/autocrine motility factor mediates epithelial-mesenchymal transition regulated by miR-200 in breast cancer cells, Cancer Res. 71 (9) (2011) 3400–3409.
[142] G. Babaei, N. Raei, A. Toofani Milani, S. Gholizadeh-Ghaleh Aziz, N. Pourjabbar, F. Geravand, The emerging role of miR-200 family in metastasis: focus on EMT, CSCs, angiogenesis, and anoikis, Mol. Biol. Rep. 48 (10) (2021) 6935–6947.
[143] A. Ahmad, S.H. Sarkar, B. Bitar, S. Ali, A. Aboukameel, S. Sethi, Y. Li, B. Bao, D. Kong, S. Banerjee, S.B. Padhye, F.H. Sarkar, Garcinol regulates EMT and Wnt signaling pathways in vitro and in vivo, leading to anticancer activity against breast cancer cells, Mol. Cancer Ther. 11 (10) (2012) 2193–2201.
[144] I. Górecki, B. Rak, The role of microRNAs in epithelial to mesenchymal transition and cancers; focusing on mir-200 family, Cancer Treat. Res. Commun. 28 (2021), 100385.
[145] J. Zhang, Z. Hu, C.A. Horta, J. Yang, Regulation of epithelial-mesenchymal transition by tumor microenvironmental signals and its implication in cancer therapeutics, Semin Cancer Biol. 88 (2023) 46–66.

[146] S. Deng, J. Wang, L. Zhang, J. Li, Y. Jin, LncRNA HOTAIR promotes cancer stem-like cells properties by sponging miR-34a to activate the JAK2/STAT3 pathway in pancreatic ductal adenocarcinoma, Onco Targets Ther. 14 (2021) 1883–1893.
[147] H. Huang, L. Wei, T. Qin, N. Yang, Z. Li, Z. Xu, Circular RNA ciRS-7 triggers the migration and invasion of esophageal squamous cell carcinoma via miR-7/KLF4 and NF-κB signals, Cancer Biol. Ther. 20 (1) (2019) 73–80.
[148] H. Chen, Y. Li, Circular RNA hsa_circ_0000915 promotes propranolol resistance of hemangioma stem cells in infantile haemangiomas, Hum. Genom. 16 (1) (2022) 43.
[149] Z. Zhang, C. Sun, Y. Zheng, Y. Gong, circFCHO2 promotes gastric cancer progression by activating the JAK1/STAT3 pathway via sponging miR-194-5p, Cell Cycle 21 (20) (2022) 2145–2164.
[150] Y. Gao, H. Qian, X. Tang, X. Du, G. Wang, H. Zhang, F. Ye, T. Liu, Superparamagnetic iron oxide nanoparticle-mediated expression of miR-326 inhibits human endometrial carcinoma stem cell growth, Int. J. Nanomed. 14 (2019) 2719–2731.
[151] Y. Zhou, Y. Zhang, H. Gong, S. Luo, Y. Cui, The role of exosomes and their applications in cancer, Int. J. Mol. Sci. 22 (22) (2021).
[152] J. El-Saghir, F. Nassar, N. Tawil, M. El-Sabban, ATL-derived exosomes modulate mesenchymal stem cells: potential role in leukemia progression, Retrovirology 13 (1) (2016) 73.