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Review Article

Shedding light on function of long non-coding RNAs (lncRNAs) in glioblastoma

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ABSTRACT

The brain tumors and especially glioblastoma, are affecting life of many people worldwide and due to their high mortality and morbidity, their treatment is of importance and has gained attention in recent years. The abnormal expression of genes is commonly observed in GBM and long non-coding RNAs (lncRNAs) have demonstrated dysregulation in this tumor. LncRNAs have length more than 200 nucleotides and they have been located in cytoplasm and nucleus. The current review focuses on the role of lncRNAs in GBM. There two types of lncRNAs in GBM including tumor-promoting and tumor-suppressor lncRNAs and overexpression of oncogenic lncRNAs increases progression of GBM. LncRNAs can regulate proliferation, cell cycle arrest and metastasis of GBM cells. Wnt, STAT3 and EZH2 are among the molecular pathways affected by lncRNAs in GBM and for regulating metastasis of GBM cells, these RNA molecules mainly affect EMT mechanism. LncRNAs are involved in drug resistance and can induce resistance of GBM cells to temozolomide chemotherapy. Furthermore, lncRNAs stimulate radio-resistance in GBM cells. LncRNAs increase PD-1 expression to mediate immune evasion. LncRNAs can be considered as diagnostic and prognostic tools in GBM and researchers have developed signature from lncRNAs in GBM.

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1. Introduction

The most common malignant tumors of brain are gliomas [1] and majority of gliomas is comprised of glioblastoma (GBM) (57.7%). GBM forms 48.6% of tumors in central nervous system and its treatment is still a challenging process for physicians [2,3]. There are differences between glioma and GBM. The glioma is a general term utilized to show the malignant tumors arising from glial cells, while the GBM is a specific type of glioma with more malignancy and tendency to proliferate and metastasize. In terms of differences in grade, glioma have different grades from I and IV that the growth is slow in low-grade gliomas. However, GBM is the grade IV tumor with high malignancy, abnormal growth and the tendency to develop therapy resistance. In terms of symptoms, both glioma and GBM demonstrate a number of general symptoms including headache, seizure and neurological deficits. However, such symptoms are not specific, leading to the diagnosis of tumors at advanced stages. The recent studies have highlighted the major features of glioma and GBM [4–7]. The gold standard for treatment of newly detected GBM was represented in 2005 that includes surgical resection, radiotherapy and combination therapy with temozolomide (TMZ) [8]. Although this therapy regime is aggressive and uses a combination of methods, it has been reported that only 25% of patients survive two years after initial diagnosis. Furthermore, GBM patients demonstrate relapse after 7 months of starting treatment [9]. Upon recurrence of GBM, median progression-free survival of appears to be 9 weeks [10,11]. GBM cells are poorly differentiated, they have round shape and are multinucleated and anaplastic [12]. There are two major kinds of GBM based on the origin including primary GBM derived from de novo of glial cells, and secondary GBM derived from preexisting lower grade astrocytoma [13]. GBM is considered as a malignant condition that could cause death in six months or less; it appears that addition of bevacizumab to treatment regimen of GBM does not affect overall survival, but it is beneficial in improving progression-free survival. GBM can occur in any age, but it is more common between 55 and 60 years. The incidence rate of GBM is suggested to be higher in males compared to females. The incidence rate of GBM is higher in developed and Western countries compared to developing countries. The incidence rate of GBM is less than 10 per 100,000 people [14]. The current treatments for the GBM are mainly chemotherapy and surgery, but radiotherapy and immunotherapy can also be considered other options. In the chemotherapy of GBM, temozolomide is the most common drug, but DNA damage repair [15], non-coding RNAs [16] and epigenetic regulation [17] cause temozolomide insensitivity. However, regarding to the involvement of different molecular factors, the focus should be directed on the main modulators and regarding to the pleiotropic function of lncRNAs, the control of lncRNAs in affecting wide variety of biological and molecular mechanisms is suggested. Moreover, the chemotherapy does not have ability in complete suppression of all tumor cells and the surviving cancer stem cells (CSCs) are able to re-new and develop new colonies, causing the tumor recurrence. The process of cancer relapse is also observed after surgical resection, since the remaining tumor cells can proliferation and migrate again, significantly reducing the survival rate of GBM. For the application of radiotherapy, the dysregulation of molecular pathways such as NF-κB upregulation by LITAF can also cause resistance [18]. Although immunotherapy opens new hopes in the treatment of GBM, the increase in endothelial metabolism induced by PHGDH can also mediate immunoresistance [19]. For improving its ability, a combination of immunotherapy and radiotherapy is utilized. However, the presence of CD103+ regulatory T cells can interfere with function of $CD8^+$ T cells, causing resistance to radio-immunotherapy in GBM [20]. Therefore, it can be concluded that dysregulation of genetic and epigenetic factors in GBM can ensure tumorigenesis and resistance to the current therapies.

CSCs or cancer-initiating cells (CIS) are a certain subpopulation that are responsible for tumor initiation and development. The CSCs have capacity of self-renewing and they account for progression and relapse of cancer [21]. In addition to cancer relapse and progression, CSCs induce resistance to therapy [22]. The presence of quiescent human GBM CSCs can cause the tumor expansion and relapse upon chemotherapy [23]. Chimeric antigen receptor T cells have ability of targeting GRP78 to impair and eradicate GBM and CSCs [24]. Upon tumor development, the immune system is activated to impair progression of cancer cells. Noteworthy, GBM CSCs are able to downregulate TLR4 expression to evade the anti-cancer activity of innate immune system and maintain their self-renewal ability [25]. In addition, the GMB cells have shown high potential in the development of chemoresistance and radioresistance. The Rbfox21-induced alternative splicing can be regulated by FBXO7, highlighting function of FBXO7 in the development of drug resistance and enhancing mesenchymal features [26]. PTRF/Cavin-1 has been suggested as a mechanism in the development of drug resistance in GBM mediated through efflux of temozolomide from tumor cells through extracellular vesicles [27]. The upregulation of Akt by LGR6 can enhance the progression of GBM and this mediates the development of drug resistance [28]. Due to the malignancy of GBM cells, they have ability of develop resistance to radiotherapy. Upon radiotherapy, the expression level of DGAT1 enhances and its downregulation using genetic tools can enhance radiosensitivity [29]. AHIF shows interaction with factors of migration and angiogenesis in exosomes to induce radioresistance. The downregulation of AHIF enhances apoptosis and radiosensitivity in GBM [30]. More importantly, the epigenetic factors such as miRNAs and circRNAs participate in the regulation of radioresistance in GBM [31,32].

The rapid growth of GBM cells leads to induction of hypoxia in tumor microenvironment (TME). Then, need for oxygen stimulates angiogenesis and results in anaerobic glycolysis. Then, accumulation of lactate enhances to decrease pH level of TME, causing tumorigenesis [33]. The GBM could develop resistance to apoptosis [34]. In addition, radio-resistance commonly occurs in GBM cells [35] and they are able to mediate immune evasion [36]. The signaling networks mediate a significant function in malignancy GBM. The overexpression of CTLA4 occurs in GBM and mediates immunosuppression. Furthermore, upregulated CTLA4 stimulates infiltration of macrophages into TME [37]. The dysfunction of NK cells happens in GBM and suppression of TGF-β or integrins can improve capacity of NK cells in inhibiting GBM stem cells [38]. RECQ1 is suggested to be involved in facilitating GBM malignancy and RECQ1 recruits PARP1 to increase DNA replication [39]. The poor prognosis of GBM is observed in XRCC5 upregulation and it can also mediate TMZ resistance [34]. 17β-estradiol is capable of inducing Nrf2 signaling to reduce ROS, leading to TMZ resistance and decreased cell death in GBM [40]. The current therapies for the treatment of GBM have faced difficulties, especially chemotherapy that aggressive GBM cells are capable of developing drug resistance. The increasing evidences have shown the function of lncRNAs in the stimulation of drug insensitivity in GBM, especially resistance to temozolomide as major chemotherapy drug utilized in GBM suppression [41–43]. Since various kinds of molecular networks are dysregulated in the drug resistance in GBM and lncRNAs are master modulators of pathways in tumors, the focus on the lncRNA function in reversing GBM resistance appears rational. Moreover, the sensitive location of GBM makes it hard to perform surgical resection for the removal GBM, although the cancer cells may have already disseminated into other tissues. Therefore, the new therapeutics should be introduced for the treatment of GBM and due to the versatile role of lncRNAs in the control of cancer progression and affecting therapy response and biological behavior of GBM, the control of lncRNAs is suggested. Both pharmacological and gene-based strategies can be utilized in the regulation of lncRNAs. Therefore, current review highlights the role of lncRNAs in the GBM and provides the notion that manipulation of lncRNA expression can affect various downstream pathways and targets. Frist, an overview of lncRNAs in the oncology is provided and then, the role of lncRNAs in the control of growth, metastasis and stemness through affecting CSCs is discussed. In order to broaden the knowledge towards function of lncRNAs in GBM, the

regulation of immune evasion, chemoresistance and radio-resistance is discussed. Finally, the application of lncRNAs as biomarkers in the clinical level is discussed.

2. LncRNAs in oncology

The findings of Human Genome Project has highlighted the fact that genome is mainly occupied by the non-coding sequences and only 1.5% of genome is occupied by protein-coding sequences [44]. Therefore, the DNA sequences undergo transcription to the non-coding RNAs comprising majority of RNA transcripts [45,46]. There are several types of non-coding RNAs that were discussed considered as dark matter or noises of transcription [47]. However, further improvements in the biology and sequencing revealed the prominent action of ncRNAs in the regulation of gene expression, chromatin remodeling, epigenetic memory, RNA splicing and translation, among others [48–50]. The current ideas demonstrate the multiple functions of lncRNAs in the physiological and pathological conditions. The lncRNAs have more than 200 nts and until now, more than 10,000 lncRNAs have been recognized [51]. The lncRNAs can be present in the nucleus and cytoplasm, depending on the role that they exert and they conduct important roles including transcriptional and post-transcriptional control as well as regulating epigenetic mechanisms [52]. LncRNAs lack open reading frames and these functional RNA molecules are able to generate short polypeptides [53]. Moreover, peptides produced by a number of lncRNAs can exert biological functions in cancer [54]. Interestingly, a number of lncRNAs have demonstrated potential of micropeptide synthesis. It has been reported that LINC00908 has capacity of encoding ASRPS containing 60-amino acid, and lncRNA MIR155HG is able to synthesize miPEP155 containing 17-aminoa acid [55]. The sponge function of lncRNAs diminishes miRNA expression. The dysregulation in lncRNA expression can cause tumorigenesis. LncRNAs exert vital functions at both transcriptional and post-transcriptional levels and their biological function is attributed to regulating differentiation, apoptosis, autophagy, stem cell maintenance and embryonic development. Autophagy is a critical process in tumorigenesis with dual function in the tumorigenesis/cancer suppression. Since the certain role of autophagy in cancer has not been determined and it affects chemoresistance and tumorigenesis [56,57], its regulation by lncRNAs requires more investigation. In respect to abnormal expression of lncRNAs in cancers, they are implicated in process of carcinogenesis as inducers or inhibitors [58].

LncRNAs are key players in different cancers. For instance, lncRNA EIF3J-DT downregulates miRNA-188–3p to mediate stabilization of ATF14 mRNA, resulting in autophagy activation and subsequent chemoresistance [59]. LncRNA AC079630.4 causes proliferation inhibition and decreased colony formation capacity [60]. LncRNA FAM230B undergoes overexpression in gastric tumor and increases growth and metastasis. Silencing FAM230B stimulates apoptosis in gastric tumor and for exerting carcinogenic impact, FAM230B downregulates miRNA-27a-5p to elevate TOP2A expression [61]. Circulating lncRNA UCA1 and PGM5-AS1 demonstrate upregulation and down-regulation in colorectal cancer, respectively and can be considered as diagnostic factors [62]. Through reducing miRNA-217 expression, lncRNA SNHG20 increases growth and metastasis of ovarian tumor [63]. LncRNA TUSC8 downregulates VEGFA in impairing growth and invasion of esophageal tumor [64]. The association among lncRNAs and their downstream targets (KLF6, miRNA-424–5p, miRNA-103, among others) affects tumorigenesis, invasion and therapy response are tightly regulated by lncRNAs (Table 1).

3. LncRNAs in proliferation and invasion

Different molecular pathways regulate growth and metastasis of GBM cells [82]. For instance, ECM1 overexpression increases progression of glioblastoma; brusatol administration decreases ECM1 in GBM suppression [83]. RUNX1T1 undergoes down-regulation in GBM and it

Table 1
An overview of lncRNAs in oncology.

LncRNA	Signaling network	Remarks	Refs
UCA1	miR-27a-5p/ UBE2N	UCA1 elevates UBE2N level via miR-27a-5p inhibition Inducing cisplatin insensitivity in ovarian tumor	[65]
NEAT1	miR-377/FGFR1	Silencing NEAT1 induces apoptosis miR-377 inhibition by NEAT1 to elevate FGFR1 in exerting its oncogenic function	[66]
LINC00160	STAT3/ LINC00160/ RCAN1	STAT3 promotes expression level of LINC00160 to inhibit RCAN1 expression Increased growth and metabolism of tumor cells	[67]
GPC5-AS1	miR-93/106a/ GPC5	LncRNA GPC5-AS1 participates in upregulating GPC5 via miR-93/106a sponging Inhibiting growth	[68]
LINC00473	miR-195	LINC00473 suppresses miR-195 EMT induction and increasing progression of colorectal cancer Association with poor prognosis	[69]
SNHG7	Notch1/ Jagged1/Hes-1	Overexpression of SNHG7 in pancreatic tumor and positive association with stemness and folfirinox resistance Induction of Notch1 signaling by SNHG7	[70]
MAFG-AS1	miR-3612/ FKBP4	Overexpression of MAFG-AS1 and FKBP4 and down-regulation of miR-3612 Apoptosis inhibition Facilitating cancer progression miR-3612 down-regulation by MAFG-AS1 and subsequent FKBP4 overexpression Autophagy inhibition	[71]
AC02278.4	–	Overexpression of lncRNA AC02278.4 and association with clinical stage Increasing invasion and growth rate of tumor cells	[72]
T-UCR Uc.339	miR-339/ SLC7A11	miR-339 down-regulation by T-UCR Uc.339 to increase SLC7A11 expression Silencing T-UCR Uc.339 prevents tumor progression	[73]
MIR503HG	miR-224–5p/ TUSC3	Poor expression of MIR503HG and TUSC3 in gastric cancer, while miR-224–5p expression enhances MIR503HG promotes TUSC3 expression via miR-224–5p inhibition to impair carcinogenesis	[74]
HOTAIR	–	Cancer-associated fibroblasts secrete CCL5 to increase HOTAIR to mediate cisplatin resistance	[75]
LINC01410	miR-506–3p/ Notch2	MYC promotes LINC01410 expression in accelerating glioma progression miR-506–3p down-regulation by LINC01410 to induce Notch2 signaling	[76]
RUNDC3A-AS1	miR-151b/ SNRPB	Silencing RUNDC3A-AS1 induces apoptosis and impairs proliferation miR-151b inhibition by RUNDC3A-AS1 to upregulate SNRPB	[77]
SNHG3	miR-139–5p/ MYB	Increasing gastric tumorigenesis SNHG3 promotes MYB via miR-139–5p down-regulation	[78]
LINC00665	miR-181a-5p/ FHDC	Increasing proliferation of ovarian cancer and preventing apoptosis LINC00665 reduces miR-181a-5p expression to upregulate FHDC	[79]
PART1	miR-503–5p/ FOXK1	PART1 promotes FOXK1 level via miR-503–5p inhibition Increasing viability and progression of ovarian cancer	[80]

(*continued on next page*)

Table 1 (*continued*)

LncRNA	Signaling network	Remarks	Refs
HOXA-AS2	miR-567/CDK8	Increased progression of oral cancer cells by lncRNA HOXA-AS2 HOXA-AS2 promotes CDK8 expression via miR-567 inhibition	[81]

can mediate degradation of HIF-1α by recruiting PHD2 and GSK3β to suppress tumor progression [84]. The microglia cells present in brain can participate in progression of GBM. Cytokines originated from microglia cells stimulate Pyk2 and FAK in tumorigenesis [85]. Upon reduction in expression level of Tim-1, Wnt suppression occurs that is of importance in impairing GBM progression [86]. SKA3 stimulates Akt and Wnt in enhancing GBM progression [87]. RNF12 is involved in down-regulation of RB1 and induces MAPK in GBM progression [88]. Tat-NTS is suggested to be involved in preventing nuclear translocation of annexin-A1 for carcinogenesis [89].

The lncRNA DLGAP1-AS1 upregulation occurs in GBM and suppresses apoptosis. Silencing DLGAP1-AS1 stimulates apoptosis in GBM. DLGAP1-AS1 suppresses miRNA-515–5p to enhance ROCK1 and NFE2L1 levels, evoking Wnt-mediated GBM progression [90]. LncRNAs mainly reduce expression level of their target in an indirect mechanism. EZH2 is a key player in cancer and binds to gene promoter [91]. LncRNA H19-mediated recruitment of EZH2 increases NKD1 levels in GBM inhibition [92]. LncRNA HOXA-AS2-induced miRNA-885–5p suppression increases RBBP4 to accelerate tumorigenesis [93]. LncRNA LINC01410 increases GBM survival and inhibits apoptosis. LINC01410 depletion stimulates apoptotic cell death and diminishes survival rate. LINC01410 suppresses miRNA-370–3p to down-regulate PTEN, causing Akt-mediated tumorigenesis [94].

The proliferation of GBM increases by lncRNA GAS8-AS1. Based on the expression analysis, lncRNA GAS8-AS1 has downregulation, while lncRNA NEAT1 increases in plasma of GBM patients. In order to decrease proliferation of GBM cells, lncRNA GAS8-AS1 down-regulates NEAT1 expression. Silencing lncRNA GAS8-AS1 elevates tumorigenesis via Wnt overexpression [95]. STAT1 upregulates lncRNA MIR31HG that in turn induces Wnt in increasing proliferation and suppressing apoptosis [96]. SOX2-OT shows upregulation in GBM and its silencing is correlated with apoptosis. LncRNA SOX2-OT suppresses miRNA-192–5p to overexpress RAB2A, evoking ERK and subsequent elevation in proliferation of GBM [97].

LncRNA SLC16A1-AS1 shows upregulation in GBM. Although SLC16A1-AS1 expression increases in GBM, miRNA-149 shows a decrease in expression. For exerting its carcinogenic impact, SLC16A1-AS1 diminishes miRNA-149 expression to increase growth rate and colony formation capacity [98]. LncRNA MIR4435-2HG promotes growth and migration of GBM and for this purpose, lncRNA MIR4435-2HG down-regulates miRNA-1224–5p expression to upregulate TGFBR2, resulting in GBM progression [99]. Inhibition of MATN1-AS1 happens in GBM and provides low survival. MATN1-AS1 decreases expression of RELA, ERK1/2, Bcl-2, survivin and MMP-9 in impairing growth and metastasis of GBM. For upregulating RELA, lncRNA MATN1-AS1 down-regulates E2F6 expression [100].

Knock-down of lncRNA HOXD-AS2 stimulates apoptosis in GBM and impairs proliferation and metastasis. miRNA-3681–5p expression decreases by lncRNA HOXD-AS2 to promote MALT1. Overexpression of miRNA-3681–5p or MALT1 down-regulation diminishes in malignant behavior of GBM [101]. LncRNA XIST facilitates tumorigenesis and suppresses miRNA-448. The overexpressed lncRNA XIST down-regulates miRNA-448 expression to upregulate ROCK1, accelerating tumorigenesis [102]. LncRNA OXCT1-AS1 overexpression mediates undesirable prognosis and it inhibits miRNA-195. Then, overexpressed CDC25A causes GBM progression [103].

The function of lncRNAs as ceRNA in the miRNA sponging can cause changes in the GBM progression. miRNAs are considered as primary targets of lncRNAs in GBM that their expression can reduced through sponging. The carcinogenic potential of GBM cells reduces through the function of lncRNA MIR143HG that sponges miR-504 in upregulating p53, reducing tumorigenesis [104]. The expression level of such lncRNAs with suppressive functions on GBM reduces in cancer progression. The SATB2-AS1 is capable of sponging miR-671–5p to enhance levels of CDR1 and VSNL1 in suppressing cancer progression [105]. Hence, it can be concluded that lncRNAs are main regulators of cancer progression through sponging miRNAs.

EMT mechanism is a physiological process during embryogenesis and tissue development, but tumor cells exploit it as a leverage for increasing their metastasis. Induction of EMT is a common process in GBM and various molecular mechanisms such as TGF-β and Akt/mTOR, among others can regulate it in tumor cells [78,106]. Anti-cancer agents such as eriodictyol are able to inhibit EMT in GBM suppression [107]. LncRNAs have demonstrate close association with EMT in GBM cells [108]. HOXA-AS functions as sponge for miRNA-455–5p to upregulate USP3 and evoke EMT [102]. LINC00152 is another lncRNA implicated in EMT-related metastasis of GBM cells. LINC00152 mediates miRNA-107 down-regulation to increase HMGA2, resulting in EMT and increased metastasis of GBM [109]. LncRNA SAMMSON depletion suppresses PI3K/Akt to inhibit EMT in decreasing progression GBM [84]. Based on the discussions, lncRNAs are vital modulators of metastasis and proliferation. Most of the studies have focused on tumor-promoting lncRNAs and there is a need for focusing on tumor-suppressor lncRNAs. Furthermore, studies have mainly focused on miRNAs as downstream targets of lncRNAs and others factors related to GBM progression and their association with lncRNAs should be highlighted (Fig. 1).

4. LncRNAs and cancer stem cells

The field of cancer therapy has been improved by targeting CSCs [110,111]. BRM270 can be co-administered with paclitaxel and gefitinib in elimination of CSCs and preventing drug resistance [112]. Quiescent human GBM CSCs mediate tumorigenesis and relapse after chemotherapy [23]. By suppressing TGF-β/Smad pathway, miR-663a decreases CSC features of glioma cells [113]. Inhibition of Akt and FOXM1 pathways by MELK suppresses GBM [114].

CSCs are responsible for progression of GBM and they can mediate relapse of tumor that is an increasing challenge in recent years. Different experiments have shown association between lncRNAs and GBM stemness that can be considered and attributed to their impact on CSCs. For instance, lncRNA SNHG20 elevates GBM tumorigenesis and it facilitates stemness. LncRNA SNHG20 triggers PI3K/Akt/mTOR to elevate stemness of GBM [115]. Surgery is an option in GBM treatment and postoperative survival is important in the patients. LncRNA RPSAP52 enhances expression level of TGF-β1 to promote stemness in GBM. Knock-down of RPSAP52 diminishes number of CD133+ cells [116]. A number of markers associated with CSC are considered and CD133, SOX2 and ALDH1A1 are among them. LINC01503 demonstrates localization in cytoplasm and nucleus, and its overexpression is correlated with GBM stemness. ENST00000444125 transcript of lncRNA LINC01503 can increase stability of GLI2 via preventing its ubiquitination by FBXW1 to increase levels of CD133, SOX2, NESTIN, ALDH1A1 and MSI1, leading to GBM stemness [117]. TMZ as a chemotherapeutic agent has capacity of targeting CSCs in treatment of GBM. However, CSCs can obtain resistance to TMZ chemotherapy and lncRNAs are involved in this case. LncRNA TP73-AS1 demonstrates positive association with progression of GBM cells and mediates TMZ resistance in CSCs. LncRNA TP73-AS1 increases stemness of GBM and upregulates ALDH1A1 to induce TMZ resistance in CSCs [118]. In addition to chemotherapy, radiotherapy is employed in affecting CSCs for purpose of GBM treatment. It has been reported that lncRNA TALNEC2 as a new emerging non-coding RNA, is capable of increasing growth rate of GBM

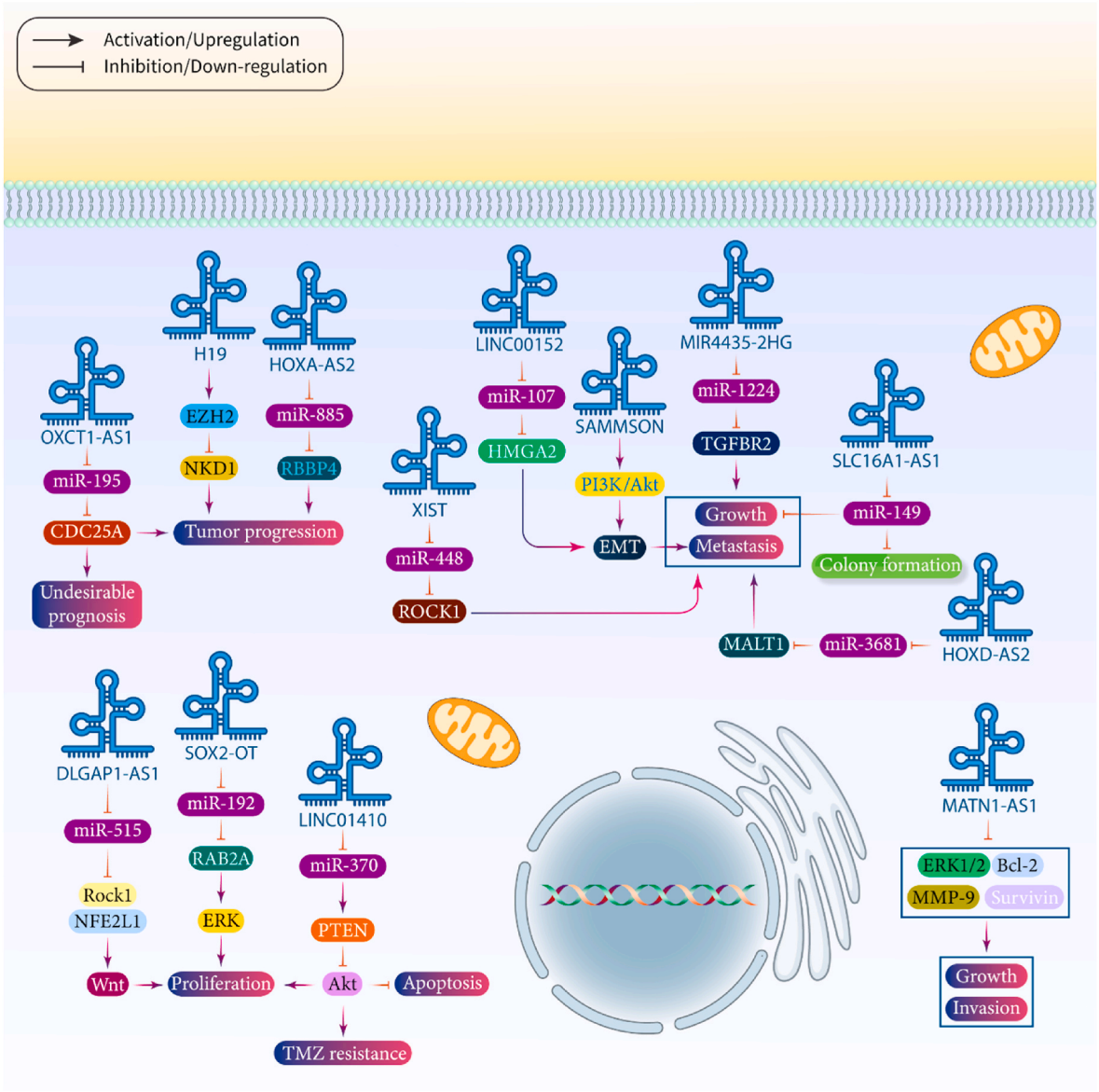

Fig. 1. Function of lncRNAs in growth and metastasis of GBM. This figure obviously demonstrates that a wide variety of signaling networks are influenced by lncRNAs in cancer therapy. In terms of metastasis, EMT could be controlled by lncRNAs in regulating GBM metastasis. In regulating proliferation, Wnt and PI3k/Akt molecular pathways are the most vital ones.

cells. LncRNA TALNEC2 shows overexpression in GBM, decreases expression levels of miRNA-21 and miRNA-191, reduces overall survival of patients and increases carcinogenic impact of CSCs, leading to radiation resistance of tumors [119]. These studies highlight the fact that stemness of GBM cells is a barrier towards the effective treatment of this malignant disease and lncRNAs can regulate expression of CSC markers. Therefore, targeting lncRNAs is a promising strategy in treatment of GBM (Fig. 2).

5. LncRNAs in therapy response

5.1. Drug resistance

The recent experiments have demonstrated potential of GBM in obtaining resistance to TMZ. CircRNA-ASAP1 level increases in GBM by EIF4A3 and by sponging miRNA-502–5p, circRNA stimulates NRAS signaling, leading to TMZ resistance of GBM cells [120]. Warburg effect is involved in promoting expression level of exosomal circRNA-0072083 to upregulate NANGO, causing TMZ insensitivity [121]. Another experiment reveals that CD147 induces Akt signaling to prevent degradation of Nrf2 in mediating TMZ resistance in GBM cells [122]. Hence, GBM cells have high capacity in TMZ resistance. According to the function of lncRNAs in controlling different signaling networks, experiments have emphasized on revealing lncRNA association with TMZ resistance in GBM. LncRNA TUSC7 demonstrates low expression in GBM cells and restoring its expression reverses TMZ resistance. Mechanistically, lncRNA TUSC7 diminishes expression level of miRNA-10a to suppress MRP1, resulting in TMZ sensitivity of GBM cells [123]. LncRNA XIST possesses a tumor-promoting role in GBM and its depletion mediates apoptosis induction, migration and proliferation inhibition as well as reduction in glucose metabolism of tumor cells. For exerting its tumorigenesis activity, lncRNA XIST suppresses miRNA-126, leading to induction of IRS1/PI3K/Akt axis [124]. Silencing such lncRNAs is of importance in chemosensitivity. For instance, silencing lncRNA CRNDE inhibits pro-survival autophagy in GBM cells via decreasing expression levels of LC3 II/I, Beclin-1 and ATG-5, and overexpression of p62 to induce TMZ sensitivity [125].

In pancreatic cancer, lncRNA SOX2OT induces ubiquitination of FUS

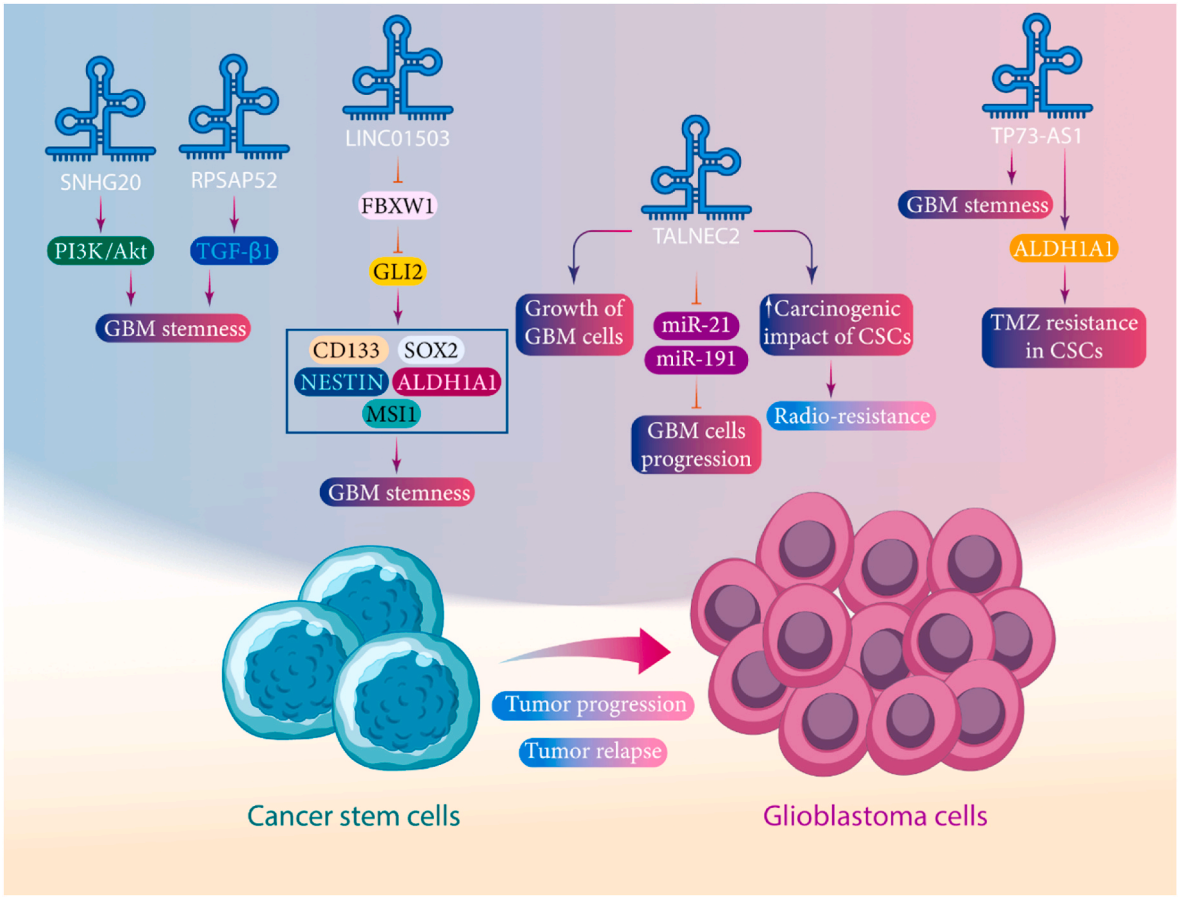

Fig. 2. LncRNAs and cancer stem cells in GBM. Cancer stem cells are rare populations in tumors and after cancer treatment, they can lead to generation of new colonies and provide tumor recurrence. In addition to cancer relapse, cancer stem cells can cause significant progression of tumor progression that are responsible for stemness and therapy resistance. LncRNAs such as SNHG20 and TP73-AS1 regulate cancer stem cells in GBM.

protein to reduce its stability in increasing growth and metastasis [126]. In TNBC, PAI-1 upregulates lncRNA SOX2OT to reduce miRNA-942–5p expression via sponging, resulting in stimulation of PI3K/Akt and subsequent enhancement in migration and invasion of tumor [127]. A same phenomenon occurs in GBM and lncRNA SOX2OT is capable of increasing tumor progression and mediating TMZ insensitivity. For this purpose, lncRNA SOX2OT recruits ALKBH5 to mediate demthylation of SOX2, resulting in an increase in its expression, apoptosis inhibition, proliferation increase and resistance to TMZ chemotherapy [128]. Regarding to role of lncRNA OIP5-AS1 in inducing TMZ resistance in GBM, its inhibition disrupts tumor progression. LncRNA OIP5-AS1 and IGF2BP2 demonstrate upregulation in GBM, while miRNA-129–5p shows a decrease in expression in GBM cells. Silencing OIP5-AS1 promotes expression level of miRNA-129–5p to down-regulate IGF2BP2, leading to TMZ sensitivity of GBM cells [129]. The malignant behavior of GBM cells can result in TMZ resistance. An experiment has shown that overexpression of lncRNA MALAT1 can lead to TMZ resistance in GBM cells. Silencing MALAT1 promotes sensitivity of GBM cells to TMZ chemotherapy and decreases expression levels of ZEB1, MDR1, MRP5 and LRP1 as downstream targets. Noteworthy, ZEB1 is involved in metastasis and EMT induction in GBM cells. Therefore, MALAT1 promotes ZEB1 expression to induce EMT and along with increasing migration and invasion of GBM cells, it can mediate TMZ resistance [130]. The methylation status of lncRNA promoter affects its expression level. For instance, lncRNA SNHG12 shows an increase in expression in GBM and it induces TMZ resistance. Poor DNA methylation of lncRNA SNHG12 promoter is observed in GBM cells that provides the condition for attachment of SP1 to its promoter. Then, overexpressed lncRNA SNHG12 decreases expression level of miRNA-129–5p in cytoplasm to induce MAPK1 and E2F7, leading to TMZ resistance [41].

The studies provide new insights towards association of lncRNAs with TMZ resistance and each experiment proposes a unique pathway. The TMZ-resistant GBM cells demonstrate overexpression of lncRNA ADAMTS9-AS2 and it reduces IC_{50} of TMZ and is correlated with undesirable prognosis and low overall survival. Silencing lncRNA ADAMTS9-AS2 suppresses growth rate of GBM cells and prevents their migration. LncRNA ADAMTS9-AS2 prevents the ubiquitination and degradation of MDM2 by FUS to mediate TMZ resistance in GBM cells [131]. One of the factors that complicate signaling networks involved in progression of GBM and mediating TMZ resistance is presence of feedback loop. Due to tumor-promoting function of lncRNA RMRP, its knock-down induces apoptosis and impairs proliferation and invasion of tumor cells. Furthermore, silencing RMRP reduces TMZ resistance and interferes with tumor growth in animal models. LncRNA RMRP decreases expression level of ZNRF3 to induce Wnt/β-catenin signaling and to mediate TMZ resistance. There is a positive feedback loop and activated Wnt signaling can promote expression level of RMRP in providing GBM progression and triggering TMZ resistance [132].

Exosomes are small extracellular vesicles and they can transfer bioactive molecules such as lipids, proteins and nucleic acids to communicate among cells. Tumor microenvironment and immune system response are affected by exosomes and they can enter to cells via endocytosis [133–141]. An experiment has revealed that lncRNA SBF2-AS1 can be transferred by exosomes to GBM cells and it mediates TMZ resistance. Mechanistically, exosomal lncRNA SBF2-AS1 acts as ceRNA to diminish expression level of miRNA-151a-3p, resulting in upregulation of XRCC4 and subsequent TMZ resistance. Noteworthy, exosomal lncRNA SBF2-AS1 can be detected in high levels in serum of

patients and it can be used as marker for determining response to chemotherapy [142]. These studies highlight the fact that drug resistance is an increasing challenge in GBM and lncRNAs affect different major pathways to regulate TMZ response in tumor cells. More studies in future can focus on tumor-suppressor lncRNAs in GBM (Fig. 3).

5.2. Radio-resistance

Both chemotherapy and radiotherapy have been employed in treatment of GBM. However similar to chemotherapy, GBM cells have demonstrated high potential in developing radio-resistance. The stimulation of oncogenic factors and the prevention of cell death can cause radioresistance in GBM. The regulation of cell death mechanism by cathepsins has made them promising factors to the control of radio-resistance in GBM [143]. On the other hand, metabolic replenishment can be stimulated in GBM through protective autophagy induction by NRBF2 to accelerate radio-resistance [144]. The stimulation of glucose metabolism by PKM2 can reinforce the antioxidant defense system in the development of radio-resistance in GBM [145]. miRNA-671–5p undergoes down-regulation by MSI1 in GBM and it can mediate CSC features and metastasis of tumor cells [146]. Noteworthy, miRNA-671–5p down-regulation results in activation of STAT3 and TRAF2 as two downstream targets to mediate radio-resistance in GBM cells [146]. The nuclear translocation of Rad51 can mediate radio-resistance in GBM cells. Notably, CD81 functions as upstream mediator and stimulates radio-resistance in GBM inducing nuclear translocation of Rad51 [147]. The hypoxia in tumor microenvironment can induce radio-resistance feature of GBM cells. Noteworthy, AMPK overexpression leads to upregulation of ATM via Sp1 to increase radio-resistance property of GBM cells [148]. Therefore, appropriate response of GBM cells to radiotherapy is a troublesome problem [149,150]. Most of the studies have focused on the role of lncRNAs in mediating chemo-resistance in GBM. However, there are a few experiments showing that lncRNAs can also determine response of GBM cells to radiotherapy. LINC01057 is a tumor-promoting factor in GBM and its overexpression enhances malignancy of tumor cells. Notably, silencing LINC01057 impairs growth and invasion of GBM cells, and increases radio-sensitivity of tumors. The in vivo experiment has also shown role of LINC01057 in increasing tumor growth. LINC01057 preserves nuclear localization of IKKα to mediate NF-κB activation, resulting in GBM progression and radio-resistance [151]. It has been reported that overexpression of lncRNA HOTAIRM1 mediates poor prognosis and reduces overall survival of GBM patients. Knock-down of HOTAIRM1 decreases growth and colony formation of GBM cells. Silencing HOTAIRM1 induces mitochondrial dysfunction and significantly promotes reactive oxygen species (ROS) generation in tumor cells. Silencing HOTAIRM1 diminishes expression level of TGM2 and promotes sensitivity of GBM cells to radiotherapy [152]. These studies advocate the fact that application of radiotherapy is advantageous in impairing progression of GBM cells; however, its efficacy has been greatly reduced due to emergence of resistance. The current section revealed that lncRNAs are able to regulate response of GBM cells to radiotherapy and by affecting various molecular pathways in cytoplasm and nucleus, they affect progression of tumor cells.

6. LncRNAs and immune evasion

The application of checkpoint inhibitors for the treatment of

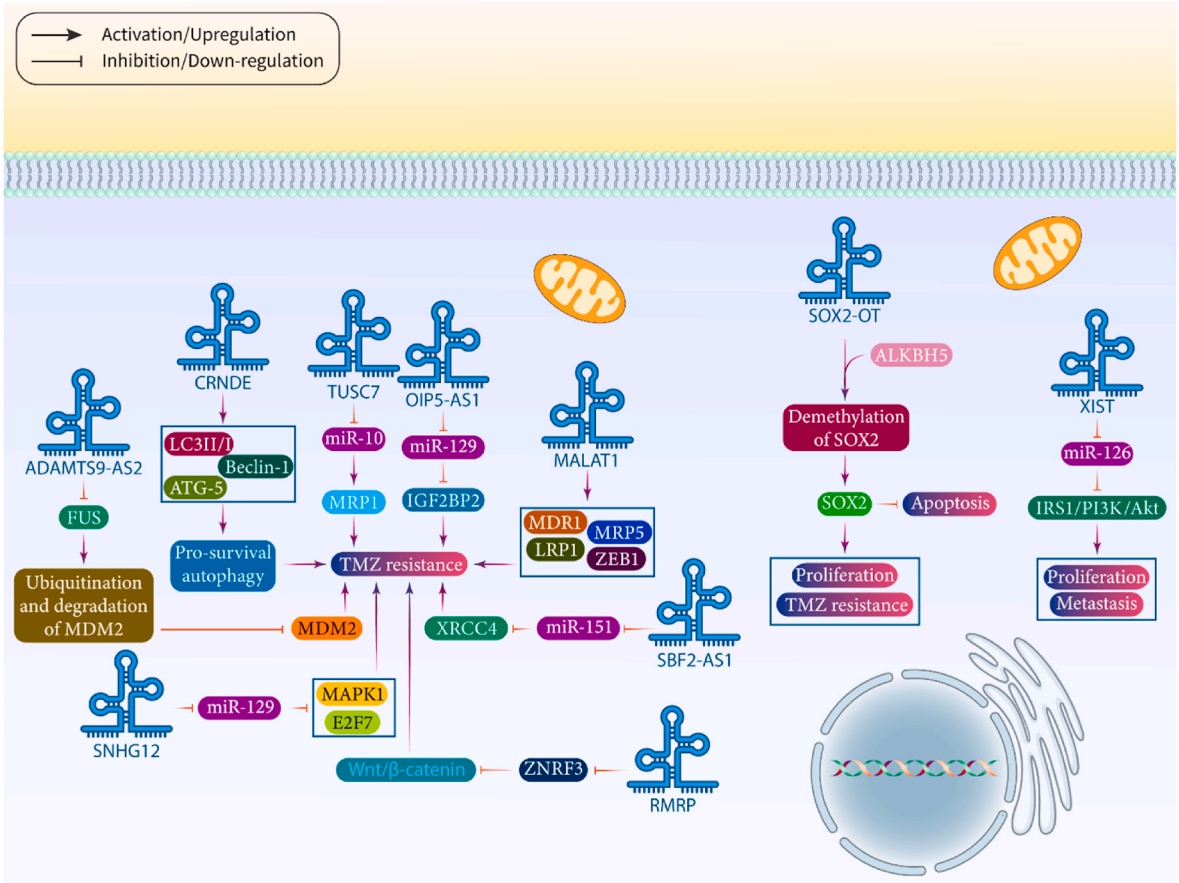

Fig. 3. LncRNAs and drug resistance in GBM. TMZ is the most common anti-cancer agent in GBM treatment. Apoptosis inhibition, metastasis acceleration and increased proliferation can lead to TMZ resistance in GBM. MALAT, SNHG12, SOX2-OT and TUSC7 are among the lncRNAs regulating TMZ resistance in GBM. Their interactions with downstream targets can affect drug resistance in GBM.

melanoma brought the novel idea that cancer treatment can be accelerated by immunotherapy [153]. The function of immune system and the reason of its development are to combat the attacks by microorganisms. The immune system works properly to distinguish between self and non-self-cells in the body [154]. The tumor cells have been developed as a result of genetic alterations and they are able to invade the function of immune system and establish different masses and colonies of cancer cells. In the recent years, the application of monoclonal antibodies and immune checkpoint inhibitors has improved the function of immune system against the tumor cells. However, the genetic alterations in the tumor cells can cause the resistance into immunotherapy and the GBM cells have also shown the potential for immune evasion. The oxidation of fatty acids can cause radio-resistance in GBM that collaborates with CD47 in the stimulation of immune evasion [36]. Moreover, aerobic glycolysis contributes to the immune evasion that can be induced by the upregulation of HK2 [155]. The overexpression of PD-L1 can be mediated by β-catenin that subsequently mediates the immune evasion [156]. An important hypothesis developed by Zhang and colleagues has shown that circ-EZH2 is able to encode EZH2-92aa that downregulates NKG2D ligands in the stimulation of immune evasion in GBM [157]. The infiltration of $CD8^+$ T cells into tumor microenvironment suppresses tumor growth. However, GBM cells increase expression level of PD-1 to induce immunosuppressive actions. It has been reported that β-catenin signaling increases expression level of PD-1 to reduce infiltration of $CD8^+$ T cells in GBM and to mediate immune evasion. Noteworthy, inhibiting β-catenin or Akt signaling decreases PD-1 expression that is of importance for inducing anti-tumor immunity against GBM [156]. The extracellular vesicles derived from GBM cells contain PD-L1 as the ligand of PD-1 that can bind to PD-1 to inhibit T-cell activation and proliferation, leading to immune evasion [158]. These studies highlight the fact that immune evasion commonly occurs in GBM. There is one experiment showing that lncRNAs may be involved in process of immune evasion in GBM. The clinical samples from GBM patients have demonstrated that PTRF induces immune evasion via increasing expression level of PD-L1. The immunosuppressive role of PTRF in GBM is attributed to its capacity in affecting expression level of lncRNA NEAT1. PTRF promotes stability and expression of NEAT1 to induce NF-κB signaling. Then, inhibition of UBXN1 occurs to increase transcription of PD-L1, leading to immune evasion in GBM. In fact, the stability of lncRNA NEAT1 can be affected by PTRF as upstream mediator. Owing to the oncogenic function of PTRF, it increases NEAT1 stability and expression to stimulate both NF-κB and PD-L1 pathways in immune evasion. Moreover, upregulated NEAT1 downregulates UBXN1 in upregulation of NF-κB. Subsequently, the activated NF-κB axis increases PD-L1 expression to cause immune evasion [159]. Since the expression level of miRNAs is regulated by lncRNAs and the miRNAs are able to modulate PD-L1 expression and other factors involved in immune evasion, the regulatory function of lncRNAs on the miRNA in terms of immune evasion should be evaluated. The macrophages and cancer-associated fibroblasts participates in the immune evasion in GBM that their regulation by lncRNAs requires investigation (Fig. 4).

7. Biomarker function

According to dysregulation of lncRNAs in GBM and their association with progression of tumor cells, there have been efforts in using them as biomarkers for diagnosis and prognosis [160]. Due to development in field of biology, researchers have created prognostic and diagnostic signatures from different lncRNAs to increase specificity in GBM patients. In a recent effort, four lncRNAs were used as signatures for evaluating prognosis of GBM patients. LncRNA H19, HOTAIRM1, AGAP2-AS1 and AC002456.1 are considered as high-risk lncRNAs in GBM and their low expression provides good prognosis of patients [161]. In another effort, 219 patients were examined and a signature of six lncRNAs was produced including lncRNA AC005013.5, UBE2R2-AS1, ENTPD1-AS1, RP11-89C21.2, AC073115.6, and XLOC_004803. This signature is associated with immune response of GBM cells and they can provide a better performance for risk stratification [162]. However, there have been also efforts in using single lncRNA as prognostic and diagnostic tools in GBM. It has been shown that lncRNA AGAP2-AS1 functions as a tumor-promoting factor in GBM and its overexpression decreases overall survival of patients. Silencing lncRNA AGAP2-AS1 impairs growth and metastasis of GBM cells and induces apoptosis in tumor. It can function as prognostic factor and its upregulation mediates poor survival of patients [163]. The development of signature for GBM prognosis and diagnosis is complicated and should

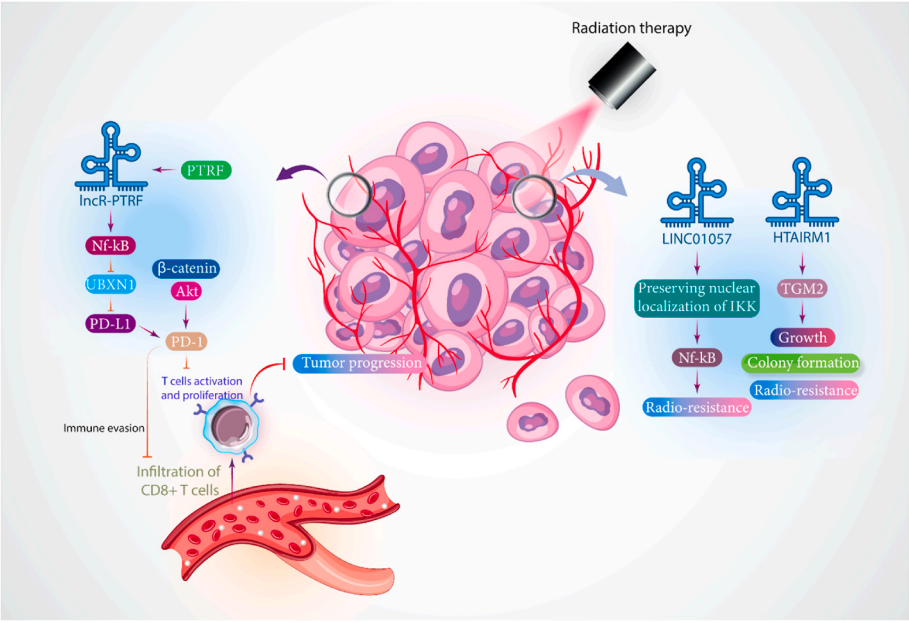

Fig. 4. LncRNAs, radio-resistance and immune evasion in GBM. Due to special location of GBM in brain, it is hard to do surgery for elimination of tumor cells. Furthermore, advanced stages of GBM cells lead to their dissemination to various regions of body. Therefore, radiotherapy is used to eliminate cancer cells. LINC01057, HTAIRM1 and PTRF can affect molecular pathways such as Akt, PD-1 and so on to regulate radiotherapy response and immune evasion of GBM cells.

be based on insights and validations from other experiments. For instance, a recent experiment has used 5 lncRNAs including AGAP2-AS1, STXBP5-AS1, DPP10-AS1, RNF144A-AS1, NDUFA6-DT for developing a signature in prognosis of GBM [164]. The results of this study appear to be validated and reliable, as previous researches confirm them. For instance, lncRNA AGAP2-AS1 is correlated with undesirable prognosis in GBM and it can increase proliferation and invasion of tumor cells [165,166]. For lncRNA STXBP5-AS1, although there is no evidence in GBM, but evaluations on other kinds of tumors demonstrate that abnormal expression of this lncRNA occurs in other kinds of tumors such as cervical cancer, gastric cancer and lung cancer [167–169]. For lncRNA DPP10-AS1 and RNF144A-AS1, their abnormal expressions have been shown in other cancers [170,171]. Therefore, such lncRNAs are potential and key players in cancer and understanding their expression level in GBM can greatly help in developing a reliable prognostic and diagnostic tool in GBM. Taking everything together, it appears that lncRNAs are reliable biomarkers in GBM and researchers have focused on developing signatures based on the most dysregulated lncRNAs for diagnosis and prognosis of GBM [133,172–180]. Table 2 provides a summary of lncRNAs involved in regulating GBM progression.

8. Conclusion and remarks

Cancer treatment is a troublesome problem and it is still incurable in spite of significant progresses in field of medicine. Among the cancers, treatment of brain tumors is more difficult compared to others due to presence of blood-brain barrier. The inability in treatment of brain tumors, especially GBM can result from poor understanding of genetic and epigenetic factors involved in their progression. One of the most dysregulated factors in GBM is lncRNAs and due to their function in affecting various mechanisms in cells, current review was allocated to understanding role of lncRNAs in GBM progression to pave the way for developing novel therapeutics in near future. The non-coding RNAs including miRNAs, lncRNAs and circRNAs. The new researches have focused on lncRNAs in cancer and their role in GBM is emerging. EMT induction promotes metastasis and invasion of GBM cells and lncRNAs are able to regulate EMT mechanisms in affecting migration of tumor cells. Furthermore, cell cycle progression and growth rate of GBM cells are tightly regulated by lncRNAs. The role of lncRNAs in increasing GBM progression has been approved in vitro and in vivo. Based on the experiments, silencing oncogenic lncRNAs interrupts GBM progression even in animal models and advocates the fact that novel therapeutics in near future can focus on targeting lncRNAs. Regardless of role of lncRNAs in proliferation and invasion of GBM cells, it has been shown that lncRNAs affect response of tumor cells to radiotherapy and chemotherapy. The most well-known and popular chemotherapeutic agent in treatment of GBM is TMZ and various kinds of oncogenic lncRNAs have been identified to be involved in triggering TMZ resistance in GBM cells. Furthermore, lncRNAs induce PD-1 expression to trigger immune evasion of GBM cells. One of the interesting points is the involvement of lncRNAs as biomarkers for GBM. The lncRNAs can be employed as diagnostic and prognostic factors in GBM and researchers have used bioinformatic tools to develop signatures of lncRNAs in providing prognosis and diagnosis of GBM patients with high specificity.

Currently, the lncRNAs can be divided into two types including tumor-suppressor and tumor-promoting factors. The lncRNAs including H19, TP73-AS1 and MALAT1 are oncogenic factors, while TUSC7, MIR143HG and SATB2-AS1 are onco-suppressor factors. As a result, a signature of such lncRNAs with highest dysregulation can be developed for predicting the response of GBM to therapy and also, application of prognostic factor. The lncRNAs HOTAIR, MALAT1, H19 and LINC-ROR [220] have been shown to regulate the survival rate and therefore, they can be utilized as prognostic and diagnostic factors in GBM. The studies have demonstrated that changes in the expression levels HOTAIR and SAMMSON are significant among others and their high levels can

Table 2
The role of lncRNAs in regulating GBM progression.

LncRNA	Signaling network	Remark	Ref
CASC2	miR-18a/EMT	Inhibiting proliferation of tumor cells in vitro and in vivo EMT inhibition and reducing invasion of cancer cells CASC2 suppresses EMT via miRNA-18a down-regulation	[181]
EWSAT1	miR-152–3p	Decreased expression level of miR-152–3p by lncRNA EWSAT1 Increasing growth and invasion of tumor cells Mediating tumor occurrence	[182]
FLVCR1-AS1	miR-30b-3p	Silencing lncRNA decreases growth and invasion of cancer cells LncRNA decreases miR-30b-3p expression via sponging	[183]
HOTAIRM1	miR-873–5p/ ZEB2	HOTAIRM1 acts as sponge and reduces expression level of miR-873–5p ZEB2 overexpression and increasing progression of tumor cells Apoptosis inhibition	[184]
Unigene56159	miR-194–5p	Acting as competing endogenous RNA to reduce expression level of miR-194–5p by Unigene56159 Enhancing proliferation and metastasis of cancer cells	[185]
SNHG11	miR-154–5p	Enhanced growth and metastasis of tumor cells by SNHG11 Overexpression of SNHG11 in GBM tissues Negative regulation of miR-154-5 by lncRNA SNHG11	[186]
DLEU1	TRAF4	Upregulation of DLEU1 and TRAF4 in GBM tissues Silencing DLEU1 decreases TRAF4 expression, showing direct and positive association Increasing growth rate of GBM cells	[187]
HOXB-AS1	miR-885–3p/ HOXB2	Localization of HOXB-AS1 in cytoplasm HOXB-AS1 decreases miR-885–3p expression via sponging to upregulate HOXB2 Enhancing proliferation and metastasis of tumor cells	[188]
LINC01426	miR-345–3p/ VAMP8	Overexpression of LINC01426 in GBM and positive association with progression of tumor cells LINC01426 decreases miR-345–3p expression to upregulate VAMP8	[189]
MIR22HG	Wnt/β-catenin	MIR22HG increases progression of GBM cells via induction of Wnt/ β-catenin	[179]
PRADX	PRC2/STAT3	Upregulation of PRADX in mesenchymal GBM PRADX recruits EZH2 to suppress BLCAP Activation of STAT3 signaling and increasing GBM progression	[190]
RP3-439F8.1	miR-139–5p/ NR5A2	Positive association of RP3-439F8.1 with GBM progression RP3-439F8.1 decreases miR-139–5p expression via sponging to increase NR5A2 expression	[191]
TPT1-AS1	miR-23a-5p/ ECM1	Increasing proliferation rate of GBM cells TPT1-AS1 promotes ECM1 expression via miR-23a-5p sponging	[192]
TUSC7	miR-10a	Poor expression of TUSC7 in cancer cells and tissues miR-10a down-regulation by TUSC7 to decrease	[123]

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Table 2 (*continued*)

LncRNA	Signaling network	Remark	Ref
		expression level of MDR1 in reversing temozolomide resistance	
CASP5	–	Overexpression of CASP5 in GBM cells Silencing CASP5 suppresses proliferation of GBM cells and stimulates G1 arrest Apoptosis induction Decreased invasion of GBM cells upon CASP5 knock-down	[193]
HOXA-AS2	miR-373/EGFR	Upregulation of HOXA-AS2 in tumor cells miR-373 down-regulation by HOXA-AS2 EGFR overexpression and subsequent increase in expression levels of MMP-2 and MMP-9 Mediating malignant behavior of glioma cells Inducing vasculogenic mimicry function	[194]
AC023115.3	miR-26a/ GSK3β/Mcl-1	Preventing cisplatin resistance in tumor cells Autophagy inhibition Apoptosis induction miR-26a down-regulation by AC023115.3 Overexpression of GSK3β to enhance Mcl-1 degradation	[195]
BCAR4	miR-2276/ MMP-7	Increased proliferation and metastasis of tumor cells Inducing carcinogenesis Overexpression of BCAR4 in tumor tissues and cells Down-regulation of miR-2276 by BCAR4 to promote MMP-7 expression	[196]
TUG1	miR-299/VEGF	Angiogenesis induction and increasing progression of GBM TUG1 promotes VEGF expression via miR-299 sponging Silencing TUG1 impairs tumor progression in vitro and in vivo	[197]
VIM-AS1	miR-105–5p/ WEE1	Apoptosis inhibition Enhanced growth and invasion of GBM cells Association of VIM-AS1 with poor prognosis miR-105–5p down-regulation by VIM-AS1 WEE1 overexpression and increasing tumor progression	[198]
FER1L4	–	Overexpression of FER1L4 in high-grade tumors compared to low-grade tumors Silencing FER1L4 by siRNA leads to apoptosis and a significant decrease in invasion and survival rate of tumor cells	[199]
LINC00525	miR-338–3p/ EMT	Silencing LINC00525 impaired invasion and metastasis of tumor cells LINC00525 increases mesenchymal markers and reduces epithelial markers EMT induction	[200]
UCA1	miR-182/ PFKFB2	CXCL14 undergoes overexpression in tumor cells and leads to an increase in expression level of UCA1 UCA1 decreases miR-182 expression to promote PFKFB2 expression, leading to glycolysis and increased progression of tumor cells	[201]
PVT1	miR-1301–3p/ TMBIM6	Upregulation of PVT1 in GBM cells and tissues PVT1 increases TMBIM6 expression via miR-1301–3p down-regulation	[202]

Table 2 (*continued*)

LncRNA	Signaling network	Remark	Ref
MYCNOS	miR-216b/ FOXM1	Increased growth rate of GBM cells Upregulation of MYCNOS in tumor cells and tissues MYCNOS promotes FOXM1 expression via miR-216b inhibition	[203]
RP1-86C11.7	miR-144–3p/ TFRC	RP1-86C11.7 promotes TFRC expression via miR-144–3p sponging Silencing RP1-86C11.7 impaired GBM progression	[204]
CRNDE	PI3K/Akt/ mTOR	Overexpression of CRNDE in tumor cells and mediating temozolomide resistance Increasing growth and survival of tumor cells Preventing apoptosis Autophagy induction via stimulation of PI3K/Akt/mTOR axis	[125]
HOTAIR	miR-301a-3p/ FOSL1	Enhanced proliferation and metastasis of tumor cells HOTAIR promotes FOSL1 expression via miR-301a-3p sponging Mediating tumor pathogenesis	[205]
PVT1	COPS5/TRIM24	PVT1 is involved in increasing GBM progression in vitro and in vivo PVT1 promotes colony formation and growth of tumor cells PVT1 recruits COPS5 to stabilize TRIM24	[206]
HOXD-AS2	miR-3681–5p/ MALT1	Increased growth and invasion of GBM cells miR-3681–5p down-regulation by HOXD-AS2 to enhance MALT1 expression in elevating GBM progression	[101]
LINC01410	miR-370–3p/ PTEN/Akt	Upregulation of LINC01410 in GBM cells Knock-down of LINC01410 decreases viability of tumor cells and induces apoptosis LINC01410 decreases miR-370–3p expression to induce Akt signaling via PTEN down-regulation	[94]
DLGAP1-AS1	miR-515–5p/ ROCK1/ NFE2L1/Wnt	Distinguished overexpression of DLGAP1-AS1 in GBM cells Silencing DLGAP1-AS1 stimulates apoptosis and reduces growth of tumor cells DLGAP1-AS1 sponges miR-515–5p to activate Wnt signaling	[207]
SOX2-OT	miR-192–5p/ RAB2A ERK	Knock-down of SOX2-OT induces apoptosis and decreases growth rate of tumor cells, demonstrating oncogenic function of this lncRNA in GBM SOX2-OT promotes RAB2A expression via miR-192–5p sponging SOX2-OT also induces ERK signaling	[97]
PITPNA-AS1	miR-223–3p/ EGFR/PI3K/Akt	LncRNA promotes growth of tumor cells and prevents apoptosis PIPNA-AS1 sequesters miR-223–3p to induce PI3K/Akt signaling via EGFR overexpression Exerting oncogenic function	[208]
HLA-F-AS1	MEG3	Overexpression of lncRNA HLA-F-AS1 in GBM cells and down-regulation of MEG3 Down-regulation of MEG3 by HLA-F-AS1 to increase proliferation of tumor cells and to prevent apoptosis	[209]
FEZF1-AS1	miR-363–3p/ NOB1	Upregulation of FEZF1-AS1 in GBM cells and tissues FEZF1-AS1 promotes NOB1	[210]

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Table 2 (*continued*)

LncRNA	Signaling network	Remark	Ref
		expression via miR-363–3p down-regulation Increasing growth rate of tumor cells	
RP11-390F4.3	miR-148a/ ROCK1	Overexpression of RP11-390F4.3 and ROCK1 in cancer cells and down-regulation of miR-148a RP11-390F4.3 promotes ROCK1 expression via miR-148a down-regulation Increasing metastasis of tumor cells	[211]
HOXC-AS3	miR-216/F11R	Increased progression of tumor cells in vitro and in vivo HOXC-AS3 promotes F11R expression via miR-216 sponging	[212]
Linc00645	miR-205–3p/ ZEB1	Linc00645 stimulates EMT and enhances metastasis of tumor cells Silencing linc00645 impaired tumor progression in vivo Linc00645 promotes ZEB1 expression via miR-205–3p down-regulation to stimulate EMT	[213]
SEMA3B-AS1	miR-195/cyclin D1	SEMA3B-AS1 promotes miR-195 expression to down-regulate cyclin D1 in impairing progression of tumor cells	[214]
LPP-AS2	miR-7-5p/ EGFR/PI3K/ Akt/c-Myc	Overexpression of LPP-AS2 and mediating carcinogenesis miR-7-5p sponging by LPP-AS2 to induce PI3K/Akt signaling in increasing cancer progression	[215]
XIST	miR-152	XIST promotes malignancy and progression of GBM cell Silencing XIST leads to miR-152 overexpression and impairing tumor progression	[216]
HOTAIR	HOXA9	HOXA9 promotes expression level of lncRNA HOTAIR in tumor cells Overexpression of HOTAIR mediates poor survival and prognosis	[217]
HOTAIR	EZH2	HOTAIR recruits EZH2 to exert its oncogenic function Silencing HOTAIR or down-regulating EZH2 can lead to GBM suppression	[218]
HIF1A-AS2	–	HIF1A-AS2 is vital for hypoxia adaptation of tumor cells and preserving stemness features	[219]

change the prognosis and survival rate of patients. Furthermore, since CSCs are regulated by GBM and they can participate in the relapse of GBM, the relevant lncRNAs including TP73-AS1 and LINC01503, among others, can be considered as factors involved in the recurrence of GBM. Noteworthy, the expression level of lncRNAs is mainly lower compared to protein-coding genes and therefore, the main candidates for GBM diagnosis should be detectable with current tests.

Ethics approval

Not applicable.

Consent to participate

I confirm that the all authors have contributed at least in the part of preparing this research and preparing the manuscript. I also paid attention to the Authorship Roles.

Consent for publication

I confirm that the all authors have consent for publication.

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Mehrdad Hashemi: Conceptualization. **Sophie Mousavian Roshanzamir:** Conceptualization. **Sima Orouei:** Validation. **Pouria Daneii:** Writing – original draft, Data curation. **Rasoul Raesi:** Writing – review & editing. **Haleh Zokaee:** Writing – review & editing, Data curation. **Pooria Bikarannejad:** Visualization, Investigation. **Kiana Salmani:** Visualization, Investigation. **Ramin Khorrami:** Writing – review & editing. **Mahshid Deldar Abad Paskeh:** Validation. **Shokooh Salimimoghadam:** Visualization, Investigation. **Mohsen Rashidi:** Supervision. **Kiavash Hushmandi:** Supervision. **Afshin Taheriazam:** Supervision. **Maliheh Entezari:** Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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