Radiotherapy (RT) is a key therapeutic strategy for lung cancer, the most common cause of cancer-related deaths worldwide, but radioresistance often occurs and leads to failure of RT. It is therefore important to clarify the mechanism underlying radioresistance in lung cancer. Cancer stem cells (CSCs) are considered the fundamental reason for radioresistance. MicroRNAs (miRNAs) have been regarded as important regulatory molecules of CSCs, carcinogenesis, and treatment response of cancers. It is crucial to clarify how regulation of miRNAs affects repair of DNA damage, redistribution, repopulation, reoxygenation, and radiosensitivity (5R) of lung cancer stem cells (LCSCs). A thorough understanding of the regulation of miRNAs affecting 5R of LCSCs has potential impact on identifying novel targets and thus may improve the efficacy of lung cancer radiotherapy.

1. Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide, and non-small-cell lung cancer (NSCLC) accounts for approximately 80–84% of all lung cancers [1]. Despite recent advances in understanding the molecular biology of lung cancer and introduction of new therapeutic agents to lung cancer treatment, only 15.9% of patients could survive for 5 years [2]. According to the latest Guidelines of National Comprehensive Cancer Network (NCCN) [2, 3], thoracic radiotherapy (TRT) is an important treatment for early- and advanced-stage NSCLC, as a radical or palliative therapy. For example, stereotactic body RT (SBRT) allows local tumor control rate to reach 85%–90% in unresectable patients with stage I-II disease [4, 5]. For patients with stage IIIA-IIIB cancer, concurrent chemoradiotherapy (CRT) would be potentially curative. About 60%–70% of all NSCLC patients develop one or more indications for a radical or palliative radiotherapy (RT) during the course of the disease [6]. However, most of radical or palliative RT cannot eradicate tumors, thus leading to relapse of residual tumors. The local recurrence rate for patients with advanced NSCLC who underwent conventionally fractionated radiotherapy (CFRT) (60 Gy/30 F/6 W) is up to 60%–70% in two years despite application of modern equipment and techniques [7]. Therefore, the radiobiological mechanism underlying radioresistance needs to be explored to improve the efficacy of RT.

2. Lung Cancer Stem Cells and Radioresistance

Numerous studies indicate that cancer stem cells (CSCs) may be the fundamental reason for carcinogenesis, metastasis, relapse, and chemoradioresistance of cancer [8–10]. Existence of CSCs has been confirmed in hematopoietic malignancies and all kinds of solid tumors [11, 12]. Lung cancer stem cells (LCSCs) have also been reported. These cells are a rare population with capabilities of unlimited self-renewal, multilineage differentiation, floating sphere formation, and evasion from cytotoxic cancer therapies. More than a dozen of cancer centers have identified and isolated LCSCs from lung cancer cell lines or primary lung tumors [13–28]. These
studies demonstrate that LCSCs possess heterogeneity with divergent surface markers (Table 1). Heterogeneity of CSCs is another topic, which will not be further discussed here.

Although there is no generally accepted surface marker, LCSCs have been widely explored for radioresistance phenotype. ALDH1$^+$ A549 and SK-BR-3 cells have stem-like properties and indication of radioresistance, which has been confirmed by colony formation assay and γH2AX (phosphorylated H2AX, H2AX is a family member of H2A) foci formation assay [48]. LCSCs sorted from lung cancer cell lines (H125, A549, H1299, and H23) show a reduced apoptotic response and increased survival after irradiation (IR) [49]. Another research indicates that IR decreases proliferation, increases apoptosis, and induces mitochondrial damage in main population (MP) cells, but not in side population (SP) cells which contribute to lung tumorigenesis [50]. All these studies demonstrate that LCSCs make crucial contribution to radioresistance. It is therefore significant to elucidate the radiobiological response of LCSCs, which may have translational implications.

### 3. MicroRNAs (miRNAs) Regulate Biological Behaviors of LCSCs

MiRNAs are a class of evolutionarily conserved, endogenous, small, noncoding RNAs about 17–27 nt in length, which result in translational repression and gene silencing, typically by binding to the 3'-untranslated region (3'-UTR) or amino acid coding sequence (CDS) of the complementary mRNA sequence. Until now, 2588 miRNAs have been identified in human beings (June 2014, the miR Base 21.0), which regulate 60% of the whole genome-wide genes [51]. It has been revealed that miRNAs may play important roles in the regulation of carcinogenesis, self-renewal and differentiation of CSCs, and cancer treatment [52].

A lot of miRNAs have been validated to cause unlimited self-renewal of LCSCs. Lung cancer SP cells express let-7 and miR-31 at lower levels than non-SP cells do. These two miRNAs play opposite roles to keep balance between differentiation and quiescence [53]. In other two studies on lung adenocarcinoma, miR-145 significantly inhibits the proliferation of LCSCs and reduces radiosensitivity by targeting Oct4/Sox2/Fascin1 [29, 30]. In our previous study, we combined paclitaxel with serum-free medium culture (inverse-induction) to enrich CD133$^+$CD326$^+$ subpopulation, featuring unlimited self-renewal capacity, from A549 cells. Aberrantly expressed miRNAs, such as miR-29ab, miR-183, miR-17-5p, and miR-127-3p, play critical roles in regulating CD133$^+$CD326$^+$ subpopulation [21]. Therefore, miRNAs could substantially affect the biobehaviors of LCSCs including their radiobiological response by controlling the signaling pathways of LCSCs. Here, we focus on the potential roles of miRNAs in affecting repair of DNA damage, redistribution, repopulation, reoxygenation, and radiosensitivity (5R).

### 4. Repair of DNA Damage

Cancer cell death during RT is mainly due to DNA double-strand breaks (DSBs) induced by IR. As a result, DNA damage response (DDR) is triggered. It initiates the repair of DNA damage by homologous recombination repair (HRR) or nonhomologous end-joining (NHEJ). This response involves multistep processes and multiple molecules, such as DNA-dependent protein kinase (DNA-PK), ataxia telangiectasia-mutated (ATM) kinase, Kruppel-associated protein 1 (KAPI), complementation group D2 (FANCd2), XRCC2, and XRCC4 [10, 49, 54]. It is reported that CSCs have a more efficient DNA repair mechanism [8, 9]. In ALDH1$^+$ LCSCs, repair of DSBs is enhanced [48], and expressions of γH2AX, DNA-PK, ATM, KAPI, and FANCd2 are increased [49]. To some degree, IR remains unselective and indiscriminate to eradicate persistent, drug-resistant tumor stem cell pools [55].

MiRNAs have been proved to regulate the expression of important targets in the DDR pathway. In our previous study, radioresistant lung cancer cells demonstrate stem cell-like properties and downregulated miR-18a expression [56]. And miR-18a inhibits the expression of ATM by constitutively binding to its 3'-UTR [31]. In that case, radioresistant lung cancer cells with downregulated miR-18a possess high capacity of DNA repair and HRR, high phosphorylation level, and nuclear foci formation of γH2AX and 53BP1 [31]. Other miRNAs, such as miR-7 [32] and miR-101 [33, 34], could also directly repress either DNA-PK or ATM and radiosensitize lung cancer cells in vitro and in vivo. In contrast, miR-210 promotes a more efficient repair of DSBs [35]. Thus, miRNAs could regulate DNA repair of LCSCs in multiple ways.

### 5. Redistribution

Tumor cells in different phases of cell cycle display different degrees of radiosensitivity. After IR, the remaining tumor cells less sensitive to radiation often increase their radiosensitivity through redistribution of cell cycle. However, CSCs
exhibit defect in the transition of G1/S and G2/M checkpoints during IR. LCSCs show a reduced apoptotic response, increased survival, less pronounced G2 phase arrest, and S/G2-phase block after IR [49].

Several miRNAs are involved in the regulation of cell cycle in LCSCs. MiR-31 and let-7 induce proliferation of lung cancer SP cells by impacting G0/G1 and G1/S phase transitions [53]. MiR-18a abrogates the IR-induced cell cycle arrest and sensitizes cells to IR [31]. MiR-574-5p significantly promotes the cell cycle entry by inhibiting checkpoint suppressor 1 (Ches1) [36]. MiR-193b represses the expressions of cyclins D1 and uPA and significantly decreases proliferation, migration, and invasion capacities of tumor cells [37]. MiR-26a greatly suppresses the enhancer of zeste homolog 2 (EZH2), inhibits cell proliferation, blocks GI/S transition, and induces tumor cell apoptosis [38]. Hence, miRNAs could play crucial roles in regulating redistribution of cell cycle in LCSCs.

6. Repopulation

Repopulation of tumor cells is one of the most common radiobiological responses responsible for the failure of IR. The regrowth rate of a tumor after a sublethal dose of radiation exceeds the growth rate of the untreated tumor. The repopulation of treatment-resistant lung cancer cells, usually with stem-like phenotype [12], is observed from an asymmetric type to a symmetric form in cell division that results in two proliferative daughter stem cells [57]. Signaling pathways, such as Notch, Wnt, and Hedgehog (Hh), able to realize the switch from an asymmetric to a symmetric form in cell division and induce stem cell apoptosis [39]. Hence, miRNAs could play crucial roles in regulating redistribution of cell cycle in LCSCs.

7. Reoxygenation

Reoxygenation during the interfraction intervals is generally believed to be able to improve the efficacy of IR by enhancing tumor radiosensitivity. It would be interesting to know more about the radiobiological response of CSCs at varying oxygenation levels. Under hypoxia, LCSCs elevate angiogenesis by releasing vascular growth factors, stromal-derived factor, and hypoxia-inducible factors (HIF) and yield highly vascularized remodeling in areas of vasculogenic mimicry [16, 64]. LCSCs are protected from radiation by increasing free radical scavengers and decreasing reactive oxygen species (ROS) [65].

Studies report that miRNAs take part in the process of reoxygenation in LCSCs. Under hypoxia, cancer cells expressing miR-210 show a lower mortality rate owing to a decrease in apoptosis, able to grow even at an IR dose of 10 Gy. A further study shows that miR-210 is induced by HIF-1 and stabilizes HIF-1 in turn through a positive regulatory loop [35]. Another study shows that hypoxia induces miR-155 expression. Vice versa, increasing miR-155 protects lung cancer cells from radiotherapy [42]. All these results confirm that miRNAs play roles in reoxygenation of LCSCs.

8. Radiosensitivity

Recently, radiosensitivity has been regarded as the 5th R in radiobiological response of tumors [66]. Basically, radiosensitivity is referred to as the sensitivity of tumor tissues. As mentioned above, the sensitivity of tumor tissues is determined by the CSC subpopulation. Since heterogeneity exists in LCSCs, radiosensitivity of CSCs is also controlled by internal molecules and signaling pathways.

In recent researches, many molecules and signaling pathways are found to function in self-renewal and radiosensitivity of LCSCs, including p53 mutation [67], Kras mutation [43], NF-κB1 activation [45], and senescence inhibition [46]. Studies reveal that miRNAs are usually involved in these signaling pathways. MiR-34 family, effector of p53 activation, significantly reduces cell survival at an IR dose lower than 4 Gy [47]. A regulatory network (let-7-lin28) formed by let-7a and its repressor lin28 keeps the balance of Kras function by attenuating or activating Kras expression [43, 44]. Down-regulated miR-9 and let-7g play critical roles in activation of NF-κB1 [45]. Uregulated miR-214 is the essential reason for radiosensitivity by inhibiting senescence [46].

In addition, some miRNAs play duplicate or multiple roles in regulating radiobiology of LCSCs. For example, miR-210 could stabilize HIF to promote DNA repair [35] and activate Notch signaling pathway in angiogenesis [60]. And some miRNA families (miR-34 family [47], miR-30 family [68], miR-8/200 family [65], and let-7-lin28 family [43, 44]) are involved in radiosensitivity of LCSCs. These miRNAs, located in the intersection of different signaling pathways, are possible targets for therapeutic strategies to overcome radiosensitivity of LCSCs.

9. Potential Therapeutic Strategies

Since LCSCs are the source of radioresistance of lung cancer, it seems reasonable and promising to cure lung cancer by eliminating this subpopulation. Mounting preclinical data on putative LCSC target have emerged. For example, LCSCs express c-kit receptor and produce stem cell factor (SCF), and blocking SCF–c-kit signaling by SCF-neutralizing antibodies or by imatinib (Gleevec) is sufficient to abrogate LCSC proliferation and improve antitumor efficacy [69]. Some potential therapeutic strategies are developed from the knowledge of
miRNA involvement in the radioresistance mechanisms in LCSCs. Combining an artificial miRNA (amiR) designed to target 3′-UTR of XRCC2 (an HRR factor) or XRCC4 (an NHEJ factor) with an siRNA to target the gene coding region could more efficiently knock down these genes and radiosensitize lung cancer cells to IR-induced killing [70]. Overexpressed miR-18a is used to downregulate ATM expression by targeting its 3′-UTR and to sensitize cells to IR [31]. Thus, based on the 5R radiobiology, interventions should be given at any level of radiobiological response from repair of DNA damage to reoxygenation and radiosensitivity. We could expand predictions for different therapeutic strategies in combination with radiation. On the one hand, miRNA agonir (for underexpressed miRNAs in LCSCs) or antagonir (for overexpressed miRNAs in LCSCs) should be used in combination with IR to eliminate LCSCs [56]. On the other hand, characteristic miRNAs should be used to selectively image LCSCs by fluorescence in vivo. We utilize mir-155, an miRNA enriched in lung cancer cells and LCSCs, combined with molecular beacon to image lung cancer cells in vivo [71]. Theoretically, the best approach should be able to monitor CSCs accurately in malignant tissues. A higher dose of IR could thus be given to the CSC-enriching areas so that radioresistance would be managed aggressively [72]. It must be emphasized, however, that at the time of writing this review, lots of approaches to modify radiobiology have not been developed yet. And individual patients differ in their tolerance to RT. If findings on miRNAs associated with radiobiological response of LCSCs could be translated into clinical application, it would be possible to improve the efficacy of radiotherapy.

10. Conclusions

By summarizing the principles in modulated radiobiology, we list the important miRNAs and their potential roles in regulating radiobiological response of LCSCs (Table 2). We also draw a diagram on theoretical radiobiology of LCSCs and regulatory miRNAs (Figure 1). Collectively, after IR, the volume of lung tumor decreases, and LCSCs are enriched in the remaining tumors and their percentage increases. The LCSCs not completely sterilized by IR demonstrate an aberrant miRNA profile including overexpressed miRNAs (miR-210, miR-155, let-7, etc.) and underexpressed miRNAs (miR-43a, miR-18a, miR-145, etc.). Therefore, DNA repair and repopulation of LCSCs are enhanced, while redistribution and reoxygenation are blocked, and radiosensitivity decreases, leading to the comprehensive effects of radioresistance.

Accumulating evidence indicates that LCSCs and miRNAs play critical roles in the radiobiological response in lung cancer, and they can effectively control tumor radiosensitivity by affecting pathogenetic cascade of radiobiological effects. Improved understanding of the radiobiology involved in radioresistance offers great promise for developing more effective cancer therapies. Further studies are needed to better understand the mechanism underlying radioresistance and to find a powerful tool to cure lung cancer.
Figure 1: MiRNAs regulate 5R of lung cancer stem cells (LCSCs). After irradiation, lung tumor size is reduced while LCSCs are enriched in the remaining tumors. An aberrant miRNA profile in LCSCs includes over- and underexpressed miRNAs. Thus, DNA repair and repopulation of LCSCs are enhanced, whereas redistribution and reoxygenation are blocked, and radiosensitivity decreases, leading to radioresistance.

Abbreviations
5R: Repair of DNA damage, redistribution, repopulation, reoxygenation, and radiosensitivity
CSCs: Cancer stem cells
LCSCs: Lung cancer stem cells
RT: Radiotherapy
TRT: Thoracic radiotherapy
IR: Irradiation
DDR: DNA damage response.

Conflict of Interests
The authors declare that they have no competing interests.

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References
[1] A. Jemal, F. Bray, M. M. Center, J. Ferlay, E. Ward, and D. Forman, “Global cancer statistics,” CA Cancer Journal for Clinicians, vol. 61, no. 2, pp. 69–90, 2011.
[2] D. S. Ettinger, W. Akerley, H. Borghaei et al., “Non-small cell lung cancer: clinical practice guidelines in oncology,” Journal of the National Comprehensive Cancer Network, vol. 10, no. 10, pp. 1236–1271, 2012.
[3] A.-R. Jazieh, H. Bamefleh, A. Demirkazik et al., “Modification and implementation of NCCN guidelines on non-small cell lung cancer in the Middle East and North Africa region,” Journal of the National Comprehensive Cancer Network, vol. 8, supplement 3, pp. S16–S21, 2010.
[4] A. van Baardwijk, W. A. Tomé, W. van Elmpt et al., “Is high-dose stereotactic body radiotherapy (SBRT) for stage i non-small cell lung cancer (NSCLC) overtreatment? A systematic review,” Radiotherapy and Oncology, vol. 105, no. 2, pp. 145–149, 2012.
[5] S. Senthi, C. J. A. Haasbeek, B. J. Slotman, and S. Senan, “Outcomes of stereotactic ablative radiotherapy for central lung tumours: a systematic review,” Radiotherapy and Oncology, vol. 106, no. 3, pp. 276–282, 2013.
[6] S. Tyldesley, C. Boyd, K. Schulze, H. Walker, and W. J. Mackillop, “Estimating the need for radiotherapy for lung cancer: an evidence-based, epidemiologic approach,” International Journal of Radiation Oncology Biology Physics, vol. 49, no. 4, pp. 973–985, 2001.
[7] B. Dessard-Diana, D. Manoux, C. Diana, M. Housset, and F. Baillet, “Discussion on the role of radiotherapy in non-small cell lung cancer apropos of 137 non-metastatic cases,” Cancer Radiothérapie, vol. 1, no. 2, pp. 154–158, 1997.
[8] S.-H. Chiou, C.-L. Kao, Y.-W. Chen et al., “Identification of CD133-positive radioreistant cells in atypical teratoid/rhabdoid tumor,” PLoS ONE, vol. 3, no. 5, Article ID e2090, 2008.
[9] S. Bao, Q. Wu, R. E. McLendon et al., “Glioma stem cells promote radioresistance by preferential activation of the DNA damage response,” Nature, vol. 444, no. 7120, pp. 756–760, 2006.
[10] F. Pajonk, E. Vlashi, and W. H. McBride, “Radiation resistance of cancer stem cells: the 4 Rs of radiobiology revisited,” Stem Cells, vol. 28, no. 4, pp. 639–648, 2010.
[11] T. Lipidot, C. Sirard, J. Vormoor et al., “A cell initiating human acute myeloid leukaemia after transplantation into SCID mice,” Nature, vol. 367, no. 6464, pp. 645–648, 1994.
[12] Á. Fábián, G. Vereb, and J. Szöllösi, “The hitchhikers guide to cancer stem cell theory: markers, pathways and therapy,” Cytometry Part A, vol. 83, no. 1, pp. 62–71, 2013.

[13] Y. Shi, X. Fu, Y. Hua, Y. Han, Y. Lu, and J. Wang, “The side population in human lung cancer cell line NCI-H460 is enriched in stem-like cancer cells,” PLoS ONE, vol. 7, no. 3, Article ID e33358, 2012.

[14] M. M. Ho, A. V. Ng, S. Lam, and J. Y. Hung, “Side population in human lung cancer cell lines and tumors is enriched with stem-like cancer cells,” Cancer Research, vol. 67, no. 10, pp. 4827–4833, 2007.

[15] S. Singb, N. Bora-Singhal, J. Kroger, H. Laklai, and S. P. Chellappan, “βarrestin-1 and Mcl-1 modulate self-renewal growth of cancer stem-like side-population cells in non-small cell lung cancer,” PLoS ONE, vol. 8, no. 2, Article ID e55982, 2013.

[16] B. Cao, J. Jia, L. Ma et al., “Recombinant human endostatin could eliminate the pro-angiogenesis priority of SP cells sorted from non-small cell lung cancer cells,” Clinical and Translational Oncology, vol. 14, no. 8, pp. 575–585, 2012.

[17] C. F. Bender Kim, E. L. Jackson, A. E. Woolfenden et al., “Identification of bronchioalveolar stem cells in normal lung and lung cancer,” Cell, vol. 121, no. 6, pp. 823–835, 2005.

[18] A. Eramo, F. Lotti, G. Sette et al., “Identification and expansion of the tumorigenic lung cancer stem population,” Cell Death and Differentiation, vol. 15, no. 3, pp. 504–514, 2008.

[19] P. Wang, Z. Suo, M. Wang et al., “In vitro and in vivo properties of CD133 expressing cells from human lung cancer cell lines,” Experimental Hematology & Oncology, vol. 2, no. 1, article 16, 2013.

[20] X. Meng, M. Li, X. Wang, Y. Wang, and D. Ma, “Both CD33+ and CD133+ subpopulations of A549 and H446 cells contain cancer-initiating cells,” Cancer Science, vol. 100, no. 6, pp. 1040–1046, 2009.

[21] S. Lin, J.-G. Sun, J.-B. Wu et al., “Aberrant microRNAs expression in CD133+/CD326+ human lung adenocarcinoma initiating cells from A549,” Molecules and Cells, vol. 33, no. 3, pp. 277–283, 2012.

[22] E. L.-H. Leung, R. R. Fiscus, J. W. Tung et al., “Non-small cell lung cancer cells expressing CD44 are enriched for stem cell-like properties,” PLoS ONE, vol. 5, no. 11, Article ID e14062, 2010.

[23] K. Okudela, T. Woo, H. Mitsui, M. Tajiri, M. Masuda, and K. Ohashi, “Expression of the potential cancer stem cell markers, CD133, CD44, ALDH1, and β-catenin, in primary lung adenocarcinoma-their prognostic significance,” Pathology International, vol. 62, no. 12, pp. 792–801, 2012.

[24] X. Li, L. Wan, J. Geng, C.-L. Wu, and X. Bai, “Aldehyde dehydrogenase 1A1 possesses stem-like properties and predicts lung cancer patient outcome,” Journal of Thoracic Oncology, vol. 7, no. 8, pp. 1235–1245, 2012.

[25] W. C. Zhang, N. Shyh-Chang, H. Yang et al., “Glycine decarboxylase activity drives non-small cell lung cancer tumor-initiating cells and tumorigenesis,” Cell, vol. 148, no. 1-2, pp. 259–272, 2012.

[26] F. Karimi-Busheri, V. Zadorozhny, T. Li, H. Lin, D. L. Shawler, and H. Fakhrai, “Pivotal role of CD38 biomarker in combination with CD24, EpCAM, and ALDH for identification of H460 derived lung cancer stem cells,” Journal of Stem Cells, vol. 6, no. 1, pp. 9–20, 2011.

[27] Y. Zheng, C. C. de la Cruz, L. C. Sayles et al., “A rare population of CD24+ITGB4+Notch1+ cells drives tumor propagation in NSCLC and requires Notch3 for self-renewal,” Cancer Cell, vol. 24, no. 1, pp. 59–74, 2013.

[28] Z. Xiao, Q. Jiang, J. Willette-Brown et al., “The pivotal role of IKKα in the development of spontaneous lung squamous cell carcinomas,” Cancer Cell, vol. 23, no. 4, pp. 527–540, 2013.

[29] G.-Y. Chiou, J.-Y. Cheng, H.-S. Hsu et al., “Cationic polyurethanes-short branch PEI-mediated delivery of Mir145 inhibited epithelial-mesenchymal transdifferentiation and cancer stem-like properties and in lung adenocarcinoma,” Journal of Controlled Release, vol. 159, no. 2, pp. 240–250, 2012.

[30] S. Zhang, Y. Wu, D. Feng et al., “miR-145 inhibits lung adenocarcinoma stem cells proliferation by targeting OCT4 gene,” Chinese Journal of Lung Cancer, vol. 14, no. 4, pp. 317–322, 2011.

[31] L. Song, C. Lin, Z. Wu et al., “MiR-18a impairs DNA damage response through downregulation of Ataxia telangiectasia mutated (ATM) kinase,” PLoS ONE, vol. 6, no. 9, Article ID e25454, 2011.

[32] K. M. Lee, E. J. Choi, and I. A. Kim, “MicroRNA-7 increases radiosensitivity of human cancer cells with activated EGFR-associated signaling,” Radiotherapy and Oncology, vol. 101, no. 1, pp. 171–176, 2011.

[33] S. Chen, H. Wang, W. L. Ng, W. J. Curran, and Y. Wang, “Radiosensitizing effects of ectopic miR-101 on non-small-cell lung cancer cells depend on the endogenous miR-101 level,” International Journal of Radiation Oncology Biology Physics, vol. 81, no. 5, pp. 1524–1529, 2011.

[34] D. Yan, W. L. Ng, X. Zhang et al., “Targeting DNA-PKcs and ATM with miR-101 sensitizes tumors to radiation,” PLoS ONE, vol. 5, no. 7, Article ID e13197, 2010.

[35] S. Grosso, J. Doyen, S. K. Parks et al., “MiR-210 promotes a hypoxic phenotype and increases radioresistance in human lung cancer cell lines,” Cell Death and Disease, vol. 4, no. 3, article e544, 2013.

[36] Q. Li, X. Li, Z. Guo et al., “MicroRNA-574-5p was pivotal for TL9 signaling enhanced tumor progression via down-regulating checkpoint suppressor 1 in human lung cancer,” PLoS ONE, vol. 7, no. 11, Article ID e48278, 2012.

[37] H. Hu, S. Li, J. Liu, and B. Ni, “MicroRNA-193b modulates proliferation, migration, and invasion of non-small cell lung cancer cells,” Acta Biochimica et Biophysica Sinica, vol. 44, no. 5, pp. 424–430, 2012.

[38] X. Dang, A. Ma, L. Yang et al., “MicroRNA-26a regulates tumorigenic properties of EZH2 in human lung carcinoma cells,” Cancer Genetics, vol. 205, no. 3, pp. 113–123, 2012.

[39] M. Saito, H. I. Suzuki, M. Horie et al., “An integrated expression profiling reveals target genes of TGF-beta and TGF-alpha possibly mediated by microRNAs in lung cancer cells,” PLoS ONE, vol. 8, no. 2, Article ID e56587, 2013.

[40] M. Cao, M. Seike, C. Soeno et al., “MiR-23a regulates TGF-β-induced epithelial-mesenchymal transition by targeting E-cadherin in lung cancer cells,” International Journal of Oncology, vol. 41, no. 3, pp. 869–875, 2012.

[41] L. Zhi-Yong, Z. Guang-Ling, W. Mei-Mei, X. Ya-Nan, and C. He-Qin, “MicroRNA-663 targets TGFB1 and regulates lung cancer proliferation,” Asian Pacific Journal of Cancer Prevention, vol. 12, no. 11, pp. 2819–2823, 2011.

[42] J. A. Babar, J. Czochor, A. Steinmetz, J. B. Weidhaas, P. M. Glazer, and F. J. Slack, “Inhibition of hypoxia-induced miR-155 radiosensitizes hypoxic lung cancer cells,” Cancer Biology and Therapy, vol. 12, no. 10, pp. 908–914, 2011.

[43] J.-S. Oh, J.-J. Kim, J.-Y. Byun, and I.-A. Kim, “Lin28-let7 modulates radiosensitivity of human cancer cells with activation of K-Ras,” International Journal of Radiation Oncology Biology Physics, vol. 76, no. 1, pp. 5–8, 2010.
S.-H. Jeong, H.-G. Wu, and W.-Y. Park, “LIN28B confers radioresistance through the posttranscriptional control of KRAS,” Experimental and Molecular Medicine, vol. 41, no. 12, pp. 912–918, 2009.

H. Arora, R. Qureshi, S. Jin, A.-K. Park, and W.-Y. Park, “miR-9 and let-7g enhance the sensitivity to ionizing radiation by suppression of NFκB,” Experimental and Molecular Medicine, vol. 43, no. 5, pp. 298–304, 2011.

H. Salim, N. S. Akbar, D. Zong et al., “miRNA-214 modulates radiotherapy response of non-small cell lung cancer cells through regulation of p38MAPK, apoptosis and senescence,” British Journal of Cancer, vol. 107, no. 8, pp. 1361–1373, 2012.

J. Balca-Silva, S. S. Neves, A. C. Gonçalves et al., “Effect of miR-34b overexpression on the radiosensitivity of non-small cell lung cancer cell lines,” Anticancer Research, vol. 32, no. 5, pp. 1603–1609, 2012.

I. Mühlisch, M. Toulany, P. M. Bareiss et al., “Selection of radioresistant tumor cells and presence of ALDH1 activity in vitro,” Radiotherapy & Oncology, vol. 99, no. 3, pp. 300–306, 2011.

L. Lundholm, P. Hååg, D. Zong et al., “Resistance to DNA-damaging treatment in non-small cell lung cancer tumor-initiating cells involves reduced DNA-PK/ATM activation and diminished cell cycle arrest,” Cell Death & Disease, vol. 4, article e478, 2013.

P. Xia, W.-F. Gou, J.-J. Wang et al., “Distinct radiosensitivity of lung carcinoma stem-like side population and main population cells,” Cancer Biotherapy and Radiopharmaceuticals, vol. 28, no. 6, pp. 471–478, 2013.

R. C. Friedman, K. K.-H. Farh, C. B. Burge, and D. P. Bartel, “Most mammalian miRNAs are conserved targets of microRNAs,” Genome Research, vol. 19, no. 1, pp. 92–105, 2009.

P. Sartipy, B. Olsson, J. Hyllner, and J. Synnergren, “Regulation of ‘stemness’ and stem cell differentiation by microRNAs,” IDrugs, vol. 12, no. 8, pp. 492–496, 2009.

S. Hua, X. Xiaotao, G. Renhua et al., “Reduced miR-31 and let-7 maintain the balance between differentiation and quiescence in lung cancer stem-like side population cells,” Biomedicine and Pharmacotherapy, vol. 66, no. 2, pp. 89–97, 2012.

L. Zhao, A. M. Bode, Y. Cao, and Z. Dong, “Regulatory mechanisms and clinical perspectives of microRNA in tumor radiosensitivity,” Carcinogenesis, vol. 33, no. 11, pp. 2220–2227, 2012.

H. Willers, C. G. Azzoli, W. L. Santivasi, and F. Xia, “Basic mechanisms of therapeutic resistance to radiation and chemotherapy in lung cancer,” Cancer Journal, vol. 19, no. 3, pp. 200–207, 2013.

L. Wu, J. G. Sun, R. Xu et al., “miR-18a enhancing radiosensitivity of A549 cells and its molecular mechanism,” The Journal of Third Military Medical University, vol. 35, no. 9, pp. 870–873, 2013 (Chinese).

Y. Tang, J. Hou, G. Li et al., “ABCG2 regulates the pattern of self-renewing divisions in cisplatin-resistant non-small cell lung cancer cell lines,” Oncology Reports, vol. 32, no. 5, pp. 2168–2174, 2014.

J. D. O’Flaherty, M. Barr, D. Fennell et al., “The cancer stem-cell hypothesis: Its emerging role in lung cancer biology and its relevance for future therapy,” Journal of Thoracic Oncology, vol. 7, no. 12, pp. 1880–1890, 2012.

V. Tirino, R. Camerlingo, K. Bifulco et al., “TGF-β1 exposure induces epithelial to mesenchymal transition both in CSCs and non-CSCs of the A549 cell line, leading to an increase of migration ability in the CD133+ A549 cell fraction,” Cell Death and Disease, vol. 4, no. 5, article e620, 2013.

Y.-L. Lou, F. Guo, F. Liu et al., “MiR-210 activates notch signaling pathway in angiogenesis induced by cerebral ischemia,” Molecular and Cellular Biochemistry, vol. 370, no. 1-2, pp. 45–51, 2012.

V. G. Da Ros, I. Gutierrez-Perez, D. Ferres-Marco, and M. Dominguez, “Dampening the signals transduced through hedgehog via microRNA miR-7 facilitates notch-induced tumourigenesis,” PLoS Biology, vol. 11, no. 5, Article ID e1001554, 2013.

D. M. Vallejo, E. Caparros, and M. Dominguez, “Targeting Notch signalling by the conserved miR-8/200 microRNA family in development and cancer cells,” The EMBO Journal, vol. 30, no. 4, pp. 756–769, 2011.

G. Song, Y. Zhang, and L. Wang, “MicroRNA-206 targets notch3, activates apoptosis, and inhibits tumor cell migration and focus formation,” Journal of Biological Chemistry, vol. 284, no. 46, pp. 31921–31927, 2009.

H. Iida, M. Suzuki, R. Goitsuka, and H. Ueno, “Hypoxia induces CD133 expression in human lung cancer cells by up-regulation of OCT3/4 and SOX2,” International Journal of Oncology, vol. 40, no. 1, pp. 71–79, 2012.

M. Diehn, R. W. Cho, N. A. Lobo et al., “Association of reactive oxygen species levels and radiosensitivity in cancer stem cells,” Nature, vol. 458, no. 7239, pp. 780–783, 2009.

J. M. Brown, D. J. Carlson, and D. J. Brenner, “The tumor radiobiology of SRS and SBRT: are more than the 5 Rs involved?” International Journal of Radiation Oncology Biology Physics, vol. 88, no. 2, pp. 254–262, 2014.

B. Liu, H. Zhang, X. Duan et al., “Adenovirus-mediated wild-type p53 transfer radiosensitizes H1299 cells to subclinical-dose carbon-ion irradiation through the restoration of p53 function,” Cancer Biotherapy and Radiopharmaceuticals, vol. 24, no. 1, pp. 57–65, 2009.

G. Bridge, R. Monteiro, S. Henderson et al., “The microRNA-30 family targets DLI4 to modulate endothelial cell behavior during angiogenesis,” Blood, vol. 120, no. 25, pp. 5063–5072, 2012.

V. Levina, A. Marrangoni, T. Wang et al., “Elimination of human lung cancer stem cells through targeting of the stem cell factor-c-kit autocrine signaling loop,” Cancer Research, vol. 70, no. 1, pp. 338–346, 2010.

Z. Zheng, W. L. Ng, X. Zhang et al., “RNAi-mediated targeting of noncoding and coding sequences in DNA repair gene messages efficiently radiosensitizes human tumor cells,” Cancer Research, vol. 72, no. 5, pp. 1221–1228, 2012.

Q. Yao, A.-M. Zhang, H. Ma et al., “Novel molecular beacons to monitor microRNAs in non-small-cell lung cancer,” Molecular and Cellular Probes, vol. 26, no. 5, pp. 182–187, 2012.

M. Baumann, M. Krause, and R. Hill, “Exploring the role of cancer stem cells in radioresistance,” Nature Reviews Cancer, vol. 8, no. 7, pp. 545–554, 2008.