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Deregulated MicroRNA Signature Following Glioblastoma Irradiation

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Abstract

Glioblastoma (GBM), the most common and aggressive brain tumor in adults, shows resistance to treatment, particularly radiotherapy. One method for effective treatment is using a group of radiosensitizers that make tumor cells responsive to radiotherapy. A class of molecules whose expression is affected by radiotherapy is the microRNAs (miRNAs) that present promising regulators of the radioresponse. Eighteen miRNAs (miR-26a, -124, -128, -135b, -145, -153, -181a/b, -203, -21, -210, -212, -221/222, -223, -224, -320, and -590), involved in the pathogenesis of GBM and its radioresponsive state, were reviewed to identify their role in GBM and their potential as radiosensitizing agents. MicroRNAs-26a, -124, -128, -145, -153, -181a/b, -203, -221/222, -223, -224, -320, and -590 promoted GBM radiosensitivity, while microRNAs-135b, -21, -210, and -212 encouraged radioresistance. Ectopic overexpression of the radiosensitivity promoting miRNAs and knockdown of the radioresistant miRNAs represent a prospective radiotherapy enhancement opportunity. This offers a glimmer of hope for a group of the most unfortunate patients known to medicine.

Keywords

Glioblastoma, microRNAs, radioresistance, radiosensitivity, review

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Introduction

Glioblastoma (GBM) is the most common and lethal brain tumor in adults.[1,2] It is a grade IV tumor characterized by a heterogeneous population of cells that are genetically unstable, highly infiltrative, angiogenic, and resistant to chemotherapy and radiotherapy.[3] Exploring the mechanisms underlying tumor resistance and recurrence is warranted to design future molecularly targeted therapies.[2]

The current first-line therapy is surgical resection, followed by a combination of the chemotherapeutic agent temozolomide (TMZ) and regional fractionated ionizing radiation (IR).[4] In addition, personalized therapeutic modalities against molecular deregulated targets that drive tumor growth have been tried in several clinical trials. However, almost all patients with GBM undergo inevitable tumor recurrence.[1,3] This could be attributed to the incomplete resection of the infiltrative tumor tissues, as well as the extensive hypoxic nature of GBM tumors that limits the efficiency of chemotherapy and radiotherapy.[5,6]

Multiple factors can affect resistance to radiotherapy, for example, tumor location, size, microenvironment, and most

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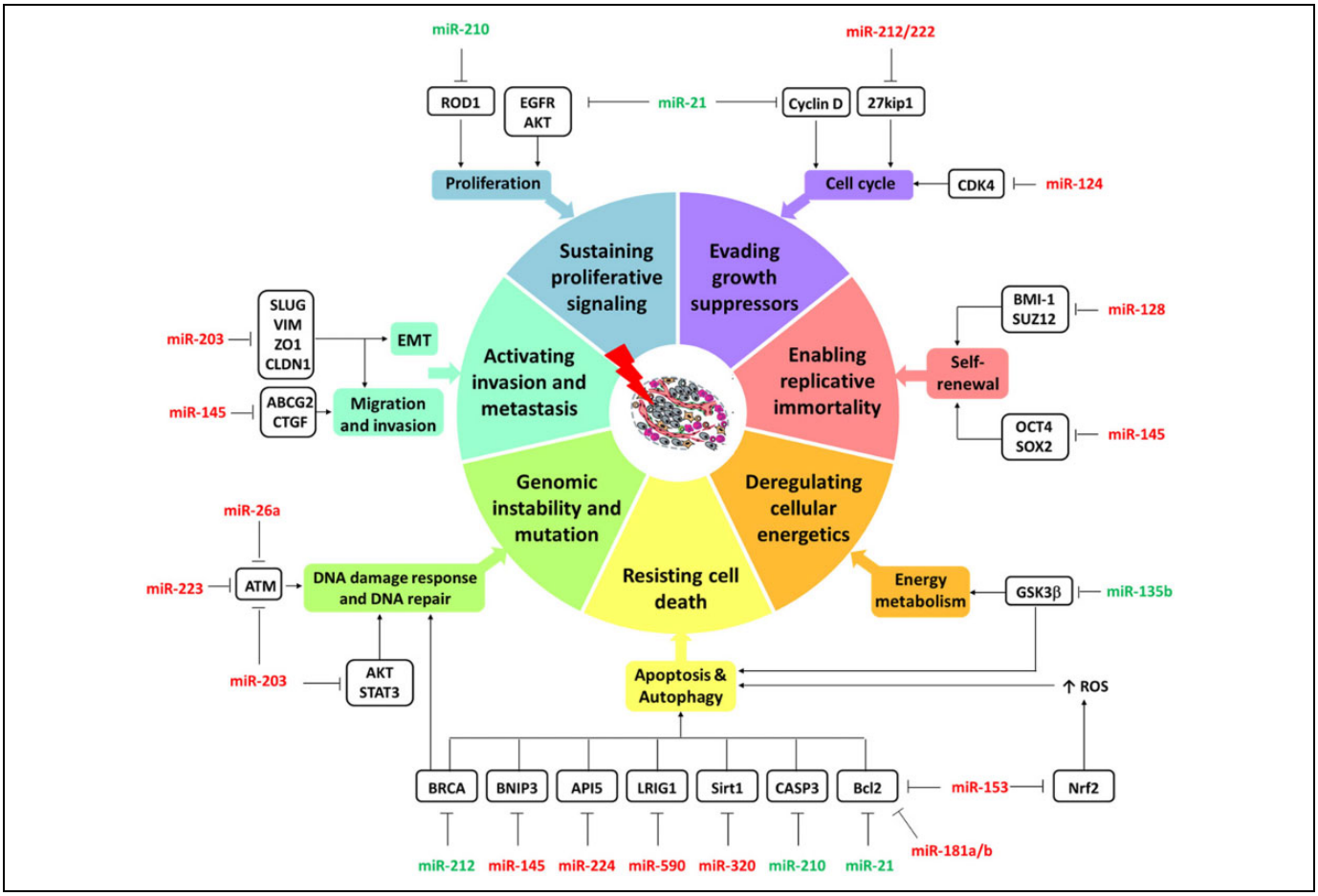

Figure 1. Mechanisms of radioresistance in glioblastoma (GBM). The figure shows deregulated microRNAs following irradiation of GBM. They are involved in hallmarks of cancer (colored donut). Micro-RNAs-26a, -124, -128, -145, -153, -181a/b, -203, -221/222, -223, -224, -320, and -590 (red) promoted GBM radiosensitivity, while microRNAs-135b, -21, -210 and -212 (green) encouraged radioresistance via targeting various cancer-related genes (black box).

importantly, genetic influences.[7] Some of the major genetic elements regulating tumorogenesis as well as the radioresistance are microRNAs (miRNAs). In the following sections, we will address the role of miRNAs in GBM and the differential miRNA genomic landscape of pre- and posttreated GBM cells for a better understanding of the miRNA-related tumor regression and resistance.

MicroRNAs: Key Players in Glioblastoma

MicroRNAs are small noncoding RNA molecules that regulate gene expression at a posttranscriptional level by either cleaving or repressing the translation of messenger RNA targets via binding to complementary sequence.[8] They control various cellular processes including apoptosis, proliferation, cell cycle, invasion, and angiogenesis.[9] Several miRNAs have been recently reported to be involved in modulation of GBM development and progression.[10] The miRNAs can function as oncogenes or tumor suppressors according to the genes or pathways that they target.[11] Emerging evidence demonstrated the potential role of miRNAs in the response of chemotherapy and radiotherapy, a finding that opens new avenues for identifying potentially more effective therapeutic targets in an attempt of improving patient survival.[12]

Role of MicroRNAs in Modulation of Radiosensitivity in Glioblastoma

Radiotherapy is widely used in cancer treatment and biological studies where the IR damages cancer cells through producing free radicals and intermediate ions that cause single- or double-stranded breaks in the DNA. This usually triggers activation of the DNA damage response, which is one of the main reasons of radioresistance.[13]

DNA, however, is not the only component affected by radiation, where growing evidence suggests that radiation can disturb the expression of miRNAs. Since miRNAs regulate DNA repair,[14] cellular homeostasis,[15] and response to stress,[16] they can modulate the radiosensitivity of GBM tumor cells. In that context, miRNAs could have the potential to be either radiosensitizers or radioprotectors.[17]

Multiple miRNAs deregulated in GBM were found to affect the tumor response to radiotherapy. The mechanisms of those miRNAs in GBM are displayed in Figure 1 and reviewed below together with their association with IR.

MicroRNAs Involved in Radiosensitivity Enhancement in GBM

MicroRNA-26a. In GBM, miRNA-26a (miR-26a) was frequently amplified at the DNA level in human glioma.[18] It was found to promote low expression of the tumor suppressors phosphatase and tensin homolog (*PTEN*) and retinoblastoma 1.[19] Furthermore, Guo et al showed that overexpression of miR-26a can enhance radiosensitivity and reduce the DNA repair ability of cells by targeting ataxia–telangiectasia mutated (*ATM*) gene with subsequent inhibition of the homologous recombination repair pathway. In contrast, miR-26a knockdown in U87 GBM radiosensitive cells reverses this phenotype.[20]

MicroRNA-124. MicroRNA-124 (miR-124), a brain-specific miRNA, was identified to be markedly downregulated in human brain glioma. Aberrant expression of miR-124 resulted in cyclin-dependent kinase 4 (*CDK4*) upregulation, which in turn caused radioresistance and disease relapse. Ectopic expression of miR-124 and knockdown of *CDK4* could confer radiosensitivity in glioma cell lines and animal models.[7]

MicroRNA-128. MicroRNA-128 (miR-128), which is also enriched in brain cells, has previously been observed to be underexpressed in GBM.[21,22] It could function as a tumor suppressor in glioma stem cells (GSCs) by negatively regulating tumor cell proliferation and invasion.[23] Downregulation of miR-128, frequently encountered in GBM cells, could mediate tumorigenesis, promote cancer stem cell self-renewal, and enhance radiation resistance through targeting the oncogenes *Bmi-1* and *SUZ12*, 2 members of the polycomb repressor complex (PRC).[24,25] Ye et al[25] reported that low expression of miR-128 in U87 GBM cells following high doses of irradiation enhanced the escape of cells from radiation-induced senescence resulting in radioresistance. However, miR-128 upregulation decreased the expression of PRC genes and rendered GSC more sensitive to radiation.[26]

MicroRNA-145. Another tumor suppressor, microRNA-145 (miR-145), has been reported to be downregulated in GBM. The recovery of its expression level can induce apoptosis via targeting Bcl2/adenovirus E1b 19-kDa interacting protein 3[27] and inhibit migration and invasion of GSC via interaction with ATP-binding cassette subfamily G member 2[28] and connective tissue growth factor.[29] In GBM-CD133 (+) cells, delivery of miR-145 using a therapeutic vehicle can inhibit the malignant phenotype and cancer stem cell–like abilities by targeting octamer-binding transcription factor 4 (*Oct4*) and SRY-box 2 (*Sox2*). This was found to effectively suppress the expression of drug resistance and antiapoptotic genes and synergistically increase the sensitivity of the cells to radiation both in vivo and in vitro.[30]

MicroRNA-153. MicroRNA-153 (miR-153), a brain-enriched miRNA, is abnormally downregulated in GBM. This miRNA has the ability to reverse stem cell properties and induce apoptosis via targeting B-cell lymphoma/leukemia-2 (Bcl-2) and myeloid cell leukemia sequence 1 proteins.[31] Upregulation of miR-153 suppressed the oxidative stress transcription factor nuclear factor erythroid 2-related factor 2 and increased reactive oxygen species level, with subsequent enhancement of apoptosis, differentiation, and radiosensitivity in GSCs in vitro and increased survival in mice bearing human GSCs.[26,32]

MicroRNA-181a/b. MicroRNA-181a/b (miR-181a/b), members of the miR-181 family, was one of the downregulated miRNAs in U87GBM cells.[33] In response to radiation treatment, the radiation-responsive miR-181a was significantly overexpressed transiently, leading to malignant glioma (MG) cell sensitization to radiotherapy via targeting the apoptotic regulator Bcl-2 protein.[33]

MicroRNA-203. MicroRNA-203 (miR-203), another known cancer-associated miRNA, was downregulated in glioma and correlated with prognosis.[34] Overexpression of miR-203 increased the radiation sensitivity in U251, U373, and T98G human MG cell lines, prolonged radiation-induced γ-H2AX (H2A Histone Family Member X) foci formation, which is an indicator of double-strand DNA damage, and inhibited DNA damage repair by downregulating *ATM* and modulating *AKT* and *STAT3* signaling pathways.[35] Moreover, upregulated miR-203 suppressed invasion, epithelium–mesenchyme transition, and migration potentials via inhibiting prosurvival signaling, neural crest transcription factor SLUG (a member of the Snail family of zinc finger transcriptional repressors), has been implicated in the acquisition of invasive behavior during tumor progression, and the intermediate filament protein (Vimentin) and increasing the expression of the senescence-associated epithelial membrane protein 1 (Claudin-1) and the tight junction protein (Zona Occludens 1).[26,35,36] Therefore, miR-203 could potentially contribute to the modulation of radiation sensitivity in MG cell lines.[26]

MicroRNAs-221/222. MicroRNAs-221/222 (miR-221/222) play key roles in modulating DNA damage response.[26] In GBM tissues and cells, miR-221/222 were found to be upregulated and correlated with the stage of disease.[37] They regulate glioma tumorigenesis and invasiveness through the control of protein phosphate PTPμ.[37] In contrast, transfection with miR-221/222 antisense oligonucleotides halted GBM proliferation in the U251 human glioblastoma cell line and U251 glioma subcutaneous mice.[38] Knocked down cells exhibited cell cycle arrest via increasing the cell cycle inhibitor *p27Kip1* which in turn suppressed G1/S shift in the cell cycle in vitro and in vivo[38] and reduced tumor volume in a GBM xenograft mouse model.[26] Combining anti-miR-221/222 with tumor irradiation synergistically enhanced mitotic cell death and decreased S-phase fraction.[38]

MicroRNA-223. MicroRNA-223 (miR-223) was identified as a key regulator in cancer cell differentiation, proliferation, adhesion, and motility via targeting several proteins as forkhead box O 1 transcription factor and insulin-like-growth factor 1 receptor, expression of erythrocyte membrane protein band 4.1.-like 3, and F-box/WD repeat-containing protein 7. In U87 MG cells, miR-223 overexpression downregulates the serine/threonine kinase *ATM* expression and sensitizes U87 cells to radiation in vitro and in vivo, thus highlighting its putative utility as a cancer-targeting therapy.[39]

MicroRNA-224. The influence of microRNA-224 (miR-224) on cell growth has been well characterized in GBM cell lines and primary GBM tumor tissues.[40] Low expression level in patients with GBM was associated with poor prognosis. Exogenous introduction of miR-224 reduced clonogenic potential of U87GBM cells by 30% to 55% with a more synergistic effect reaching 85% to 90% upon combination with irradiation with a dose of 6G that when applied solely produced a 50% reduction.[40] Therefore, miR-224 increased radiation sensitivity in GBM tumor partially by targeting apoptosis inhibitor 5 gene.

MicroRNA-320. MicroRNA-320 (miR-320) has been demonstrated to be closely correlated with the development of glioma. Downregulated miR-320 along with upregulated forkhead box protein M1 was encountered in radioresistant glioma tissues and cells. However, miR-320 overexpression dramatically enhanced radiosensitivity, promoted apoptosis, and improved γ *H2AX* expression and caspase 3 activity in glioma cells through downregulation of sirtuin 1.[41]

MicroRNA-590-3p. MicroRNA-590-3p (miR-590-3p) was reported as a mediator for glioma initiation and development. Its upregulation was observed in high-grade glioma tissues and radioresistant human GBM cells (U251 R) through targeting leucine-rich repeats and immunoglobulin-like domains protein 1 (*LRIG1*). Inhibiting miR-590-3p promoted radiosensitivity of U251 R cells by enhancing apoptosis and suppressing cell viability.[42]

MicroRNAs Involved in Radioresistance in GBM

MicroRNA-21. MicroRNA-21 (miR-21) profile was observed to be significantly increased in MG cell lines and tissues, promoting cell survival, tumor growth, and chemo- and radioresistance.[43] It is one of the major players in glioma radioresistance through the regulation of autophagy.[44] It was upregulated 1.4.9-fold in radioresistant cell line SHG-44 (R) relative to the SHG-44 cells.[45] Application of anti-miR-21 resulted in radiosensitization of U373 and U87 cells, whereas overexpression of miR-21 led to a decrease in radiosensitivity of LN18 and LN428 cells.[44] Moreover, knockdown of miR-21 combined with tumor irradiation synergistically enhanced mitotic death and apoptosis in glioma cell lines and xenograft tumor models.[44] Blocking miR-21 decreased the expression of the epidermal growth factor receptor,[46] phospho-AKT,[44] caspase-3,[45] cyclin D, and Bcl-2, as well as induced cell cycle arrest and autophagy.[26]

MicroRNA-210. High expression of microRNA-210 (miR-210) was found in some types of cancer, especially in GBM.[46] It is involved in cell survival, stemness maintenance, and hypoxia adaptation,[47-49] and its expression is modulated by hypoxia inducible factor and nuclear factor κB.[50] It regulates cell proliferation and apoptosis via targeting regulator of differentiation 1 in GBM cells.[51] Knockdown of miR-210 increased the apoptotic rate, reduced the antioxidant capacity, and sensitized hypoxic GSCs following irradiation,[52] thus suggesting the putative beneficial role of combining miR-210 inhibition and radiotherapy to halt GBM cells.[26]

MicroRNA-212. MicroRNA-212 (miR-212) revealed inconsistent altered expression patterns in various types of tumors. However, in GBM, it functioned as a tumor suppressor whose expression was significantly downregulated.[53] Overexpression of miR-212 decreased viability of GBM cells *in vitro* and suppressed tumor growth *in vivo* by directly targeting serum and glucocorticoid-inducible kinase 3 (*SGK3*).[53] In human U251 and SHG-44 GBM cells, miR-212 was identified as negatively associated radiation-induced miRNA that was downregulated following γ-ray exposure.[17] Transfection of miR-212 mimic in irradiated U251 and SHG-44GBM cell lines has been shown to attenuate radiation-induced apoptosis, alter the expression of apoptosis-related proteins (downregulation of Bcl-2 and upregulation of cleaved-caspase-3), and increase colony formation ability in response to radiation, hence suggesting its contribution in radioresistance via targeting breast cancer susceptibility gene 1.[17]

MicroRNA-135b. The tumor suppressor microRNA-135b (miR-135b) was recognized to play a critical role in GBM development. It was the most downregulated miRNA in patient-derived GBM stem-like cells, and its restoration decreased tumorigenic potentiality and reduced brain infiltration in GBM animal models.[54] However, miR-135b expression was found to be upregulated in the U87R radio-GBM cell line compared to parent U87 cells. Its knockdown increased radiosensitivity by direct regulation of glycogen synthase kinase-3b (*GSK3*β), a negative regulator of cell growth.[54] Similarly, in patients with GBM, miR-135b overexpression and *GSK3*β downregulation were encountered in recurrent tumors compared to primary ones after treatment with IR, highlighting the correlation of miR-135b/ *GSK3*β axis with radiotherapy.[26,55]

Functional Enrichment Analysis

Taking into consideration the "off-target phenomenon" associated with miRNA therapy, we used DIANA tools[56] to investigate the miRNA molecular target pathways and gene ontology and define how each miRNA can influence the downstream signaling pathway in each target. Radiotherapy-related miRNAs were analyzed, and ontology terms were filtered according to the significance of the interaction ($P < .01$) and intersected as depicted in Figure 2. Among the 18 selected miRNAs, miR-320 and miR-210, modulators for radiosensitivity and radioresistance, respectively, were involved in few

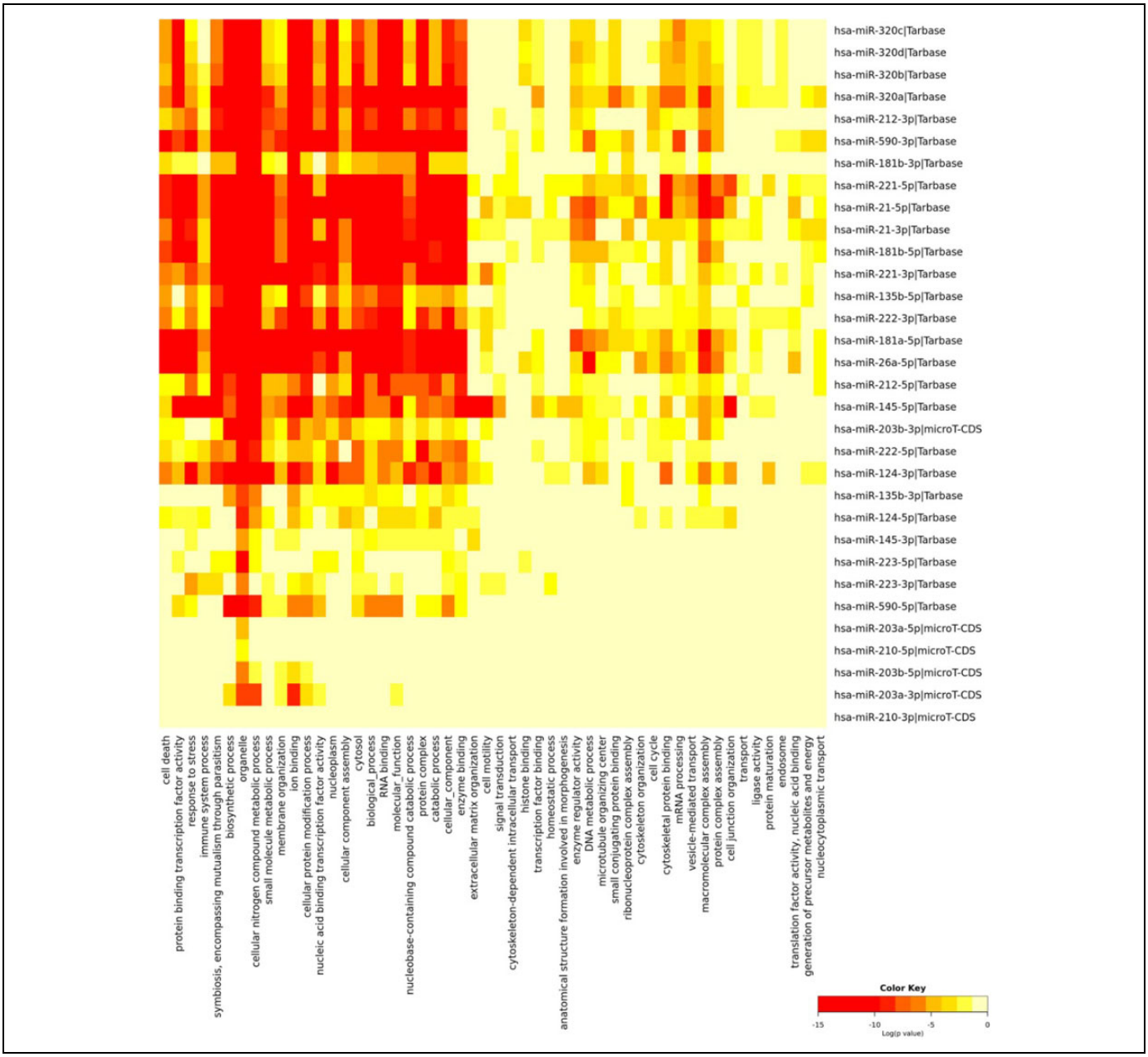

Figure 2. Functional enrichment analysis of glioblastoma-related microRNAs (miRNAs). Gene ontology analysis of 18 miRNAs (miR-26a, -124, -128, -135b, -145, -153, -181a/b, -203, -21, -210, -212, -221/222, -223, -224, -320 and -590) involved in the pathogenesis of glioblastoma (GBM), and its radioresponsive state was carried out by DIANA-miRPath v3.0 tool using experimentally validated gene targets stored in TarBase v7.0 database.[56]

biological processes, which could indicate minimal off-target effects upon using these miRNAs in therapeutic purpose.

MicroRNA Delivering System in Glioblastoma

Micro-RNA-based therapies (miRNA mimics or antagonists) could be delivered locally or systemically in the form of naked or modified nucleic acids, conjugated with lipids and other molecules or carried in various forms of nanoparticles and vectors.[57] However, such therapies present several challenges including inadequate penetration to tumor cells, miRNA degradation and reduced half-life, undesired effects on other genes, and systemic toxicities.[57] Although the blood–brain barrier, which limits passage of miRNAs to the brain tissue, represents another major hurdle in GBM, some studies have described effective miRNA therapy techniques.[58] For instance, Shatsberg et al used miR-34a nanogels in mice with human GBM cell line U-87 MG and succeeded in suppressing tumor progression.[59] Malhotra et al adopted cyclic arginine-glycine-aspartic-targeted poly(lactic-co-glycolic acid) nanoparticles in GBM mouse models and reported an enhancement in therapeutic response to TMZ.[60] Also noted was the in vitro and in vivo

inhibition of GBM growth after using ribonucleoprotein containing anti-miR-21.[61] Delivery through mesenchymal stem cells has also proved worthwhile in GBM.[62,63] Further clinical trials are required to test the side effects of such therapies.

Conclusions and Prospectives

Taken together, miR-26a, miR-124, miR-128, miR-145, miR-153, miR-181a/b, miR-203, miR-221/222, miR223, miR-224, miR-320, and miR-590-3p increase the radiosensitivity of GBM cells, while miR-21, miR-210, miR-212, and miR-135b decrease it. Therefore, overexpressing the former group or knocking down the latter group could help increase the response of GBM cancer cells to radiotherapy, ultimately contributing to cancer control and improving patient survival.

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