UNDERGRADUATE RESEARCH IN NATURAL AND CLINICAL SCIENCE AND TECHNOLOGY (URNCST) JOURNAL
Read more URNCST Journal articles and submit your own today at: https://www.urncst.com

REVIEW OPEN ACCESS

The Role of Endogenous Circular RNAs in Glioblastoma Treatment Resistance: A Literature Review

Sejal Mohapatra, BSc Student [1]*

[1] Department of Neuroscience, McGill University, Montreal, Quebec, Canada H3A 1S2

*Corresponding Author: sejm630@gmail.com

Abstract

Introduction: Glioblastomas are a high-grade primary brain cancer of astrocytes, a glial cell. The average survival upon diagnosis is 15 months. Researchers have been continuously attempting to develop new drugs and therapies that would exhibit greater efficiency against this cancer. However, tumor resistance is often observed in glioblastomas. Circular RNA is a relatively novel finding of non-coding RNA that is highly stable compared to linear RNA. Recent studies have found a variation in circular RNA expression levels in resistant versus non-resistant cancer cell lines. Thus, researchers have been exploring this endogenous entity to understand the role it may play in chemo- and radioresistant glioblastomas.

Methods: A comprehensive look into the most recent findings on this topic was done using Google Scholar and PubMed search engines. Key words used include "circRNA," "glioblastoma," and "chemo- and radio-resistance". This review mainly stems from primary research published between 2017 and 2024.

Results: Only a few specific circular RNAs have been found to be implicated in chemoresistance. Research has focused on understanding resistance to temozolomide. However, variation in certain circular RNA expression has also been noted in cisplatin and histone deacytlase inhibitor therapies for glioblastoma treatment. These circular RNAs inhibit the cytotoxic effects of chemotherapeutics primarily though microRNA sponging. Additionally, similar results were found in radioresistant glioblastoma tumors, whereby specific circular RNAs block apoptosis by altering various protein mechanisms through microRNA sponging and inhibiting translocation.

Discussion: Developing methods that inhibit this tumor's ability to resist otherwise effective therapies may be an ideal method of treatment. Many studies have attempted to modify cellular pathways to facilitate apoptosis of cancer cells. However, due to complex interactions and possible off-target effects, these methods are inefficient. Circular RNAs may serve as improved therapeutic targets due to their tissue specificity and increased stability.

Conclusion: The newly identified circular RNAs involved in glioblastoma therapy resistance may be used to increase cancer cell susceptibility to treatments. Knock-out and overexpression analysis indicate these molecules to be sufficient in altering resistance abilities of these cells. Highly specific targeting techniques may therefore be a viable solution for chemo- and radioresistance.

Keywords: circular RNA; circRNA; glioblastoma; chemoresistance; radioresistance

Introduction

Gliomas are one of the most common types of central nervous system tumors in adults that arises from the dysregulation of glial cells. Glioblastomas (GB) are grade IV gliomas that originate in astrocytes, a glial cell involved in neurotransmission, blood flow regulation, and immunity of the brain [1, 2]. Arising from such an important cell, it is understandable that this is the most aggressive and the most fatal primary tumor of the central nervous system [1, 3]. The median overall survival upon diagnosis is less than 15 months [1]. Current treatment of this disease includes immediate surgical resection of the tumor followed by radiotherapy and chemotherapy [3]. Temozolomide (TMZ) is the most common drug used in the treatment of GB [3]. Though this therapy has not been successful in curing patients, research does show a significant decrease in disease progression compared to an untreated tumor, lengthening the lifespan by a noticeable amount [3, 4]. However, despite recent advancements in cancer research, GB survival rate remains very low compared to other forms of tumors. The main reason for this discrepancy is due to the ability of this disease to be both chemo- and radioresistent [4]. Thus, lasting remission is nearly impossible to achieve with the current techniques.

Circular RNA (circRNA) is a relatively recent cellular discovery. It belongs to the family of non-coding, single stranded RNA, though it has been found to encode some genes, and is quite stable compared to other members of

this family due to the lack of exposure of the 3' and 5' ends [5]. The biogenesis of these molecules is still debated and its function is not fully known (Figure 1). However, circRNAs have been found to play a rather critical role in microRNA (miRNA) sponging and gene expression regulation [7, 8]. These RNAs are found in seemingly all cells of the body and appear to have some tissue-specificity [5]. Notably, many studies have found that certain circRNAs may act as oncogenes or tumor suppressor genes, with their expression altered during tumor formation [9]. Due to the high prevalence of circRNAs, and the evolutionary conservation of these molecules, it is assumed that they play an essential role in the proper functioning of our cells [5, 7]. Interestingly, researchers have found that circRNAs are quite prominent in neuronal tissues, making up around 20% of the coding region in neuronal cells. Thus, their dysregulation is presumably a causative factor in neurological disease [10].

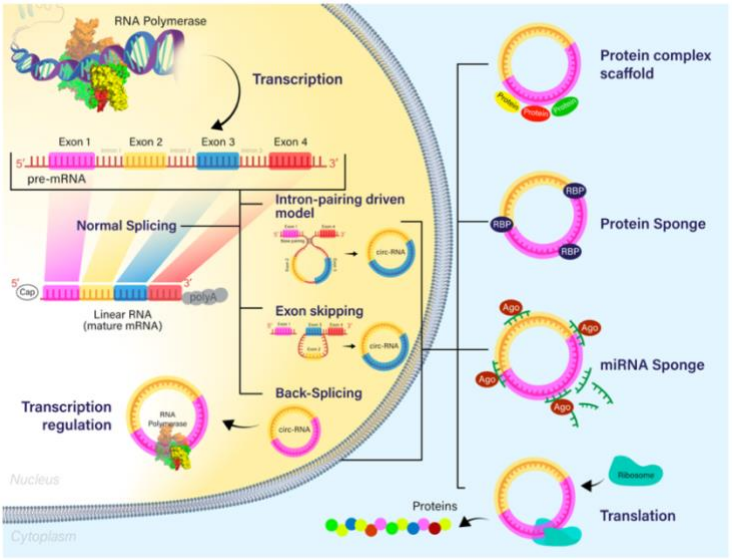

Figure 1. Biogenesis and function of circular RNA. These non-coding RNAs can be generated in multiple ways including through back splicing and exon skipping. Their main functions include miRNA sponging, altering translocation, modifying protein activity and acting as a protein scaffold. Through these various roles circular RNAs are able to alter normal cellular function and increase resistance to treatment induced apoptosis. Adapted from Tirpe et al. (2023) with permission from Dr. Tirpe from the International journal of Molecular Science published by MDPI [6].

In recent years, scientists discovered that various circRNAs are up- or downregulated in GB patients compared to healthy controls. In fact, quite a few circRNAs have been identified to play a crucial role in tumor formation, cell proliferation and even found some to be linked to radio- and chemoresistance [11]. Hence, the manipulation of circRNA expression may be effective in increasing the efficiency of current therapeutic techniques for treating GB. This review aims to summarize the most recent findings on circRNA and how changes in expression levels can decrease this tumor's resistance to radiotherapy and chemotherapy.

Methods

Search Strategy

Relevant articles published between 2017 to 2024 were obtained through a computerized search through PubMed and Google Scholar. Key terms searched included "Glioblastoma", "Circular RNA" and "therapeutic interventions." Literature was selected based on relevance following abstract screening.

Selection Criteria

The selection criteria for the included articles were as follows:

- The full report was published in English.
- Only full reports were selected.
- Primary and review articles were selected, though greater emphasis was placed on primary articles.

Results

Circular RNAs Involved in Chemoresistance

Resistance to Temozolomide

Temozolomide therapy (TMZ) is the primary treatment strategy that is first prescribed to glioblastoma patients after surgical resection [3]. TMZ readily penetrates the blood-brain-barrier and kills tumor cells by inducing site-specific DNA methylation which generates DNA damage and triggers apoptosis in the cell. The enhanced cell death causes a reduction in tumor mass [12-14]. Though this is the first line of treatment, around 50% of GB patients have TMZ-resistant tumors and therefore do not respond appropriately to this drug [14]. Many studies have

identified specific chemoresistance in GB cell lines and potential pathways involved [15-20]. Only recently have researchers found circRNAs that may partake in the manipulation of these pathways.

Zhao et al. (2019) explored microarray expression profiles of circRNAs, as well as other non-coding RNAs, in these resistant cell lines and were able to identify 53 circRNAs that were differentially expressed in TMZ resistant GB tissue. Specifically, the transcription sites of these molecules were primarily related to metabolic and translation pathways. A significant portion of these circRNAs were found to be upregulated in general in GB tumors [21]. They identified circ0043949 to be of particular importance in the TMZ-resistance of GB cells. Findings of Li et al. (2022) also indicate an essential role of circ0043949 [22]. Many studies have previously shown that circRNAs participate in cell proliferation and tumorigenesis, acting as oncogenes in many cancers including GB [23-30].

The mechanisms by which these non-coding RNAs may influence a cancer's ability to withstand apoptosis has garnered great attention. Han et al. (2021) identified circ-HIPK3, a specific circRNA that appeared to be upregulated in TMZ-resistant gliomas. In contrast, they found miRNA-421 to be significantly downregulated in these tumor cells. This strongly suggested that circ-HIPK3 acts to block the expression of miRNA-421, resulting in increased resistance to TMZ. Though they were unable to identify the exact mechanism by which this resistance occurred, they confirmed this correlation via a knock-out experiment of circ-HIPK3 in xenograft mice [31].

Quite a few similar studies have been conducted identifying important circRNAs involved in glioma chemoresistance to TMZ [32-34]. Though many circRNAs have been shown to correlate to this acquired resistance, not many studies have found targetable pathways that could be useful for therapeutic intervention. Only three notable articles were published in the last few years concerning important pathways involving circRNAs and glioblastoma TMZ-resistance. These results are shown in Table 1 [22, 35, 36]. All three of the identified circRNA were found to be directly linked to the regulation of proteins implicated in cell death and cellular division.

Table 1. CircRNAs Involved in Resistance to TMZ Treatment of Glioblastomas

Source	CircRNA Identified	Methods of Study	Mechanism of Action
Wei et al. (2020) doi:10.1093/neuonc/noaa214 [35]	CircASAP1	Knockdown and overexpression analysis in vivo	Knock down of circASAP1 reduced TMZ resistance. Found circRNA led to increased levels of NRAS through sponging of miRNA-502. NRAS activation leads to increased cell proliferation and inhibition of apoptotic pathways.
Yuan et al. (2022) doi: 10.1111/cns.13821 [36]	Circ0072309	Analyzing TMZ resistance via western blotting, immunoprecipitation and rescue experiments.	Found that increasing levels of circ007239 led to increased TMZ sensitivity. Inhibits the activity of miRNA-100 which inhibits the activity of wild-type p53. p53 is involved in the regulation of cellular division, proliferation, and apoptosis
Li et al. (2022) doi:10.1007/s11011-022-01069-3 [22]	Circ0043949	Real time qPCR, flow cytometry, bioinformatics and dual luciferase reporter assay in vivo.	High levels of circ0043949 found in TMZ resistant GB cancer cells. This circRNA was found to mediate levels of integrinalpha1 by inhibiting miRNA-876. Integrinalpha1 is an oncogene that blocks apoptosis, inhibits cell proliferation and induces cell migration.

Resistance to Cisplatin

Due to the high percentage of GB patients being resistant to TMZ therapy, physicians may indicate the use of various other therapeutic agents that could be used in the treatment of this cancer [37, 38]. Cisplatin is one of many platinum-based drugs used in cancer chemotherapy. Like TMZ, cisplatin interacts with the DNA and damages it leading to a list of downstream events including inducing apoptosis, inhibiting cell division, and preventing transcription [39, 40]. While this drug is quite efficient, it has many side effects and there are some GB tumors that have developed resistance to this drug [39].

Findings presented by Luo et al. (2021) show that circPTN plays a significant role in cisplatin resistance in many GB cells. This is a circRNA that is often highly expressed in GB tumors in general with an even greater expression found in the cytoplasm of cisplatin-resistant GB cells. Through a knockout analysis of circPTN, they found increased sensitivity of these tumors to cisplatin therapy indicating an important role in resistance. Upon further investigation, they found circPTN to be involved in the downregulation of miRNA-542, which directly targets and inhibits PIK3, a kinase that is often upregulated in cancer and increases the expression of AKT [41-43]. AKT is a well-established molecule that induces cell proliferation and inhibits apoptosis (Figure 2) [45]. The increased expression of PIK3, due to the decrease in miRNA-542 levels via sponging by circPTN, can therefore counteract the effects of cisplatin treatment by blocking the death of GB cancer cells.

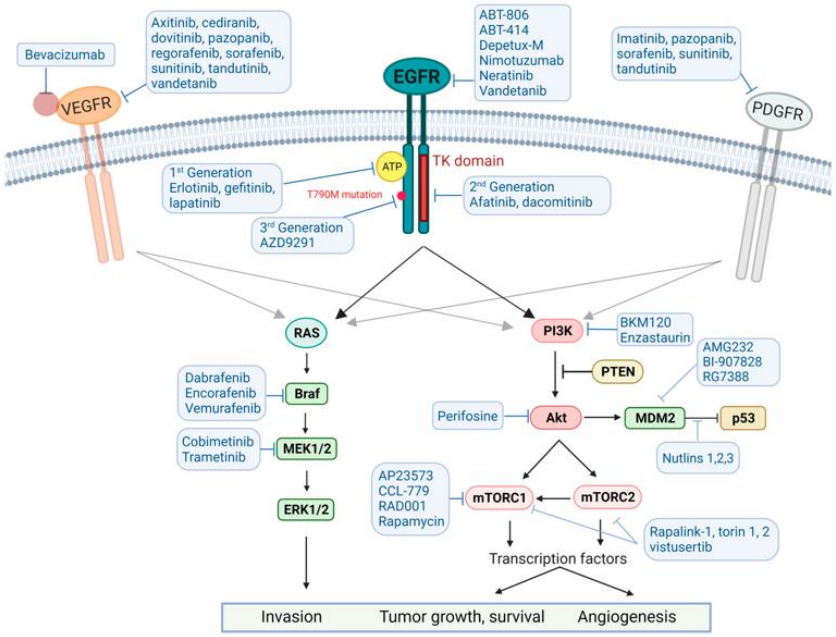

Figure 2. The important pathways implicated in cancer. The Ras and the PI3K pathways are two of the most common mechanisms of action that can be altered in cancer. Each of the proteins downstream of the growth factor receptors can act as either an oncogene or tumor suppressor gene. Subtle changes in expression levels of these proteins can increase cell survival and proliferation and thus contributes to the progression of cancer. Adapted from Obrador et al. (2024) with permission from Dr. Obrador from the International Journal of Molecular Science published by MDPI [44].

Resistance to Histone Deacetylase Inhibitors

Another prominent drug family used in the chemotherapy treatment of GB are the histone-deactylase inhibitors (HDACis). They mainly compromise short chain fatty acids such as suberoylanilide hydroxamic acid (SAHA) [46]. Unlike other therapeutic agents used in the treatment of GB, this drug does not directly modify the DNA sequence of cancerous cells. Instead, it works through an epigenetic mechanism whereby transcriptional events are altered [47, 48]. In a study by Meng et al. (2023), circ-0000741 was found to be involved in the resistance of GB cells to SAHA treatment. This circRNA decreased the expression of miRNA-379, allowing for the increased expression of tripartite motif-containing 14 protein (TRIM14) [49]. TRIM14 is an oncogene that promotes cell proliferation [50]. Thus, inhibiting the activity of circ-0000741 could increase the efficiency of SAHA treatment by reducing the cancer cells ability to resist cell death.

CircRNAs Involved in Radiotherapy Resistance

Radiation therapy is a standard treatment for most forms of cancer. It involves exposing cancerous tissue to high beams of radiation, causing DNA damage such as double strand breaks, leading to the release of reactive oxygen species. The cells will then respond to this injury by halting division and/or instigating cell death [51]. Following surgical resection, radiation therapy has been a predominant line of treatment for GB patients for the last 40 years [52]. With the development of drugs such as TMZ, researchers have noted improved prognosis and increased safety while using a combination of radiotherapy and chemotherapy tactics. Though recent technological advances are a foot to make radiation therapy more effective and safer, a large percentage of GB patients develop radioresistant tumors, rendering this treatment inefficient [53-55]. To this end, scientists are exploring the biological mechanisms by which this resistance is acquired

in attempt to reverse the cells ability to withstand apoptosis.

In the last five years, four notable circRNAs have been identified to play a causal role in a GB tumor's ability to be radioresistant. These papers have attempted to find the pathways that are acted upon by these circRNAs in order to recognize potential targets for therapeutic intervention. Table 2 summarizes the four main circRNAs involved in radioresistance of GB tumors [56-59].

Table 2. CircRNAs Involved in Radiation Therapy Resistance of Glioblastoma

Source	CircRNA Identified	Method of study	Mechanism of action
Zhao et al. (2019) doi:10.3892/or.2019.6972 [56]	circATP8B4	RNA-sequencing and bioinformatics	In radioresistant U251 cells, extracellular vesicles were found to contain circATP8B4, causing sponging of miRNA-766.
Wang et al. (2021) doi:10.7150/ijbs.57168 [57]	circMETRN	Exosome analysis from low-dose radiation induced therapy in xenograft mice	Low dose radiation therapy stimulated the secretion of exosomes which delivered high levels of circMETRN. These circRNAs increased the expression of of γ-H2AX via a miR-4709-3p/GRB14/ PDGFRα pathway. Increased γ-H2AX allows for improved DNA repair mechanisms, thus the cells could withstand radiation induced DNA damage.
Yuan et al. (2022) doi:10.1007/s12640-022-00548-w [58]	circ006055	Dual luciferase reporter assay in mice	Circ006055 binds and down regulates miRNA-197. This allows for the increased expression of API5 (apoptosis inhibitor 5). The cancerous cells can then withstand cell death from radiation induced DNA damage due to increased API5.
Xu et al. (2023) doi:10.21203/rs.3.rs-3474740 [59]	circFOXO3	Metabolic analysis of radioresistant versus radiosensitive glioblastomas	CircFOXO3 increased in radioresistant cells. Found to block the translocation of apoptosis-promoting proteins to the cytoplasm. Decreasing lipid peroxidation found to be implicated in radioresistant promoting function of circFOXO3.

Discussion

To this day, primary tumors of the central nervous system are some of the deadliest cancers due to their aggressivity and resistance to treatment. Glioblastomas constitute an especially threatening form of glial cell tumor [2]. The typical treatment strategy for GB involves immediate surgical resection followed by combination therapy using chemical agents and radiation [3]. Both chemo- and radiotherapy attempt to eliminate cancerous cells by inducing DNA damage and causing cell death and arrested cell division. Though these treatments do appear to slow the progression of the disease and increase overall survival, the 5-year survival of this cancer is still only at 10% [4]. The primary reason behind the inefficiency of these therapies is due to acquired resistance [3, 4]. Improving our current methods of treatment by preventing chemo- and radioresistance is fundamental in improving patient outcomes.

The introduction of TMZ therapy in 2005 was the last time in which we observed a significant increase in patient survival for this cancer [13]. Seeing as glioblastomas remain a fatal prognosis even with recent advancements, new strategies are vital for enhancing TMZ therapy efficiency. Studies suggest that circRNAs can promote the proliferation of cancerous cells when dysregulated, thus acting against chemical agents that aim to inhibit the cell cycle. Though many circRNAs have been identified to a have a correlational role with TMZ resistance in GB [21, 22], only three direct pathways have been found that could serve as potential targets of therapeutic intervention [22, 35, 36]. Each of these circRNAs were shown to either upregulate pro-cancer proteins or downregulate anti-cancer

proteins through the inhibition of certain miRNAs. Findings by Sang et al. (2019) demonstrate that genetically amplifying the expression of circ0025202 in a mouse model of breast cancer led to increased TMZ sensitivity and significant reduction in tumor size by allowing for the increased expression of the tumor suppressor gene, FOXO3a [60]. This was done through cloning of circ0002502 and inserting it into mice via adenovirus associated plasmids [60]. Ethically, genetic modifications such as this are not yet accepted in humans. However, this technology could potentially be of great use in future medicine. Furthermore, quite a few studies have shown successful enhancement of TMZ treatment in xenograft mice using small interfering RNAs [61-63]. Again, this is a viable gene silencing technique that may be quite useful for use in humans in years to come.

The use of platinum-based anticancer drugs such as cisplatin has also been shown to be an effective agent against GB. Though it does not cross the blood brain barrier with the same ease as TMZ, cisplatin can be a useful alternative for TMZ-resistant tumors provided the use of an appropriate delivery system [39]. As cisplatin is not the primary line of treatment for GB, little research has been done on resistance to this drug. However, like with TMZ, GB tumors often acquire resistance after repeated exposure [47]. Notably, circPTEN was found to be upregulated after many trials of cisplatin and eventually correlated with resistance to this chemotherapeutical agent through the increased expression of PIK3 and AKT [44, 45]. AKT is a protein often discussed in cancer research. It is an oncogene with the ability to both inhibit cell death and increase cell proliferation. For this reason, AKT targeted therapy has been a topic of high importance [64, 65]. Unfortunately, inhibitors of this protein are often nonspecific and cause other detrimental side effects. Two possible therapies using this approach are currently in clinical trials, but none have yet received FDA approval [66, 67]. Thus, creating a therapy that targets circRNA rather than the protein itself may prove to be a more sensible approach.

Epigenetic modifying techniques such as SAHA are relatively new as a method of chemotherapy for various cancers. Used alone, this drug has thus far proven to be inadequate in reducing tumor size. However, when combined with other anticancer agents, HDACis appear to have synergistic effects. Moreover, adding this drug into the mix has helped decrease toxicity and chemoresistance. However, like all other drugs, resistance of GB tumors to treatment does eventually occur [47, 48]. Thus, the identification of targetable pathways to inhibit onset of resistance is needed. One such pathway was found by Meng et al. (2023) whereby a circ-000074 appeared to be significantly upregulated in SAHA-resistant GB tumors, leading to the overexpression of TRIM14 [49]. Similarly, to AKT, targeted therapies for TRIM14 to inhibit cancer progression have not been successful due to lack of specificity in inhibitors [68]. Downregulating non-coding RNA using short interfering RNAs could allow for increased sensitivity to SAHA treatment [69].

Before the arrival of anticancer drugs, radiotherapy was the main treatment for cancer following surgical resection [52]. Over the last 50 years, methods of radiation therapy have seen vast improvements in terms of efficiency and safety for patients [53, 54]. As aforementioned, the current, most successful treatment plan for GB involves a combination of both chemotherapy and radiotherapy [3]. Unfortunately, a large percentage of GB tumors develop radioresistance, reducing the already low chance of patient survival [3, 4]. Recent research in circRNAs is providing a similar explanation for this resistance as it has for chemoresistance. For this reason, many scientists are turning to non-coding RNA therapies to enhance current treatment. For GB tumors, four main mechanisms of action have been identified to explain the role of circRNAs in radioresistance. Each of these pathways involves alterations in expression of genes involved in sensing DNA damage or genes involved in initiating apoptosis due to radiation induced DNA damage [56-59]. Most of these mechanisms stem from the specific miRNA sponging ability of the identified circRNAs [56-58]. However, one study demonstrated the ability of circFOXO3 to sequester proteins in order to inhibit the apoptotic pathway [59]. This function was found in another circRNA, circApotl1, in breast cancer research. In this study, it was found that circAmotl1 increases the nuclear translocation of c-myc, an oncogene, to promote tumorigenesis [70]. This is further indication that circRNA can act to interfere with radiotherapy by altering the sequestration of proteins.

Interestingly, specific circRNAs appear to be associated with specific forms of resistance in GB [5]. With this knowledge, circRNAs may be able to predict which form of therapy would be the most effective for a particular GB case. Studies mainly in lung cancer have identified specific circRNAs as effective biomarkers for prognosis. Thus, performing a circRNA microarray of a tumor prior to treatment prescription could entail a more specific and tailored therapy to decrease likelihood of resistance and drug toxicity.

Conclusions

In the articles summarized, it is apparent that circRNAs primarily function through miRNA sponging in order to cause therapy resistant tumors. Other mechanisms of action have been identified in breast, lung and gastric cancers, further outlining the important role circRNAs play in proper cellular function. The malignant nature and aggressiveness of this GB emphasize the need for highly efficient therapies, hence circRNAs may be an ideal target. Many animal studies have indicated a much improved prognosis when certain circRNAs are genetically altered in expression. Unfortunately, gene editing technology is not yet ethically safe and acceptable for use in human medicine. Thus, genetically modifying expression of these

RNAs is not a viable option. However, circRNAs may be essential therapeutic targets for pharmacological agents. Due to their increased stability and their tissue and cell-type specificity, in theory these drugs would result in less off-target action compared to proteins and other non-coding RNAs. Furthermore, the identification of alerted circRNA expression in GB tumors could be vital in deciding on the most effective treatment plan for a certain tumor cell line. As specific circRNAs correlate with specific tumor resistance, assessing cancer cell composition prior to prescription of treatment may ensure increased patient survival more effective and targeted approach. In sum, our current understanding of the role of circRNA in GB demonstrates the importance of these molecules in treatment resistance. Further analysis on the topic is essential to improve GB treatment strategies and increase patient survival.

List of Abbreviations Used
circRNA: circular RNA
GB: glioblastoma
HDACi: histone-deactylase inhibitor
miRNA: microRNA
SAHA: suberoylanilide hydroxamic acid
TMZ: temozolomide
TRIM14: tripartite motif-containing 14 protein

Conflicts of Interest
No conflicts of interest were observed in the making of the article.

Ethics Approval and/or Participant Consent
As this is a literature review, ethical approval was not necessary.

Authors' Contributions
SM: Established the design of the study and was the principle researcher on the subject. Primary contributor to collection and analysis of information, drafting and revision of the manuscript and gave final approval of the version to be published.

Acknowledgements
This study was constructed under the supervision of a mentor from the Mentored Paper Competition from URNCST. As such, I would like express how thankful I am for the support and help of my mentor, Amel Sassi, University of Toronto. Though she was very busy herself in the completion of her Master's thesis on prostate cancer, she ensured I was on track with my publication. She always provided high quality feedback and much needed guidance. I owe the completion of this article entirely to her.

Funding
This study was not funded.

References
[1] Hoogstrate Y, Draaisma K, Ghisai SA, van Hijfte L, Barin N, de Heer I, et al. Transcriptome analysis reveals tumor microenvironment changes in glioblastoma. Cancer Cell. 2023 Apr;41(4). https://doi.org/10.1016/j.ccell.2023.02.019
[2] Elshaer SS, Abulsoud AI, Fathi D, Abdelmaksoud NM, Zaki MB, El-Mahdy HA, et al. MIRNAs role in Glioblastoma Pathogenesis and targeted therapy: Signaling Pathways Interplay. Pathology - Research and Practice. 2023 Jun;246:154511. https://doi.org/10.1016/j.prp.2023.154511
[3] Fisher JP, Adamson DC. Current FDA-approved therapies for high-grade malignant gliomas. Biomedicines. 2021 Mar 22;9(3):324 https://doi.org/10.3390/biomedicines9030324
[4] Yalamarty SS, Filipczak N, Li X, Subhan MA, Parveen F, Ataide JA, et al. Mechanisms of resistance and current treatment options for glioblastoma multiforme (GBM). Cancers. 2023 Apr 1;15(7):2116. https://doi.org/10.3390/cancers15072116
[5] Misir S, Wu N, Yang BB. Specific expression and functions of circular RNAS. Cell Death & Differentiation. 2022 Feb 15;29(3):481–91. https://doi.org/10.1038/s41418-022-00948-7
[6] Obrador E, Moreno-Murciano P, Oriol-Caballo M, López-Blanch R, Pineda B, Gutiérrez-Arroyo J, et al. Glioblastoma therapy: Past, present and future. International Journal of Molecular Sciences. 2024 Feb 21;25(5):2529. https://doi.org/10.3390/ijms25052529
[7] Han B, Chao J, Yao H. Circular RNA and its mechanisms in disease: From the bench to the clinic. Pharmacology & Therapeutics. 2018 Jul;187:31–44. https://doi.org/10.1016/j.pharmthera.2018.01.010
[8] Vo JN, Cieslik M, Zhang Y, Shukla S, Xiao L, Zhang Y, et al. The landscape of circular RNA in cancer. Cell. 2019 Feb;176(4). https://doi.org/10.1016/j.cell.2018.12.021
[9] Tang Q, Hann SS. Biological roles and mechanisms of circular RNA in human cancers. OncoTargets and Therapy. 2020 Mar; Volume 13:2067–92. https://doi.org/10.2147/ott.s233672
[10] Hanan M, Soreq H, Kadener S. CircRNAs in the brain. RNA Biology. 2016 Dec 5;14(8):1028–34. https://doi.org/10.1080/15476286.2016.1255398
[11] Cui C, Yang J, Li X, Liu D, Fu L, Wang X. Functions and mechanisms of circular RNAS in cancer radiotherapy and chemotherapy resistance. Molecular Cancer. 2020 Mar 14;19(1). https://doi.org/10.1186/s12943-020-01180-y
[12] Karachi A, Dastmalchi F, Mitchell DA, Rahman M. Temozolomide for immunomodulation in the treatment of glioblastoma. Neuro-Oncology. 2018 May 4;20(12):1566–72. https://doi.org/10.1093/neuonc/noy072

[13] Kaina B. Temozolomide in glioblastoma therapy: Role of apoptosis, senescence and autophagy. comment on Strobel et al., temozolomide and other alkylating agents in glioblastoma therapy. biomedicines 2019, 7, 69. Biomedicines. 2019 Nov 11;7(4):90. https://doi.org/10.3390/biomedicines7040090

[14] Singh N, Miner A, Hennis L, Mittal S. Mechanisms of temozolomide resistance in glioblastoma - A comprehensive review. Cancer Drug Resistance. 2020; https://doi.org/10.20517/cdr.2020.79

[15] Da Ros M, De Gregorio V, Iorio A, Giunti L, Guidi M, de Martino M, et al. Glioblastoma chemoresistance: The double play by Microenvironment and blood-brain barrier. International Journal of Molecular Sciences. 2018 Sept 22;19(10):2879. https://doi.org/10.3390/ijms19102879

[16] Noch EK, Ramakrishna R, Magge R. Challenges in the treatment of glioblastoma: Multisystem mechanisms of therapeutic resistance. World Neurosurgery. 2018 Aug;116:505–17. https://doi.org/10.1016/j.wneu.2018.04.022

[17] Chernov AN, Alaverdian DA, Galimova ES, Renieri A, Frullanti E, Meloni I, et al. The phenomenon of multidrug resistance in glioblastomas. Hematology/Oncology and Stem Cell Therapy. 2021 Jun; https://doi.org/10.1016/j.hemonc.2021.05.006

[18] Ou A, Yung WK, Majd N. Molecular mechanisms of treatment resistance in glioblastoma. International Journal of Molecular Sciences. 2020 Dec 31;22(1):351. https://doi.org/10.3390/ijms22010351

[19] Oliver L, Lalier L, Salaud C, Heymann D, Cartron PF, Vallette FM. Drug resistance in glioblastoma: Are persisters the key to therapy? Cancer Drug Resistance. 2020; https://doi.org/10.20517/cdr.2020.29

[20] Zhang Y, Zhang Z, Mousavi M, Moliani A, Bahman Y, Bagheri H. Resveratrol inhibits glioblastoma cells and chemoresistance progression through blockade P-glycoprotein and targeting AKT/PTEN signaling pathway. Chemico-Biological Interactions. 2023 May; 376:110409. https://doi.org/10.1016/j.cbi.2023.110409

[21] Zhao C, Gao Y, Guo R, Li H, Yang B. Microarray expression profiles and bioinformatics analysis of mrnas, lncrnas, and circrnas in the secondary temozolomide-resistant glioblastoma. Investigational New Drugs. 2019 Dec 10;38(5):1227–35. https://doi.org/10.1007/s10637-019-00884-3

[22] Li X, Wang N, Leng H, Yuan H, Xu L. HSA_CIRC_0043949 reinforces temozolomide resistance via upregulating oncogene ITGA1 axis in glioblastoma. Metabolic Brain Disease. 2022 Oct 27;37(8):2979–93. https://doi.org/10.1007/s11011-022-01069-3

[23] Zheng J, Liu X, Xue Y, Gong W, Ma J, Xi Z, et al. TTBK2 circular RNA promotes glioma malignancy by regulating mir-217/hnf1β/derlin-1 pathway. Journal of Hematology & Oncology. 2017 Feb 20;10(1). https://doi.org/10.1186/s13045-017-0422-2

[24] Ghafouri-Fard S, Khoshbakht T, Bahranian A, Taheri M, Hallajnejad M. Circmto1: A circular RNA with roles in the carcinogenesis. Biomedicine & Pharmacotherapy. 2021 Oct;142:112025. https://doi.org/10.1016/j.biopha.2021.112025

[25] Cao L, Wang M, Dong Y, Xu B, Chen J, Ding Y, et al. Circular RNA circrnf20 promotes breast cancer tumorigenesis and Warburg effect through mir-487a/hif-1α/HK2. Cell Death & Disease. 2020 Feb 24;11(2). https://doi.org/10.1038/s41419-020-2336-0

[26] Qadir J, Wen S, Yuan H, Yang BB. CircRNAs regulate the crosstalk between inflammation and tumorigenesis: The Bilateral Association and Molecular Mechanisms. Molecular Therapy. 2023 Jun;31(6):1514–32. https://doi.org/10.1016/j.ymthe.2022.12.005

[27] Xia X, Li X, Li F, Wu X, Zhang M, Zhou H, et al. A novel tumor suppressor protein encoded by circular AKT3 RNA inhibits glioblastoma tumorigenicity by competing with active phosphoinositide-dependent kinase-1. Molecular Cancer. 2019 Aug 30;18(1). https://doi.org/10.1186/s12943-019-1056-5

[28] Zhang M, Zhao K, Xu X, Yang Y, Yan S, Wei P, et al. A peptide encoded by circular form of LINC-pint suppresses oncogenic transcriptional elongation in glioblastoma. Nature Communications. 2018 Oct 26;9(1). https://doi.org/10.1038/s41467-018-06862-2

[29] Liu Y, Li Z, Zhang M, Zhou H, Wu X, Zhong J, et al. Rolling-translated EGFR variants sustain EGFR signaling and promote glioblastoma tumorigenicity. Neuro-Oncology. 2020 Dec 16;23(5):743–56. https://doi.org/10.1093/neuonc/noaa279

[30] Gao X, Xia X, Li F, Zhang M, Zhou H, Wu X, et al. Circular RNA-encoded oncogenic E-cadherin variant promotes glioblastoma tumorigenicity through activation of EGFR–STAT3 signalling. Nature Cell Biology. 2021 Mar;23(3):278–91. https://doi.org/10.1038/s41556-021-00639-4

[31] Han C, Wang S, Wang H, Zhang J. Exosomal CIRC-HIPK3 facilitates tumor progression and temozolomide resistance by regulating mir-421/zic5 axis in glioma. Cancer Biotherapy and Radiopharmaceuticals. 2021 Sept 1;36(7):537–48. https://doi.org/10.1089/cbr.2019.3492

[32] Yang Y, Gao X, Zhang M, Yan S, Sun C, Xiao F, et al. Novel role of FBXW7 circular RNA in repressing glioma tumorigenesis. JNCI: Journal of the National Cancer Institute. 2017 Aug 29;110(3):304–15. https://doi.org/10.1093/jnci/djx166

[33] Zhang M, Huang N, Yang X, Luo J, Yan S, Xiao F, et al. A novel protein encoded by the circular form of the SHPRH gene suppresses glioma tumorigenesis. Oncogene. 2018 Jan 18;37(13):1805–14. https://doi.org/10.1038/s41388-017-0019-9

[34] Pan Z, Zhao R, Li B, Qi Y, Qiu W, Guo Q, et al. EWSR1-induced CIRCNEIL3 promotes glioma progression and exosome-mediated macrophage immunosuppressive polarization via stabilizing IGF2BP3. Molecular Cancer. 2022 Jan 14;21(1). https://doi.org/10.1186/s12943-021-01485-6
[35] Wei Y, Lu C, Zhou P, Zhao L, Lyu X, Yin J, et al. EIF4A3-induced circular RNA ASAP1 promotes tumorigenesis and temozolomide resistance of glioblastoma via NRAS/Mek1/ERK1–2 signaling. Neuro-Oncology. 2020 Sept 14;23(4):611–24. https://doi.org/10.1093/neuonc/noaa214
[36] Yuan F, Zhang S, Sun Q, Ye L, Xu Y, Xu Z, et al. HSA_CIRC_0072309 enhances autophagy and TMZ sensitivity in glioblastoma. CNS Neuroscience & Therapeutics. 2022 Feb 25;28(6):897–912. https://doi.org/10.1111/cns.13821
[37] Rajaratnam V, Islam M, Yang M, Slaby R, Ramirez H, Mirza S. Glioblastoma: Pathogenesis and current status of chemotherapy and other novel treatments. Cancers. 2020 Apr 10;12(4):937. https://doi.org/10.3390/cancers12040937
[38] Anjum K, Shagufta BI, Abbas SQ, Patel S, Khan I, Shah SA, et al. Current status and future therapeutic perspectives of glioblastoma multiforme (GBM) therapy: A Review. Biomedicine & Pharmacotherapy. 2017 Aug;92:681–9. https://doi.org/10.1016/j.biopha.2017.05.125
[39] Tchounwou PB, Dasari S, Noubissi FK, Ray P, Kumar S. Advances in our understanding of the molecular mechanisms of action of cisplatin in cancer therapy. Journal of Experimental Pharmacology. 2021 Mar; Volume 13:303–28. https://doi.org/10.2147/jep.s267383
[40] Zoń A, Bednarek I. Cisplatin in ovarian cancer treatment—known limitations in Therapy Force New Solutions. International Journal of Molecular Sciences. 2023 Apr 20;24(8):7585. https://doi.org/10.3390/ijms24087585
[41] Jiang N, Dai Q, Su X, Fu J, Feng X, Peng J. Role of PI3K/Akt pathway in cancer: The framework of malignant behavior. Molecular Biology Reports. 2020 Apr 24;47(6):4587–629. https://doi.org/10.1007/s11033-020-05435-1
[42] He Y, Sun MM, Zhang GG, Yang J, Chen KS, Xu WW, et al. Targeting PI3K/AKT signal transduction for cancer therapy. Signal Transduction and Targeted Therapy. 2021 Dec 16;6(1). https://doi.org/10.1038/s41392-021-00828-5
[43] Peng Y, Wang Y, Zhou C, Mei W, Zeng C. PI3K/AKT/mtor pathway and its role in cancer therapeutics: Are we making headway? Frontiers in Oncology. 2022 Mar 24;12. https://doi.org/10.3389/fonc.2022.819128
[44] Tirpe A, Streianu C, Tirpe SM, Kocijancic A, Pirlog R, Pirlog B, et al. The glioblastoma circularrnaome. International Journal of Molecular Sciences. 2023 Sept 26;24(19):14545. https://doi.org/10.3390/ijms241914545
[45] Yudushkin I. Control of AKT activity and substrate phosphorylation in cells. IUBMB Life. 2020 Mar 3;72(6):1115–25. https://doi.org/10.1002/iub.2264
[46] Bondarev AD, Attwood MM, Jonsson J, Chubarev VN, Tarasov VV, Schiöth HB. Recent developments of HDAC inhibitors: Emerging indications and novel molecules. British Journal of Clinical Pharmacology. 2021 May 27;87(12):4577–97. https://doi.org/10.1111/bcp.14889
[47] Attwood MM, Rask-Andersen M, Schiöth HB. Orphan Drugs and their impact on pharmaceutical development. Trends in Pharmacological Sciences. 2018 Jun;39(6):525–35. https://doi.org/10.1016/j.tips.2018.03.003
[48] Jenke R, Reßing N, Hansen FK, Aigner A, Büch T. Anticancer therapy with HDAC inhibitors: Mechanism-based combination strategies and future perspectives. Cancers. 2021 Feb 5;13(4):634. https://doi.org/10.3390/cancers13040634
[49] Meng L, Wang Y, Tu Q, Zhu Y, Dai X, Yang J. Circular RNA circ_0000741/mir-379-5p/trim14 signaling Axis promotes HDAC inhibitor (SAHA) tolerance in glioblastoma. Metabolic Brain Disease. 2023 Mar 11;38(4):1351–64. https://doi.org/10.1007/s11011-023-01184-9
[50] Xiao F, Ouyang B, Zou J, Yang Y, Yi L, Yan H. TRIM14 promotes autophagy and chemotherapy resistance of gastric cancer cells by regulating AMPK/mTOR pathway. Drug Development Research. 2020 Feb 25;81(5):544–50. https://doi.org/10.1002/ddr.21650
[51] Evans E, Staffurth J. Principles of cancer treatment by radiotherapy. Surgery (Oxford). 2018 Mar;36(3):111–6. https://doi.org/10.1016/j.mpsur.2017.12.006
[52] Lu Z, Zheng X, Ding C, Zou Z, Liang Y, Zhou Y, et al. Deciphering the biological effects of radiotherapy in cancer cells. Biomolecules. 2022 Aug 23;12(9):1167. https://doi.org/10.3390/biom12091167
[53] Minniti G, Niyazi M, Alongi F, Navarria P, Belka C. Current status and recent advances in reirradiation of glioblastoma. Radiation Oncology. 2021 Feb 18;16(1). https://doi.org/10.1186/s13014-021-01767-9
[54] Chédeville AL, Madureira PA. The role of hypoxia in glioblastoma radiotherapy resistance. Cancers. 2021 Feb 1;13(3):542. https://doi.org/10.3390/cancers13030542
[55] Mann J, Ramakrishna R, Magge R, Wernicke AG. Advances in radiotherapy for glioblastoma. Frontiers in Neurology. 2018 Jan 15;8. https://doi.org/10.3389/fneur.2017.00748

[56] Zhao M, Xu J, Zhong S, Liu Y, Xiao H, Geng L, et al. Expression profiles and potential functions of circular RNAS in extracellular vesicles isolated from radioresistant glioma cells. Oncology Reports. 2019 Jan 18; https://doi.org/10.3892/or.2019.6972

[57] Wang X, Cao Q, Shi Y, Wu X, Mi Y, Liu K, et al. Identification of low-dose radiation-induced exosomal CIRC-METRN and Mir-4709-3p/grb14/pdgfrα pathway as a key regulatory mechanism in glioblastoma progression and radioresistance: Functional validation and clinical theranostic significance. International Journal of Biological Sciences. 2021;17(4):1061–78. https://doi.org/10.7150/ijbs.57168

[58] Yuan J, Liu Z, Liu J, Fan R. Circ_0060055 promotes the growth, invasion, and Radioresistance of glioblastoma by targeting mir-197-3p/api5 axis. Neurotoxicity Research. 2022 Jul 18;40(5):1292–303. https://doi.org/10.1007/s12640-022-00548-w

[59] Xu H, Xing J, Cheng L, wang Z, zhao L, Ren L, et al. CIRCFOXO3 upregulation mediates the radioresistance of glioblastoma by affecting cellular metabolome. 2023 Oct 29; https://doi.org/10.21203/rs.3.rs-3474740/v1

[60] Sang Y, Chen B, Song X, Li Y, Liang Y, Han D, et al. Circrna_0025202 regulates tamoxifen sensitivity and tumor progression via regulating the mir-182-5p/FOXO3 A axis in breast cancer. Molecular Therapy. 2019 Sept;27 (9):1638–52. https://doi.org/10.1016/j.ymthe.2019.05.011

[61] Huang X, Li Z, Zhang Q, Wang W, Li B, Wang L, et al. Circular RNA akt3 upregulates PIK3R1 to enhance cisplatin resistance in gastric cancer via mir-198 suppression. Molecular Cancer. 2019 Mar 30;18(1). https://doi.org/10.1186/s12943-019-0969-3

[62] Liu X-Y, Zhang Q, Guo J, Zhang P, Liu H, Tian Z-B, et al. The role of circular RNAS in the drug resistance of cancers. Frontiers in Oncology. 2022 Jan 5;11. https://doi.org/10.3389/fonc.2021.790589

[63] Reshke R, Taylor JA, Savard A, Guo H, Rhym LH, Kowalski PS, et al. Reduction of the therapeutic dose of silencing RNA by packaging it in extracellular vesicles via a pre-microrna backbone. Nature Biomedical Engineering. 2020 Jan 14;4(1):52–68. https://doi.org/10.1038/s41551-019-0502-4

[64] Uko NE, Güner OF, Matesic DF, Bowen JP. Akt pathway inhibitors. Current Topics in Medicinal Chemistry. 2020 May 19;20(10):883–900. https://doi.org/10.2174/1568026620666200224101808

[65] Manning BD, Toker A. AKT/PKB signaling: Navigating the Network. Cell. 2017 Apr;169(3):381–405. https://doi.org/10.1016/j.cell.2017.04.001

[66] Turner NC, Alarcón E, Armstrong AC, Philco M, López Chuken YA, Sablin M-P, et al. Beech: A dose-finding run-in followed by a randomised phase II study assessing the efficacy of AKT inhibitor capivasertib (AZD5363) combined with paclitaxel in patients with estrogen receptor-positive advanced or metastatic breast cancer, and in a PIK3CA mutant sub-population. Annals of Oncology. 2019 May;30(5):774–80. https://doi.org/10.1093/annonc/mdz086

[67] Kim S-B, Dent R, Im S-A, Espié M, Blau S, Tan AR, et al. Ipatasertib plus paclitaxel versus placebo plus paclitaxel as first-line therapy for metastatic triple-negative breast cancer (Lotus): A multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. The Lancet Oncology. 2017 Oct;18(10):1360–72. https://doi.org/10.1016/s1470-2045(17)30450-3

[68] Hu G, Pen W, Wang M. TRIM14 promotes breast cancer cell proliferation by inhibiting apoptosis. Oncology Research Featuring Preclinical and Clinical Cancer Therapeutics. 2019 Mar 29;27(4):439–47. https://doi.org/10.3727/096504018x15214994641786

[69] Xue F, Cheng Y, Xu L, Tian C, Jiao H, Wang R, et al. LncRNA NEAT1/Mir-129/bcl-2 signaling axis contributes to HDAC inhibitor tolerance in nasopharyngeal cancer. Aging. 2020 Jul 21;12(14): 14174–88. https://doi.org/10.18632/aging.103427

[70] Yang Q, Du WW, Wu N, Yang W, Awan FM, Fang L, et al. A circular RNA promotes tumorigenesis by inducing C-MYC nuclear translocation. Cell Death & Differentiation. 2017 Jun 16;24(9):1609–20. https://doi.org/10.1038/cdd.2017.86

Article Information
Managing Editor: Jeremy Y. Ng
Peer Reviewers: Amel Sassi, Dusan Pesic
Article Dates: Received Mar 31 24; Accepted May 21 24; Published Aug 16 24

Citation
Please cite this article as follows:
Mohapatra S. The role of endogenous circular RNAs in glioblastoma treatment resistance: A literature review. URNCST Journal. 2024 Aug 16: 8(8). https://urncst.com/index.php/urncst/article/view/596
DOI Link: https://doi.org/10.26685/urncst.596