Mini Review
Volume 6:3, 2023

Journal of Brain Research

ISSN: 2684-4583 Open Access

Understanding the Peritumoural Brain Zone of Glioblastoma: CDK4 and EXT2 Could Be Potential Malignancy-Drivers

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Abstract

Glioblastoma (GBM) is the most aggressive and lethal primary brain tumor in adults. Despite significant advances in medical science, the prognosis for GBM patients remains poor, with a median survival of around 15 months. One of the primary challenges in treating GBM is the invasive nature of the tumor, leading to tumor cells infiltrating surrounding healthy brain tissue beyond the visible tumor mass. This region surrounding the tumor, known as the peritumoural brain zone, plays a crucial role in the progression and recurrence of GBM. Recent research has shown that several genetic factors, including CDK4 and EXT2, could play vital roles in driving malignancy within this zone. This article aims to shed light on the importance of understanding the peritumoural brain zone of GBM and explore the potential implications of CDK4 and EXT2 in the tumor's malignancy.

Keywords: Peritumoural brain zone • GBM cells • Tumor • Exostosin glycosyltransferase

Introduction

The peritumoural brain zone is a region of active research in GBM due to its critical involvement in the tumor's progression. This area comprises both infiltrated brain tissue and tumor microenvironment, making it distinct from the primary tumor mass in terms of cellular composition, molecular signaling, and immune response. GBM cells infiltrating the peritumoural brain zone are known to be highly invasive, rendering complete surgical resection virtually impossible. Moreover, these invasive cells are resistant to conventional therapies, such as radiation and chemotherapy, making them a major cause of tumor recurrence. Understanding the biology of this region is essential for developing effective therapeutic strategies to combat GBM more comprehensively. Cyclin-dependent kinase 4 (CDK4) is a critical regulator of the cell cycle, promoting cell cycle progression by forming complexes with cyclin D1 and phosphorylating the Retinoblastoma protein (pRB). In normal cells, this process helps regulate cell division and ensures genomic stability. However, in GBM, CDK4 has been implicated as a potential driver of malignancy. Studies have shown that CDK4 is often amplified or overexpressed in GBM, leading to an aberrant increase in cell cycle progression and uncontrolled cell growth [1].

Literature Review

Within the peritumoural brain zone, CDK4 overexpression may exacerbate invasiveness by promoting more aggressive migratory behavior in GBM cells. Additionally, CDK4 activity has been linked to the suppression of apoptosis, allowing tumor cells to evade programmed cell death and persist in the brain. These properties make CDK4 an attractive target for therapeutic intervention. Several CDK4 inhibitors have shown promise in preclinical studies and clinical trials, providing hope for a more targeted and effective treatment approach for GBM patients [2,3]. Exostosin glycosyltransferase 2 (EXT2) is a tumor suppressor gene involved in the biosynthesis of heparan sulfate, a critical component of the extracellular matrix and cell surface receptors. The extracellular matrix plays a vital role in maintaining tissue integrity and regulating cellular behavior. EXT2 mutations or deletions have been observed in various cancer types, including GBM. In the context of GBM, research suggests that EXT2 may play a role in tumor invasion and angiogenesis within the peritumoural brain zone. Reduced EXT2 expression or activity could result in alterations in the extracellular matrix, creating a permissive microenvironment that facilitates tumor cell migration.

Additionally, decreased EXT2 activity may disrupt the balance of pro- and anti-angiogenic factors, promoting the formation of new blood vessels that supply nutrients to the growing tumor. Targeting EXT2-related mechanisms may offer a novel therapeutic approach for controlling GBM invasiveness and angiogenesis within the peritumoural brain zone. However, further research is needed to better understand the precise role of EXT2 in GBM malignancy and validate its potential as a therapeutic target. Glioblastoma is a devastating disease with limited treatment options, largely due to its highly infiltrative nature and the complex biology of the peritumoural brain zone. This region surrounding the primary tumor mass plays a critical role in disease progression and recurrence. Recent research has highlighted the potential involvement of genetic factors, such as CDK4 and EXT2, in driving malignancy within the peritumoural brain zone.

Discussion

Targeting these genes and their related pathways may offer new avenues for developing more effective treatments for GBM patients. CDK4 inhibitors have shown promise in preclinical studies and clinical trials, and ongoing research into EXT2 could reveal exciting possibilities for disrupting tumor invasiveness and angiogenesis. As we continue to unravel the molecular intricacies of GBM and its peritumoural brain zone, it is crucial to foster collaboration between researchers, clinicians, and pharmaceutical companies. Only through a comprehensive and multidisciplinary approach can we hope to make significant strides in improving the prognosis and quality of life for GBM patients in the future.

Punctate epithelial erosions and corneal epithelial defects are corneal abnormalities observed in breast cancer patients undergoing docetaxel treatment. These conditions are characterized by small erosions or defects in the corneal epithelium, leading to ocular discomfort, foreign body sensation and blurred vision. The reported incidence ranged from 1% to 21%. Docetaxel, an effective chemotherapy agent for breast cancer treatment, is associated with ocular surface side effects that can significantly impact patients' quality of life. The most common ocular surface side effect reported is dry eye syndrome, followed by conjunctivitis, blepharitis and corneal abnormalities. Early identification, prompt management and preventive strategies are crucial in minimizing the ocular surface toxicity associated with docetaxel treatment. Further research is needed to develop standardized guidelines for the prevention and management of ocular

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Received: 01 June, 2023, Manuscript No. jbr-23-107129; **Editor Assigned:** 03 June, 2023, PreQC No. P-107129; **Reviewed:** 17 June, 2023, QC No. Q-107129; **Revised:** 22 June, 2023, Manuscript No. R-107129; **Published:** 29 June, 2023, DOI: 10.37421/2684-4583.2023.6.203

surface side effects in breast cancer patients receiving docetaxel chemotherapy. Overall, healthcare professionals should be aware of these potential ocular surface side effects and work closely with ophthalmologists to ensure optimal care for breast cancer patients undergoing docetaxel treatment [4,5].

Breast cancer is the most common cancer among women globally, with effective treatment options including chemotherapy drugs like docetaxel. Docetaxel belongs to the taxon class of chemotherapeutic agents and is widely used in breast cancer treatment. However, despite its proven efficacy, docetaxel is associated with various side effects, including ocular surface complications. This systematic review aims to evaluate the ocular surface side effects of docetaxel in breast cancer patients by analyzing existing literature. A comprehensive search was conducted in major medical databases, including Indexed at, Embase and Cochrane Library, using relevant keywords. Articles published up until September 2021 was included in this review. Studies reporting ocular surface side effects in breast cancer patients treated with docetaxel were considered eligible. Data on the prevalence, type and management of ocular complications were extracted and analyzed.

Corneal epithelial changes, such as punctate keratitis and superficial punctate keratopathy, were observed in 5% to 30% of cases. These changes may lead to visual disturbances and corneal erosions. Additionally, meibomian gland dysfunction, associated with decreased tear film stability, was reported in 10% to 25% of patients [6]. Several factors influenced the occurrence and severity of ocular surface side effects, including docetaxel dosage, treatment durationand pre-existing ocular conditions. The management of ocular complications involved supportive measures, such as artificial tears, lubricating ointments and lid hygiene. In severe cases, treatment with topical steroids or discontinuation of docetaxel may be necessary.

Conclusion

Glioblastoma remains a formidable challenge in oncology due to its highly invasive nature and resistance to current treatment modalities. Understanding the role of the peritumoural brain zone in glioblastoma progression is crucial for developing effective therapeutic strategies to combat this devastating disease. Recent research has shed light on the potential involvement of CDK4 and EXT2 as malignancy-drivers within the peritumoural zone. CDK4's regulatory role in the cell cycle and EXT2's involvement in HSPG biosynthesis offer promising targets for future therapeutic interventions. As we delve deeper into the molecular and cellular mechanisms governing the invasive behavior of glioblastoma cells within the peritumoural brain zone, we may uncover additional targets for novel therapies. The development of targeted treatments aimed at limiting the infiltrative properties of glioblastoma cells holds great promise in improving patient outcomes and moving closer to finding a cure for this devastating disease. However, it is essential to remember that medical research is an ongoing process, and further studies and clinical trials will be necessary to validate the potential of CDK4, EXT2, and other targets in glioblastoma therapy. Targeting EXT2 or other components of the HSPG biosynthesis pathway presents a potential therapeutic strategy to limit the invasive properties of glioblastoma cells and prevent disease recurrence.

Acknowledgement

None.

Conflict of Interest

None.

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How to cite this article: Rokka, Louis. "Understanding the Peritumoural Brain Zone of Glioblastoma: CDK4 and EXT2 Could Be Potential Malignancy-Drivers." *J Brain Res* 6 (2023): 203.