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Mechanisms of Tumor Cell Lysis by Enzymatic and Toxin-Mediated Processes: A Systematic Mapping Study

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Abstract

Cancers that affect neural tissue, particularly brain tumors, are often associated with poor prognoses. However, the precise cellular and molecular mechanisms behind their progression and associated complications remain incompletely understood. While considerable knowledge exists regarding different types of brain tumors, the processes by which they disseminate and inflict damage on adjacent brain regions are still unclear. This study examines the hypothesis that leakage of cerebrospinal fluid (CSF), along with enzymes and proteins secreted by tumor cells, may play a role in disrupting the blood-brain barrier (BBB). The research focuses on the role of CSF in brain tumors and its interaction with the BBB. The findings show that leakage typically occurs along the spinal axis, particularly in the thoracic region and the cardiorespiratory junction at the base of the brain. The study aims to identify and characterize the proteins and enzymes present in CSF by assessing: (a) the types of proteins, (b) their molecular identity, (c) their amino acid sequences, and (d) the genes responsible for their expression. In addition, this research demonstrates how tumor-derived components compromise CSF integrity and localize the specific sites of barrier disruption. The data also contribute to the identification of novel biomarkers—enzymes and toxins—released by tumor cells, providing the potential for distinguishing between normal CSF and tumor-associated proteolytic CSF profiles.

Keywords: Enzymes, Cerebrospinal fluid, Blood-brain barrier, Brain cancer

Introduction

The human brain is an exceptionally complex organ composed of extensive neuronal networks responsible for regulating essential functions such as homeostasis, cognition, behavior, and emotion. Despite significant advancements, a comprehensive understanding of the brain's intricacies remains elusive—particularly in the context of treating neurological disorders. The brain's interfaces, such as the blood-brain barrier (BBB) and choroid plexuses, are composed of specialized cells equipped with transport mechanisms that regulate the entry and exit of molecules, preserving the unique environment of the brain's interstitial fluid.

One critical element in maintaining this environment is cerebrospinal fluid (CSF), which is produced by the choroid plexuses and circulates through the ventricular system. This fluid facilitates the exchange of biochemical substances between the brain and its surrounding environment. Disruptions to CSF homeostasis—whether through leakage, altered production, shunting, or rapid absorption—can significantly impact intracranial dynamics. In some conditions, the loss or imbalance of CSF results in syndromes marked by abnormal intracranial compliance, leading to effects such as cranial displacement or pressure-related symptoms.

CSF is increasingly being studied as a diagnostic medium for detecting molecular markers associated with neurological diseases, including cancer. In particular, the presence of tumor-derived enzymes, proteins, and toxins in CSF has become a focus for understanding how brain tumors compromise neural structures, including the BBB. This research examines the current scientific

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literature regarding the biochemical components of CSF in the context of brain cancer, with a focus on enzymes and cytotoxins secreted by tumor cells.

Cancer can arise in nearly any tissue of the body, originating from uncontrolled cellular growth. Enzymes—biological catalysts that accelerate chemical reactions—play a central role in both normal physiology and pathological processes, including tumor progression. These enzymes can be isolated from tumor cells and may influence a variety of molecular pathways, potentially serving as diagnostic biomarkers or therapeutic targets.

This study is guided by the following research questions (RQs):

RQ1: What are the common signs and markers of CSF leakage, tumor-related enzymes, and secreted proteins in brain cancer?

RQ2: Which key publication sources address the breach of the blood-brain barrier and enzyme involvement in brain cancer?

RQ3: Which studies focus on genes encoding the identified enzymes/proteins and their breakdown pathways?

RQ4: What bacterial agents associated with brain cancer have been identified through CSF sampling in the literature?

Literature Review

Brain Tumors

Brain tumors are characterized by the abnormal growth of cells within the brain, either forming a mass of atypical cells or resulting from the abnormal behavior of otherwise normal cells [1]. Given the confined space of the cranial cavity, any abnormal cell proliferation can significantly impact brain function. Tumors can be classified as benign (non-cancerous) or malignant (cancerous), yet both types may elevate intracranial pressure and lead to neurological damage that could be life-threatening. Brain tumors are also categorized as primary (originating within the brain) or secondary (metastatic), the latter arising when malignant cells from cancers in other organs—such as the lungs or breasts—migrate to the brain [2].

While secondary brain tumors are more common than primary ones, most brain tumors, even benign types, can expand within brain tissue and compress nearby structures. This compression can disrupt normal brain function and, in some cases, lead to fatal outcomes. For this reason, clinicians frequently refer to these conditions collectively as “brain tumors” rather than distinguishing strictly between cancerous and non-cancerous cases [3].

One of the main concerns regarding tumors of the brain and spinal cord is their potential to infiltrate surrounding tissues and whether they can be surgically removed. Tumors can vary significantly between adults and children, differing in their location, cellular origin, biological behavior, and treatment approaches. A foundational understanding of the central nervous system (CNS)—specifically the anatomy of the brain and spinal cord—is essential for identifying, classifying, and managing these tumors [3].

Cerebrospinal Fluid (CSF) Leaks

Cerebrospinal fluid (CSF) leakage is among the most challenging complications encountered in neurosurgery. CSF is a clear fluid that circulates through the brain’s ventricles and around the surface of the brain and spinal cord. A CSF leak occurs when there is a defect or tear in the dura mater—the outermost layer of the meninges—resulting in fluid escaping through anatomical openings such as the nose (rhinorrhea) or ears (otorrhea) [4].

This leakage often arises due to traumatic head injury, complications from brain or sinus surgery, or spontaneous structural defects. Unfortunately, CSF leakage is frequently misdiagnosed as migraines, sinus infections, or other headache-related disorders, given the overlap in symptoms. Common clinical signs include orthostatic headaches (intensifying when standing and relieved when lying flat), tinnitus, blurred vision, facial numbness, nausea, and radicular symptoms such as upper limb tingling. These manifestations are nonspecific and can be mistaken for other neurological conditions [4]. In more severe or chronic cases, cognitive decline may also be observed.

RQ1: What Are the Common Signs of Cerebrospinal Fluid (CSF) Leakage?

Cerebrospinal fluid (CSF) leakage is often underdiagnosed or misattributed to other neurological or psychiatric conditions, yet it plays a significant role in central nervous system (CNS) pathology. CSF circulates through the ventricular system, starting from the lateral ventricles, flowing into the third ventricle, and then descending to the fourth ventricle via the cerebral aqueduct (also known as the aqueduct of Sylvius). It is

ultimately absorbed into the bloodstream via arachnoid granulations situated along the brain's surface.

A disruption in CSF flow or containment may result in leakage, frequently caused by trauma, dural tears, or complications from surgical procedures. Clinical signs often include orthostatic headache (worsening when upright, relieved by lying down), nausea, tinnitus, blurred vision, facial numbness, and radicular symptoms such as tingling in the upper limbs. In more persistent cases, cognitive decline has also been documented [5].

Beyond its physiological role, CSF is gaining attention as a diagnostic fluid. It harbors biomarkers significant in identifying brain tumors and other CNS pathologies. Although several molecules have been proposed, only a few have undergone systematic validation for clinical application. This area of research is increasingly being explored for its diagnostic and prognostic potential in oncology and neurology [5].

RQ2: What Are the Key Venues for Publications on Breached Blood Vessels and Enzymes of Brain Cancer?

Breaching the Blood-Brain Barrier

The blood-brain barrier (BBB) is a highly selective, semipermeable interface composed of endothelial cells, astrocyte end-feet, and pericytes that protect brain tissue from pathogens and toxins circulating in the blood. While this barrier is essential for maintaining CNS homeostasis, it also presents a major obstacle in delivering therapeutic agents to the brain. Cancer cells, however, are known to bypass this barrier, enabling the formation of secondary (metastatic) brain tumors from other primary sites such as the lungs or breast [6].

Current literature highlights how extracellular vesicles (EVs)—tiny, membrane-bound particles released by tumor cells—can traverse the BBB. These vesicles carry proteins, lipids, and nucleic acids that manipulate endothelial cells and facilitate barrier permeability. Through this mechanism, EVs aid in metastatic colonization and may contribute to therapy resistance [7]. Journals specializing in neuroscience, oncology, and molecular biology often serve as the primary publication venues for this research, including Neuro-Oncology, Journal of Neuroscience, and Molecular Cancer Research.

Enzymes in Brain Cancer

Enzymes, as biological catalysts, are critical in cellular metabolism and are deeply implicated in cancer progression. Glioblastoma multiforme (GBM), one of the most aggressive and common malignant brain tumors in adults, demonstrates high enzymatic activity that contributes to its invasiveness and resistance to therapy. Despite advancements in surgery, radiation, and chemotherapy, the average survival time post-diagnosis remains approximately 15 months [8].

Enzyme-related studies have shown that cancer stem cells (CSCs) within glioblastomas often survive standard treatments, leading to tumor recurrence. Understanding the enzymatic pathways that govern CSC survival and proliferation could offer new therapeutic targets. Research on this subject is frequently published in journals such as Cancer Research, Journal of Neuro-Oncology, and Frontiers in Molecular Neuroscience.

In many types of cancer, standard treatments primarily target the rapidly dividing tumor cells that form the bulk of the tumor mass. However, neoplastic stem cells divide infrequently and exhibit strong resistance to both chemotherapy and radiation. More concerning is the fact that these stem cells can become activated by treatment itself, leading to tumor recurrence [9]. This phenomenon is particularly evident in glioblastoma, recognized as the most aggressive form of brain cancer. Preventing the recurrence of glioblastoma requires therapies that specifically target these tumor-initiating stem cells. Consequently, researchers have focused on identifying unique molecular markers associated with brain tumor stem cells. Their investigation began with mouse models of glioblastoma to determine whether the identified structures also play a role in human brain tumors [10].

Several enzymes have been implicated in promoting the progression of human brain cancers. These include:

1. Acetyl-CoA synthetase 2 (ACSS2)
2. Kallikrein 6
3. Marker enzymes
4. Cyclin-dependent kinase 5 (CDK5)

Existing Work

Table 1 outlines the roles and functions of key enzymes associated with brain tumor development:

Table 1. Mechanisms and detection methods of enzymes involved in brain tumors

S. no	Type of cancer	Enzyme name	Key findings	Detection method
1	Brain cancer	Acetyl-CoA synthetase 2 (ACSS2)	ACSS2 is central to tumor survival by enabling cells to metabolize acetate as an alternative carbon source when glucose is scarce. This helps tumor cells—especially those deep in the core of the tumor mass—survive nutrient deprivation and continue to grow.	ACSS2 expression was measured using quantitative real-time PCR (qRT-PCR). Inhibition was achieved through RNA interference, and validation was performed using Western blotting.
2	Brain cancer	Kallikrein 6 (KLK6)	KLK6 contributes to resistance against chemotherapy and radiation. Higher KLK6 levels were found in Grade IV glioblastomas and were associated with shorter patient survival (276 days vs. 408 days for lower KLK6 levels). Blocking KLK6 made cells more sensitive to treatment.	A glioblastoma tissue culture model was used to show how KLK6 promotes survival signaling. KLK6 levels were correlated with patient outcomes using clinical and molecular data analysis.
3	Brain cancer	Marker enzyme (choline kinase alpha - ChoKα)	ChoKα is involved in choline metabolism, a key process in membrane synthesis. High uptake of choline-related compounds is seen in PET and MRS imaging of gliomas. ChoKα plays a major role in glioma metabolic activity and tumor grading.	Techniques included PET imaging with 18F-fluoromethylcholine (18F-FMC), magnetic resonance spectroscopy (MRS), and enzyme expression analysis. Tumor grading was assessed using metabolic profiles.
4	Brain cancer	Cyclin-dependent kinase 5 (CDK5)	Inhibiting CDK5 has been shown to halt glioblastoma growth. CDK5 regulates cancer stem cell survival and tumor progression. Its inhibition reduced tumor size and stem cell count in model organisms.	

Table 1 outlines key enzymes released by brain tumor cells, which assist in tumor growth and facilitate their spread from other regions of the body to the brain.

RQ3: Which research studies target genes encoding proteins or enzymes, and how do these enzymes contribute to tumor breakdown?

Enzymatic Breakdown and Tumor Progression

In a healthy body, enzymes are naturally produced to break down damaged tissues or combat infections. These enzymes play vital roles in immune defense by degrading bacteria, viruses, and decaying cells. However, tumors exploit these same mechanisms to their advantage.

Research shows that many cancers—particularly aggressive tumors—produce high levels of these tissue-degrading enzymes. In some cases, even normal immune cells that infiltrate tumors (like white blood cells) can release such enzymes. Though the exact origin of these enzymes in tumor environments is still being investigated, studies suggest they aid in cancer progression by breaking down surrounding healthy tissues, making it easier for cancer to invade new areas.

As tumors grow, their cores often become deprived of oxygen and nutrients due to their distance from nearby blood vessels. In response, cancer cells release angiogenic factors—molecules that promote the growth of new blood vessels (angiogenesis). These new vessels help supply oxygen and nutrients, sustaining tumor expansion. This mechanism not only involves the expression of genes encoding pro-angiogenic enzymes but also supports metastasis and resistance to therapy [11-16].

RQ4: What are the common bacterial samplings of brain cancer in CSF mentioned in the literature?

Bacterial Sampling in CSF and Brain Cancer Diagnosis

Cerebrospinal fluid (CSF) analysis plays a key role in diagnosing brain infections and cancers. If bacteria or other pathogens are found in CSF samples, it may indicate infections like meningitis (inflammation of the

membranes around the brain and spinal cord) or encephalitis. These conditions can be caused by bacteria, viruses, or fungi and may present similarly to neurological disorders.

In the context of cancer, CSF testing is often used when metastasis is suspected. Certain cancers—such as lymphoma, or metastatic breast and lung cancers—can spread to the central nervous system (CNS) via the CSF. Once inside, tumor cells may settle and form secondary growths in the brain or spinal cord.

CSF analysis includes:

- Measuring CSF pressure
- Testing for white blood cell count
- Identifying bacteria or abnormal cancer cells
- Diagnosing autoimmune diseases like multiple sclerosis (MS) or Guillain-Barré syndrome

Sampling is usually performed via lumbar puncture, and researchers test the CSF for malignant cells, especially when tumors are known to disseminate through the fluid (e.g., leptomeningeal metastasis). One of the key diagnostic methods includes cytological analysis and bacterial culture to determine infection or malignancy [17-19].

Materials and Methods

The preference for theoretical mapping is rooted in its foundational importance. It is a theory-driven approach designed to define, compare, and interpret all relevant data about a specific study topic, target area, or phenomenon of interest. Systematic mapping is a well-established research method used to systematically investigate and synthesize scientific data on a given methodology or process. This technique identifies important areas, reveals gaps or discrepancies in existing studies, and provides critical insights for researchers or clinicians, which can guide further investigations. Unlike a traditional literature review, comprehensive mapping analysis requires more time and effort. However, it offers a broader understanding of the topic, providing a solid foundation for generating valuable data on the issues explored in the reviewed studies [20-22].

This systematic mapping process is organized into five steps, as illustrated in **Figure 1**.

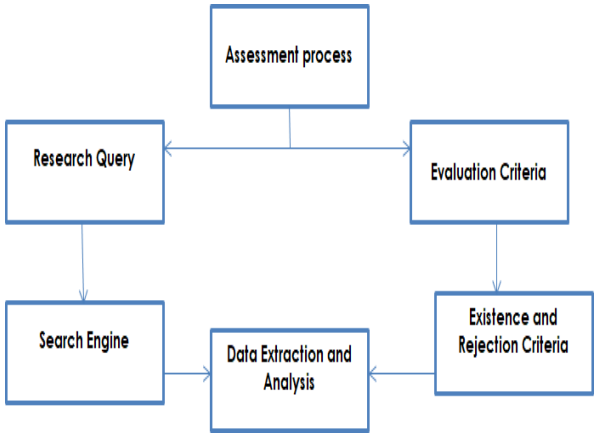

Figure 1. Stages of a systematic mapping study

Conceptual Framework for Data Collection

Figure 1 outlines the framework used for collecting data from various journal publishers. The manuscripts briefly highlight key aspects related to enzymes and the detection of brain cancer through cerebrospinal fluid (CSF), drawing from well-curated journal sources.

Criteria for Selecting Publications

This section defines the guidelines for selecting publications and describes the selection process based on the research objectives. The inclusion criteria are as follows:

- The study covered publications from 2007 to 2022. This period was chosen because most discoveries related to cancer enzymes were made starting in 2007. Although research occurred up until early 2018, the most recent relevant publications from late 2017 were considered in the systematic mapping process.

The inclusion criteria include:

- Studies focused on experimental research related to cancer enzymes.
- Articles that provide information on treatments for brain tumors, identifying cancer-associated enzymes, and methods for detecting CSF.

The exclusion criteria were:

- Articles unrelated to the field of neuroscience.
- Studies offering only guidelines, recommendations, or general overviews of various brain tumor enzymes.
- Articles not published in English.

Enzyme Categorization Results

In this section, the outcomes of the systematic mapping process are shared. A total of 162 studies were initially retrieved. After applying the inclusion and exclusion criteria, 44 articles remained for further analysis. Details of the article selection process are shown in **Table 2**. These selected studies were then thoroughly analyzed to address the research questions.

Table 2. Article selection process

Source	Retrieved	Initial selection	Final selection
IEEE	98	10	6
ACM	20	9	3
Science direct	120	100	20
Springer link	40	20	5
SAGE	30	25	10
Total	308	164	44

Table 2 presents the selection process for articles from different publishing databases. The table shows the total number of retrieved articles, the number initially selected, and the final number of studies chosen based on the defined criteria.

Table 3. Frequency of publications by venue

Library	Type	Frequency
ScienceDirect	Journal	5
ScienceDirect	Journal	3
ACM	Journal	2
IEEE	Journal	2
IEEE	Journal	2
SAGE	Journal	1
Springer	Journal	1

Table 3 illustrates the distribution of selected studies across various publishers like Science Direct, SAGE, and Springer. Notably, Science Direct published the largest number of studies in this selection, contributing 25% of the articles in the review. Springer and SAGE followed in second and third place. This table highlights journals with higher frequencies, specifically pointing out that some journals were included more than once due to their significant contributions to the field of cancer research.

Results and Discussion

This section provides a detailed analysis of the results, aligning them with the research questions to help readers fully comprehend the findings.

RQ1: What are the common signs of cerebrospinal fluid (CSF) leakage and enzymes associated with brain cancer and other secreted proteins?

To answer RQ1, all retrieved articles were carefully analyzed, and the common symptoms of CSF leakage, along with the associated enzymes, were identified. Table 4 outlines the typical signs of a CSF leak, including worsening symptoms when sitting or improvement when lying down, along with the occasional or sudden onset of leakage. The findings from the current mapping process indicate that enzymes are frequently studied, with many researchers focusing on these concerns, as shown in **Table 4**.

Table 4. Targeting CSF for brain cancer biomarker discovery [23-31]

Approach	Method	Pros	Cons
CSF cytoanalysis	CSF is examined under a microscope to detect cancerous cells.	High specificity [23]	Low sensitivity and frequent false negative results [24]
Detection of cancer cells in CSF	Cytometry analysis provides information on cell surface protein expression.	Automated method for quick analysis. Requires a small sample size [25, 26, 27].	False negatives and positives, particularly with fewer than 25 cells/µL [28].
Detection of biochemical molecules in CSF	CSF protein analysis evaluates the total protein composition in CSF.	Can differentiate between subtypes and stages of brain tumors [29, 30].	Limited sensitivity and specificity [28, 31].

Table 4 summarizes various methods for detecting brain cancer biomarkers in CSF, highlighting their respective advantages and limitations.

RQ2: What are the primary sources for publications on enzymes and brain cancer enzymes?

Five major databases—IEEE, ACM, Science Direct, SAGE, and Springer—were utilized to identify the key venues for publications. The results in Table 3 reveal that

articles retrieved from IEEE and ACM are primarily conference proceedings, with only 6 out of 98 articles from IEEE being journal publications. In contrast, the remaining three databases (Science Direct, SAGE, and Springer) predominantly contain articles from clinical journals, except for one article published in a Springer conference. This indicates that IEEE and ACM are primarily conference-based platforms, while Science Direct, SAGE, and Springer focus more on journal articles. To explore the leading journals and conferences publishing articles on enzymes in brain cancer, Table 4 presents journals that have published multiple articles from the selected studies.

RQ3: Which studies focus on genes encoding proteins/enzymes and the breakdown of enzymes in the selected research?

Detection of Enzymes in Cancer Cells within CSF

The findings from the selected studies provide important insights into the detection of cancer cell enzymes in cerebrospinal fluid (CSF). Central nervous system (CNS) cancer is a highly challenging disease that necessitates precise treatment methods. Identifying biomarkers that allow for accurate diagnosis or provide indications of disease progression is vital. CSF has been increasingly targeted in research for potential molecules that could serve as early indicators of brain cancer. However, as of now, only a few of these biomarkers have been standardized for regular medical use. This study delves into the biochemical markers in CSF that have been highlighted as key indicators of brain cancer in the literature, focusing on why many of them remain undiagnosed in tumor management [28].

RQ4: What Are the Common Bacteria Found in CSF in Brain Cancer Cases?

The data from the reviewed studies show that cancer cells can significantly alter the metabolic pathways of normal cells. Mutations in genes related to core metabolic processes (like Isocitrate dehydrogenase 1 and 2, IDH1/IDH2) are pivotal in the development of CNS tumors. This suggests that the altered metabolic states of cancer cells lead to irregular levels of metabolites within CSF. Various forms of systemic cancer are correlated with distinct changes in CSF metabolite profiles. In this study, researchers compared the concentration of 43 metabolites in the CSF from control patients and those with primary or metastatic brain tumors [28].

Research and Practical Implications

This mapping analysis brings both theoretical and practical value. It identifies the key enzymes involved in brain cancer and highlights their frequency in selected studies. This will guide researchers in pinpointing enzymes that could be targeted for therapeutic development. In the future, it may be important to explore cells that migrate between different body parts, which requires additional research. Therefore, the findings from this systematic mapping will aid researchers and practitioners in determining where to focus their investments, develop necessary tools, and strategize for advancements in enzyme-targeted therapies.

Conclusion

This research provides a comprehensive mapping of the effects of enzymes and tumor cell leakage in cerebrospinal cancer. A total of 44 articles were selected following a specific search strategy for this systematic review. The publications were carefully analyzed, and the study focused on six distinct enzymes discussed across these papers. The results revealed that kallikrein 6 (KLK6) and acetyl-CoA synthetase-2 (ACSS2) were the most frequently referenced enzymes in the context of brain tumors. These enzymes are particularly significant in the detection of tumor infiltration and for potential treatment methods involving enzyme-based analysis. The outcomes of this study are expected to assist the cancer research community in improving their understanding of various cancer types and in developing better therapeutic approaches.

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