

A Systematic Mapping Study of detection of Tumor Cell Targeted by Enzymes though Cerebrospinal Fluid

Abstract

Cancers, especially of the neural tissue, are often deemed a death sentence. There is, however, still no clear understanding of the underlying causes nor the cellular and molecular mechanisms of this disease. The spread and collateral damage caused by various types of brain tumors remain poorly understood, despite the information that is currently available about these diseases. A common means of diagnosing tumors is through cerebrospinal fluid (CSF) leakage, and the enzymes from brain cancer cases were investigated within this hypothesis. The purpose of this study was to investigate the role of CSF in brain cancer and BBB. This study conducted a systematic study of leakage that typically occurs at the spine level, namely in the thoracic spine region and the base of the brain along the cardiothoracic connection. This study investigated the bacteria sampling of brain cancer in CSF and determined the common method of targeting cancer cells in the brain and enzymes contained within the CSF. A further finding reveals the precise foci of this leakage and various proteins and enzymes that may be responsible for this damage, as well as evidence that the release of tumor components damages the CSF. As a result of these observations, enzymes and tumor cells are detected, and a new component identifies tumor-related CSF.

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

Introduction

Cancers – especially of the neural tissue are often deemed a death sentence, however, neither the cellular and molecular mechanisms nor the underlying causes are fully defined. Whereas much is now known about various types of brain tumors, it remains poorly understood as to how they spread and cause collateral damage to other parts of the brain. The proposed research is based on a longitudinal prospective method to collect data related to cerebrospinal fluid (CSF) leakage through Enzymes from brain cancer cases, and various secreted proteins and enzymes contained within; these I hypothesize to be responsible for the breach of the blood-brain barrier. This qualitative study is collecting the relevant sample data based on deductive reasoning and cohort studies. The researcher collects the deposited CSF leakage from the brains of cancer patients. The leakage is typically occurring at the spine level, especially in the thoracic spine region and the cardiothoracic connection at the base of the brain. Firstly, the researcher seeks to identify the foci where the secreted products breach the blood-brain barrier using MRI studies, and

they will identify and characterize the various proteins and enzymes contained within the CSF.

Joseph Cleeland, C. S(2021) defined Cancer as a variety of related diseases. Some cells in the body begin to divide uncontrollably and spread to the surrounding tissue. Cancer can begin in the human body which is made up of billions of cells.^[1] When cells get old or damaged, they die and are replaced by new cells. However, when cancer develops, this organized process is disrupted. When cells become increasingly anomalous, old or damaged cells stay alive when they die and new cells form when they are not needed.

Cancers/tumors are malignant tumors that can spread or invade nearby tissues. Furthermore, with the growth of these tumors, certain cancer cells can break away and travel through the blood or lymphatic system to distant parts of the body and form new tumors away from the original tumor. Benign tumors don't spread or invade adjacent tissues, unlike malignancies. Benign tumors can, however, sometimes be very large. They usually do not grow back

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when they are removed, whereas malignant tumors often return to benign brain tumors that may be life-threatening, unlike most benign tumors in other parts of the body. Cancer is a genetic disease, which is due to genetic changes that control the way our cells function, especially how they grow and divide.^[1]

Cancer will begin in the human frame consisting of billions of cells, almost anywhere. Human cells normally expand and separate to create new cells, which the body requires. Enzymes are biological catalysts (additionally referred to as organic catalysts) that increase biochemical reactions in dwelling organisms. They can be extracted from the cells; after which they can be used to stimulate an extensive variety of commercially vital strategies.^[2]

RQ1: What are the common methods of detection of cancer cell enzymes in the CSF?

RQ2: Which research targets compare missing enzymes in the selected studies?

RQ3: What are the common bacteria sampling of brain cancer in CSF discussed in the research?

Literature review

Detection of cancer cell enzymes in the CSF

Brains and spinal cords are components of the central nervous system. Treat central nervous system cancer (CNS), there are several treatment options available. It is extremely important to create biomarkers that can direct an accurate diagnosis of central nervous system cancer or that are useful in predicting disease progression or responding to treatment. Cerebrospinal fluid has been widely targeted to detect molecules that could be beneficial signs of cancer detection. However, only a few of these symptoms have been found in the standardized routine clinical application so far. This study evaluates current scientific understanding regarding biochemical constituents in CSF that have been described in the literature as crucial indicators of brain cancer and discusses why most of the markers have not been recognized in the management of central nervous system cancers.^[2]

RQ1: What are the common methods of detection of cancer cell enzymes in the CSF?

Neoplastic meningitis, also known as leptomeningeal disease (LC), is a rare cancer consequence that affects the entire neuraxis by spreading the disease to the membranes (meninges) surrounding the brain^[2] and spinal cord. Clinical signs of the disease can involve the cranial nerves, cerebral hemispheres, or spine. Since the condition affects all the subarachnoid and cerebrospinal fluid compartments, therapy choices and disease staging must take this into account. Neoplastic meningitis (meningitis tumors) is rarely addressed specifically in studies of patients with primary brain tumors.^[3] An analysis of neoplastic meningitis in primary brain tumors was conducted. The Treatment of neoplastic meningitis increases tumor incidence because the aggressive central nervous system (CNS) is difficult to determine. Neoplastic meningitis is usually the function of CSF cells (cytology);

secondly, neurological symptoms associated with the disease are clinically improved. CSF cells (cytology) can show rostrocaudal dissociation. The primary brain tumors are extrapolated to various randomized prospective experiments; the average survival rate for neoplastic meningitis is several months. In addition to dispersing in the cerebrospinal fluid, neoplastic meningitis occurs when malignant cells penetrate the leptomeninges and subarachnoid spaces. A significant prognostic factor for poor survival, this incidence occurs in 4–15 percent of all patients with solid tumors.^[3]

A fatal complication of solid and hematological neoplasms is neoplastic meningitis (NM), which is caused by neoplastic invasion of the subarachnoid space. Early detection of malignant involvement of the cerebrospinal fluid (CSF) has critical prognostic and therapeutic consequences, although it remains difficult. Disintegrin and Metalloprotease (ADAM) and Matrix Metalloproteases (MMPs) are possible diagnostic indicators of ECM degradation and disruption of the blood-brain barrier in cerebral pathology and metastatic dissemination of tumor cells. PrAMA substrates used in the study had unique enzyme selectivity shapes (FRET-based metalloprotease substrates with unique enzyme selectivity shapes) that the researchers were able to use to study protease activity in CSF samples from NM patients and controls in real-time, multiplex conditions.

Fluorescence variations over time can be used to track the dynamics of protease activity. A proteolytic signature can be identified and studied by simultaneously monitoring a panel of 5 FRET-substrate cleavages to infer the activity of numerous distinct proteases. The tiny amount of CSF is enough to identify the distinct patterns of substrate cleavage among the diseases and provided samples rapidly for reproducibility, and sensitivity. For every substrate, cleavage rates were associated with PrAMA computational inference and different proteases to enhance the activity of MMP-9, ADAM8, and ADAM17 in CSF samples from the patients that were useable to metalloprotease inhibitor batimastat (BB-94).^[4] These activities of proteases are responsible for the breakdown of the blood-brain barrier. CSF cells cannot be detected directly by protease activities from patient samples. This will show why the patient samples present negative cytology. In the end, PrAMA analysis of CSF samples is beneficial for diagnosing the diseases sensitively and detecting patient samples which is useful for clinical practice on normal days.

One thing that distinguishes cancer cells from normal cells is that they can move more easily. So one-way cancers spread through nearby tissues seems likely to be that cells move directly. Scientists have discovered a substance that stimulates the movement of cancer cells. Not sure yet, but this substance probably plays an important role in the spread of local cancers. This research is interesting because researchers can look for ways to stop this substance from working if the substance can help cancer cells move. They can also find ways of stopping the cancer cells that first produce the substance.^[4] Furthermore, CSF cancer cells, which are obtained by preparing CSF and examining it under a microscope for cells,

are the gold standard for identifying brain cancer with leptomeningeal and metastatic cancer moving to the brain.^[5] A sample for myeloid cytology can be collected during tumor surgery or through a lumbar or intraventricular (PCV) sedimentation hole.^[6] However, lumbar CSF is still the recommended sample for detecting malignant cells from primary CNS malignancies.^[7, 8] There is currently a one to two-week recovery period to avoid false positive results due to tumor cell shedding after surgery. Before undertaking a diagnostic cytological study of postoperative CSF,^[8-10] this is recommended. Microscopic cytoplasmic methods are critical criteria for evaluating microscopic imaging techniques. 7.5 mL of CSF fluid is usually taken and treated very away since the number of cells can decline by up to 50% within two hours of collection.^[7, 11] CSF samples are centrifuged (Cytospin®) at 800 g for 3-5 g. minutes, air dried for 10-15 minutes, and stained for 10-15 minutes with MayGrunwald Giemsa (MGG) staining solution.^[12] ThinPrep is a relatively recent liquid-based cytology technique for detecting malignant cells in CSF more accurately than solid tumors because it preserves the morphological characteristics of the cells. ThinPrep analysis is performed using CSF cells extracted using high-filtration and gentle adsorption onto a glass slide using electrochemical forces. The obtained samples should be combined with 10 ml of storage solution and allowed to stand for 15 minutes. Slides

are preserved in 95% ethanol for 15 minutes before staining with the traditional Pap smear procedure.^[12] While CSF cytology is useful, it has significant limitations (**Table 1**). First and primary, it entails the pathological detection of abnormal cells in the CSF using gamma staining, and doctors must make decisions about the presence or absence of malignant cells. CSF cellular analysis is thus completely qualitative testing that is neither quantitative nor devoid of verification.^[13] A further limitation is that because malignant cell shedding in the CSF can occur infrequently and in small quantities, an inconsistent presence of cancer cells in the CSF is expected. As a result, CSF samples may fail to catch malignant cells, which is one of the major flaws in CSF cytology. As a result, if the CSF analysis is the first negative, it is suggested that it be repeated.^[14] One disadvantage is that, while CSF cells are very selective in recognizing cancer cells, they are also hypo-allergic.

Existing work

The following table summarizes the list of approaches and methods of detection and their pros and cons for targeting cerebrospinal fluid for the discovery of brain cancer biomarkers:

Table 1. Targeting cerebrospinal fluid for the discovery of brain cancer biomarkers

Approach	Method	Pros	Cons
Detection of cancer cells in the CSF	Cytanalysis of CSF - examining the CSF for cancerous cells under a microscope	Highly specific ^[5-7]	False negatives are common due to low sensitivity. ^[3, 15-17]
	Cytometry Analysis: They can provide information on the expression of cell surface proteins	The automated method allows for rapid analysis. ^[5, 18] A smaller size of the CSF is needed. ^[9, 17]	A decrease in the number of cells may lead to false negative and false positive results, <25 cells / UL). Minimal differential power has been reported between mitosis and neoplastic cells. ^[16]
	Other tools: DNA cell measurement or fluorescent hybridization technique on-site to measure cancer cell chromosome content in cerebrospinal fluid	It is possible to detect malignant localization from genetic aberrations detected by these technologies. ^[19]	Low sensitivity ^[20]
Detection of biochemical molecules secreted by cancer for CSF	Analysis of CSF protein supplementation: Identifying and quantifying its completeness	The pattern of proteins in specific brain tumors can be used to distinguish between subtypes or degrees of cancer ^[21-24]	Some degree of sensitivity and specificity ^[25]
	MicroRNA CSF Analysis: CSF microRNA measurement	With high specificity and chemical stability ^[26, 27] , detecting miRNAs in CSF only requires small amounts of samples, offering the convenience of repeated monitoring of molecular events occurring during the treatment of cancer. ^[28]	A biomarker's specificity can be affected by factors affecting its level of expression and unknown origin ^[28-33]

Table 1 shows targeting cerebrospinal fluid for the discovery of brain cancer biomarker

Breakdown enzymes

Some normal cells produce chemicals called cell and tissue breakdown enzymes. Cells use enzymes to attack invasive viruses and bacteria. They also use it to break down and clean

up the body's affected areas. All this is part of the process of natural healing. Many cancers contain these enzymes in large quantities. Some cancers also contain many normal, enzyme-producing white blood cells. It is part of the immune response of the body to cancer. Researchers are still uncertain about the source of the enzymes, but they are likely to facilitate the spread of healthy tissue cancer. When cancer passes and

breaks normal tissue, the blood vessels in the vicinity can cause bleeding.^[4]

RQ2: Which research targets compare missing enzymes in the selected studies?

The tumor's nucleus moves away from the blood vessels in the area where it grows as it grows. As a result, the tumor center receives decreasing amounts of oxygen and nutrients. Cancer cells, like healthy cells, cannot survive in the absence of oxygen and nutrition. The endothelial cells line the inner wall of blood vessels, so they send angiogenic factors, which are signals that stimulate the migration, growth, and differentiation of endothelial cells. In the tumor, angiogenesis is controlled by chemical signals that stimulate the growth of new blood vessels. This is known as angiogenesis. A tumor cannot grow much more without a blood supply than a pinhead. Once cancer stimulates blood vessel formation, it can grow faster and bigger, and it induces the growth of hundreds of additional small blood vessels to deliver nutrition and oxygen.^[34]

When the plasma supply from the tumor surpasses the capacity of the surrounding tissues to absorb the growing fluid, edema (with associated increased interstitial pressure) and cyst development occur. Brain and spinal cord tumors (syringomyelia) frequently cause peritumoral cysts (cysts that develop right next to the tumor mass). Cysts around the peritumoral area and the cystic component of central nervous system tumors can cause clinical symptoms. Although peritoneal cysts are frequently associated with central nervous system malignancies and their accompanying mortality, improved imaging techniques, tissues, and molecules have been explored to determine the process underlying cyst genesis and spread. According to scientific research, edema is developed by peritoneal cysts in the central nervous system. The fluid leakage is caused by vascular permeability which is internally active through mediators in the tumor and/or hydrodynamic forces within the tumor's aberrant arteries. Edema and cyst development occur when these forces exceed the ability to surround tissues to reabsorb fluid. Tumor removal or medical therapies that reduce vascular permeability will resolve edema and cysts, suggesting that the tumor is the source of edema that precedes cyst formation.^[35] The underlying idea of modern cancer biology is simple: nearly all mammalian cells share comparable molecular networks that drive cell proliferation, differentiation, and death. The prevalent view, which underpins cancer research, holds that alterations in these networks cause normal cells to become malignant at the molecular, biochemical, and cell levels and that each cell has a set number of models that are very susceptible to change. In this research, we cross-check the nature of enzymes released by a tumor cell and also check the peritumoral cyst formation rates which are full of protein and fluid. We will use the mediators of vascular permeability that operate locally in the tumor and/or the hydrodynamic factors that appear to induce fluid extravasation inside abnormal tumor vasculature. These findings support identifying the level of fluid in tumor cells whether it is CSF fluid or else and their

quantity to increase the edema as well as also evaluate the spinal cord fluid leakage symptoms through the spinal tape that are sustained in brain tumor cases and their types of tumor.^[36]

RQ3: What are the common bacteria sampling of brain cancer in CSF discussed in the research?

Bacteria sampling of brain cancer in CSF

The presence of bacteria or other pathogens in the sample may indicate meningitis. This is a bacterial infection of the membranes that surround the brain and spinal cord. Infections can be caused by bacteria, fungi, and viruses, as well as infectious diseases of the brain and spinal cord such as meningitis and encephalitis. CSF infection tests seek for white blood cells, bacteria, and other chemicals in the CSF, as well as autoimmune illnesses such as Guillain-Barré syndrome and multiple sclerosis (MS).

Lymphoma develops when cancer cells migrate into the cerebrospinal fluid from the breast, lung, or any other area of the body (CSF). Once cancer cells enter the cerebrospinal fluid, they settle in one place in the brain and/or spinal cord and grow. The scientist is conducting a bacterial test to determine the disease and to investigate it through the CSF. This test is mainly used to search for cancerous cells in the CSF, the fluid that surrounds the brain and spinal cord. It is most often used if the tumor has already been diagnosed as a type that can commonly spread through CSF, such as endometriosis. This test measures the pressure within the CSF and collects a sample of the liquid for further analysis. Some neurological illnesses can be diagnosed via CSF analysis. Infections (such as meningitis) and brain or spinal cord injuries are examples. Furthermore, the author employs bacterial assays to identify the vascular endothelial growth factor (VEGF), also known as the Vascular Permeability Factor (VPF), a signal protein produced by cells that promote vascular development. Specifically, VEGF is a subset of growth factors, which is the family of the platelet-derived growth factor family of cystine node growth factors. VEGF concentration was measured by ELISA on matching CSF and serum samples collected from patient data. Patients with solid tumors with MC (n = 11) or brain metastases without concomitant MC (n = 12), nerve syndromes associated with tumors (n = 4), viral and bacterial meningitis (n = 15), and a range of non-neoplastic and non-infectious neurological illnesses (n = 100) were included. The VEGF index was developed using the CSF/serum albumin ratios to estimate the percentage of VEGF produced during the sacrifice. Immunofluorescence labeling of VEGF was done on brain tumor CM-associated breast cancer. All patients with MC had a greater amount of VEGF (mean 6,794.8 pg / mL) in their CSF, but levels of VEGF in similar sera were equivalent to other disease groups. After anticancer treatment, the levels of VEGF in CSF in patients with CM reduced dramatically. VEGF was not detected in CSF samples from patients with cerebral metastases who did not have MC. The mean CSF VEGF concentration in patients with acute bacterial meningitis was 38.6 g/mL, and only 9 of the 17 patients had measurable CSF VEGF levels. VEGF rates were much lower

in patients with bacterial meningitis than in patients with CM tumor (22.8 vs > 62.3), indicating that the percentage of VEGF produced inside the sacrifice was much greater in patients with CM with bacterial meningitis. CSF VEGF levels in patients without persisting neoplastic or infectious diseases were less than the detection limit of 25ppm/ml.^[35]

Results and Discussion

The results will be discussed in detail and mapped against the proposed research inquiries to better understand the readers' abilities.

RQ1: What are the common methods of detection of cancer cell enzymes in the CSF?

A retrospective meta-analysis found that the sensitivity of CSF cells could be as low as 45% depending on how frequently the lumbar puncture was conducted.^[20] There are 10-20% of cases of false passive cellular disease due to insufficient CSF cells as well as similar physical characteristics between benign and malignant cells.^[17-19] The absence of appropriate methodologies for acquiring and assessing CSF cytology samples, as well as the absence of genetic characterization of tumor cells, undoubtedly contribute to a wide range of sensitivity.^[3] As a result, despite its current therapeutic application, CSF cytology remains a poor alternative indication of disease response in brain / metastatic cancer.^[9]

RQ2: Which research targets compare missing enzymes in the selected studies?

Cell metabolism was changed by cancer cells. Normally, mutation genes performed the moral role of creating metabolic pathways such as isocitrate dehydrogenase 1 and 2, and IDH1 / IDH2 which is the most important factor of tumor cells in the central nervous system (CNS). In the end, we hypothesized the malignant cell which indicates the level of abnormality of CSF metabolites in the central nervous system. To check this Nobel theory, we used mass spectrometry for the investigation of 129 patients' samples related to CSF metabolites samples without cancer (n=8) and with cancer history (malignancies) for different types of the central nervous system (n=23). From CSF research, uncontrolled hierarchical cluster analysis reveals discrete tumor metabolite signatures that potentially identify tumor types. The levels of 43 metabolites in CSF from healthy people and CSF from people with central or metastatic nervous system cancer differed. A pathway analysis discovered variations in numerous metabolic pathways between HDI-mutant and HDI-wildtype gliomas (for example, glycine, choline, methionine breakdown, diptamide, and glycolysis pathways, among others). Furthermore, individuals with IDH mutant gliomas showed higher levels of CSF D-2-hydroxyglutarate when compared to patients with other types of tumors or controls. This study's findings suggest that CSF metabolite analysis could be a clinically valuable technique for detecting and monitoring patients with central or metastatic nervous system cancer.^[36]

RQ3: What are the common bacteria sampling of brain cancer in CSF discussed in the research?

In the common lesion of breast cancer which is migrated from another part of the body that infiltrates the meninges, immunochemistry demonstrated significant cytoplasmic staining of VEGF. Large levels of VEGF are released into the CSF in patients with precancerous meningitis. This work provides preliminary evidence that VEGF in CSF could be a valuable biological marker for both identifying and monitoring therapy response in precancerous meningitis.^[36]

Conclusion

In this study, enzymes and cancer cell leakage are studied to map the effects of cerebrospinal cancer on enzymes. A study conducted in this study hypothesized that central nervous system malignant cells exhibit abnormal metabolic states, resulting in abnormal levels of metabolites in CSF and that distinct types of central nervous system malignancies have unique variations in metabolite levels. This study examined the metabolites in the CSF of patients with no history of cancer as well as those with various forms of central nervous system malignancies using mass spectrometry. Compared to CSF from a patient with central or metastatic nerve cancer, CSF from healthy people had abnormalities from metabolites. Patients with IDH mutant gliomas had higher levels of CSF D-2-hydroxyglutarate when compared to patients with other types of tumors or controls, according to a pathway study. It was demonstrated in this study that CSF metabolite analysis is clinically effective for diagnosing and monitoring patients with malignancies of the central nervous system or metastatic to the nervous system. As described in the selected research, enzyme analysis can be used to detect tumor cells and provide solutions to treat them. This result shows the variety of cancer conditions that are affected by these diseases, which could provide a better understanding of how they are caused and how they can be mitigated in the cancer community.

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Conflict of interest

None.

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Ethics statement

The study received ethical approval from Neurospinal & Cancer Care Institute (NCCI), Depot Lines, Mansfield St, Karachi, Karachi City, and Sindh, Pakistan to help me in this project as a consultant in cancer research. All data had been fully anonymized before they were accessed. The Ethics Committee waived the requirement for informed consent because of no greater than minimal risk for participants.

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