Biomere

COMMUNITY BLOG

AN OVERVIEW OF CSF SAMPLING TO SUPPORT DIAGNOSIS OF BRAIN TUMORS

CNS (central nervous system) tumors are primarily located in the brain with some tumors in the spinal cord. CNS tumors can be of various types and are typically named for the cells that are involved – for example, astrocytomas are tumors growing in astrocytes[1]. Globally, over 308,000 people are estimated to be diagnosed with a CNS tumor and about 25,000 adults in the US are expected to be diagnosed per year[2]. Additionally, over 4,000 children are diagnosed with a brain tumor and most cases have a poor prognosis[2]. Given the limited therapeutic options for CNS tumors, early and accurate diagnosis of tumors is critical to improve prognosis and survival rates.

Accessing the brain tissue directly is complicated and invasive but the cerebrospinal fluid (CSF) is a viable alternative to assess cancer biomarkers. CSF is a body fluid that circulates over the brain and down the spinal cord. Since it comes into contact with brain tissue and tumors, secreted biomolecules or cancer cells diffuse into the CSF and can be detected using established analytical or cell based assays[3]. CSF sampling is typically done using a lumbar puncture where a needle is inserted into the spinal cord between the vertebrae. However, cancer cells and secreted biomarkers are not typically found in abundance in the CSF and the analysis may not always be reliable. Therefore, there is a need for more sensitive assays to identify low abundance biomarkers or cancer cells[3].

Current assays to identify cancer cells include cytology analysis where CSF samples are analyzed under a microscope, and flow cytometry analysis to identify cancer cell surface markers. A few recent studies have demonstrated that circulating tumor cells (CTCs) in the CSF can be detected used the FDA approved CellSearch® system[4]. The CellSearch system was originally approved to detect CTCs in breast, colorectal and prostate cancer[5], but it has also been successfully used to identify CTCs in breast cancer related brain metastases[6]. It is likely that as more studies with larger patient cohorts are performed, CTC detection in the CSF may become a standard diagnostic tool to identify brain metastases as well as CNS tumors.

CSF samples are rich in different biomarkers that are typically proteins or microRNAs. Changes in protein composition in CSF from normal vs cancer patients can be measured using ELISA or IHC based assays as well as proteomic analysis or mass spectrometry. A study in 2006 used a mass spectrometry-based method to identify elevated levels of carbonic anhydrase as a marker for gliomas[6]. Several studies have compared normal and malignant patient samples and have identified levels of specific markers[3]. While the results of these studies show promise, it will be important to thoroughly validate tumor type specific biomarkers to meet regulatory requirements for diagnostic testing. MicroRNAs (miRs) are short noncoding RNA fragments that bind to the 3' end of mRNA and inhibit protein translation. There has been an explosion of interest in developing miR based therapies and several miRs have been identified as high potential drugs for specific tumor types. However, as of now, no miR based therapies have been approved by the FDA but the interest in the biopharma industry continues to grow. Identifying miRs in CSF samples is of high interest as diagnostic biomarkers especially since panels of miRs can be used to diagnose specific CNS tumor types. An example of this panel type approach was reported in 2012 where 7 miRs were used to accurately identify glioblastoma and metastatic brain cancer[7].

Despite the active research in this area, there has been a high attrition rate in translating the exciting research findings into the clinic. There is a growing body of literature on the identification of novel biomarkers for specific CNS tumor types, but many of these findings have stalled at the research stage. One of the reasons is that lab to lab differences in sample preparation and analytical methods result in low correlation between studies. Additionally, standard guidelines for CSF collection, sample preparation and analysis are not available so the results are highly dependent on the expertise and experience of each lab. Another reason is that the biomarker analysis requires complex platforms and downstream analysis which is feasible in a research lab setting but may not translate well to clinical labs. In conclusion, CSF samples are a rich source of biomarkers to aid diagnosis of CNS tumors and brain metastases but a lot of process validation and standardization is required to translate research findings to the clinic.

References:

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[2] https://www.cancer.net/cancer-types/brain-tumor/statistics#
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