

This article was written for the Childhood Brain Tumor Foundation, Germantown, MD.

Proteomics

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Current diagnostic and therapeutic monitoring studies are significantly limited in their ability to accurately characterize brain tumor biology and response to therapy. With the majority of CNS tumors, a crucial need exists to develop a means to identify tumor markers that can be used to:

- Reliably assess efficacy of, and tumor response to, specific biologic-targeted therapies (i.e. small molecule inhibitors and anti-angiogenic agents), that may not have “change in tumor size” as a primary therapeutic endpoint
- Reliably detect minimal residual disease
- Aid in the rational selection of new agents for investigation in clinical trials and new targets for novel drug design and therapeutic strategies
- Better predict response to specific targeted therapies augment the ability of neuroimaging studies to differentiate tumor from post-surgical or radiation induced effects
- Add to current histopathologic classification and stratification schemes
- Advances in the technologies of protein quantification and identification are beginning to make possible the large-scale, high-throughput investigation of the proteome. Such investigations hold the promise of addressing some of the needs detailed above.

Proteins make up the structure and “moving parts” that do the work of cells. Proteomics is the study of all the proteins present in a given tissue compartment such as: the blood, an organ, a tumor, or a bodily fluid. Studying the proteins present in different tissue types or in tissues under different conditions yields information about the nature of the cells in those tissues. When applied to cancer research, proteomics often takes the form of comparing the proteins present in tumors to those present in comparable normal tissues. However, in brain tumors, the inherent risks in accessing tumor tissue create limitations to many of the applications of this type of comparative proteomic research. For example, serial sampling would be required to evaluate the tumor proteomics during therapy with a novel therapeutic agent. This could be performed with a skin cancer or leukemia but not with a brain tumor. To address the proteomics of brain tumors, we must exploit the fact that tumor cells and their microenvironment exist in an integrated state. It is therefore possible to interrogate extracellular compartments, such as blood, in order to find tumor specific proteins (also called biomarkers) in the body of a patient who has a tumor. The biomarker can then be used to assess the response to therapy, detect a recurrence of the disease, or screen for the presence of tumors in the general population. An example of a biomarker is the prostate specific antigen (PSA) used to detect prostate cancer.

Proteomics has been used successfully to identify novel biomarkers for solid tumors (1-7). The most notable effort to date involved investigators at the FDA and NCI who surveyed the blood proteome to search for a biomarker with the ability to distinguish normal subjects from those bearing stage I ovarian cancer (1). Other efforts have targeted head and neck cancer, prostate cancer, lung cancer, breast cancer, and hepatocellular carcinoma (2-7).

With the generous support of the Childhood Brain Tumor Foundation, we at Children's National Medical Center are beginning a project aimed at characterizing the proteome of cerebrospinal fluid(CSF), the fluid that bathes the brain and spinal cord, in patients with brain tumors. This endeavor will attempt to identify biomarkers in pediatric brain tumor patients. Because CSF contains a significantly less complex mixture of proteins than blood, it is hoped that the decrease in background “noise” will make tumor-specific markers more readily detected in CSF than in blood. Additionally, CSF is an attractive source of proteins due to its continuous turnover, ready availability (allowing serial sampling), and proximity to brain tissue.

The goal will be the development of a methodology that is reproducible within and between samples, is high throughput, and can be performed upon samples obtained under real world conditions. Multiple parallel techniques will be used to provide cross validation and allow for the creation of a screening profile

(analogous to a tumor fingerprint) as well as specific biomarker identification. The success of such a project could fundamentally change the way in which neuro-oncology is practiced and potentially identify many new targets for the molecularly engineered therapies that are currently emerging.

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