Molecular Neurooncology: Why is it essential?

Human nervous system tumours, like all cancers, arise from aberration(s) in the molecular controls of normal cellular developmental and biological processes. In essence cancer is a genetic disease, the understanding of which is critical toward improving our capability to diagnose, prognose, develop and select specific biological targeted therapies. In conjunction with non-targeted surgical, radiation and chemotherapy, it is the hoped that rational biological therapies will improve the overall outcome of our patients. These molecular alterations that may arise at the level of DNA, RNA or the proteins themselves, are not singular but rather multiple in human nervous system tumors.

Large scale genomic studies such as The Cancer Genome Atlas (TCGA) and upcoming proteomic based studies have already elucidated that there is much heterogeneity in the molecular profile between nervous system tumors which are pathologically similar. This is even more pronounced between pediatric and their adult counterparts. To complicate further, there likely is regional and temporal heterogeneity as the tumours adapt to different micro-environmental conditions and therapeutic interventions.

The cell of origin of nervous system tumors has created much interest with the relatively recent Cancer Stem Cell (CSC) hypothesis. Previously, cancer was thought to arise from differentiated cells such as astrocytes, with accumulation of genetic alterations. In contrast, the CSC hypothesis stipulates that the cell of origin has stem cell properties of self-renewal and differentiation, which acquires transforming genetic alterations.

The CSC differs from differentiated tumour cells, which form the bulk of the solid tumour, in terms of preferred regions of residing around blood vessels and therapeutic sensitivity. Thereby CSC can serve as a nidus for recurrence. Ongoing debate remains as to which of these model systems of the cell of origin is prevalent in both pediatric and adult nervous system tumors. Likely the answer is a composite of both theories in keeping with the heterogeneity of transformed cells and their adaptability to the tumor microenvironment.

Some of the molecular alterations are germline, either inherited or acquired denovo, and found in every cell of the body. These inherited syndromes underlie only a small percentage of human nervous system tumours, being more prevalent in pediatric tumours. The molecular understanding of these well defined group of patients, as part of cancer pre-disposition syndromes is important.

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Often the key molecular alterations in these syndromes are similar to their more common sporadically occurring counterparts. Furthermore, they form the basis of developing model systems such as transgenic mice, to enhance our understanding of the large number of genetic alterations that are being deciphered in sporadic human nervous system tumours and also to provide platforms for therapeutic interventional studies.

In summary, it is essential to understand the molecular biology of nervous system tumours. It is not due to one genetic alteration, but a large number which also evolves as does the tumour. There is already large molecular data sets for adult malignant gliomas and pediatric medulloblastomas, with other nervous system tumours pending. However, what remains the challenge is to determine what are the key molecular alterations and their interactions which “drive” the origin or progression of the tumors vs. those alterations which are secondary and “passengers”. These require experimental paradigms using in vitro and in vitro model systems.

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Dr. Guha also volunteers as a member of Brain Tumour Foundation of Canada’s Professional Advisory Group.