Defining the Immune Phenotype for Glioblastoma Multiforme: One Step Closer to Understanding Our Enemy

Rudy J. Rahme, MD, Rami James N. Aoun, MD, MPH, Andrew R. Pines, MA, Kristin R. Swanson, PhD, Bernard R. Bendok, MD, MSCI

PII: S1878-8750(16)30731-8
DOI: 10.1016/j.wneu.2016.08.063
Reference: WNEU 4474

To appear in: World Neurosurgery


This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.
Defining the Immune Phenotype for Glioblastoma Multiforme: One Step Closer to Understanding Our Enemy

Rudy J. Rahme, MD; Rami James N. Aoun, MD, MPH; Andrew R. Pines, MA; Kristin R. Swanson PhD; Bernard R. Bendok, MD, MSCI

1. Department of Neurological Surgery, Northwestern Memorial Hospital and McGaw Medical Center. Chicago, IL
2. Department of Neurological Surgery, Mayo Clinic. Phoenix, AZ

Glioblastoma Multiform (GBM) has been intensely studied over the last 30 years with little success in prolonging the overall survival as well as the progression free survival rates. The reasons behind the lack of progress are manifold and some are not yet fully understood. Some of these factors include the blood-brain barrier, the invasive nature of the tumor well beyond what is visible on imaging, and the ability of the tumor to evolve under the selection pressure of treatment leading to new resistant phenotypes. The current standard of care consists of surgery followed by radiation and temozolomide as defined by Stupp et al.’s RCT published in 2005 with median survival rates ranging between 14 to 20 months. Following the success of immunotherapy in other types of cancers, such as breast, lung, and melanoma, there has been an increased interest in applying the same concept to GBM. One of the unique challenges of treating this disease is that the immune system is unable to recognize and attack cancerous cells due to surface proteins on the GBM cells that lead to apoptosis of T cells. In other types of cancer, the development of monoclonal antibodies have helped overcome this challenge by blocking immune downregulators as well as other checkpoint inhibitors.

In order to better define the immune environment in GBM and its effect on prognosis, Cheng et al. profiled the immune phenotype of 297 gliomas from the Chinese Glioma Genome Atlas (CGGA) database. The authors first defined an immune-related gene set combining immune system process genes and immune response genes which contained 322 genes. The authors then proceeded to perform a univariate cox analysis and found 8 genes that had prognostic value whether positive (protective) or negative (detrimental). They then devised a formula to
calculate the risk score of GBM patients based on these genes and divided the patients into high risk and low risk based on the risk median value as a cutoff (Fig 1). High-risk patients in the CGGA cohort had statistically significant shorter overall survival (OS) and progression-free survival (PFS) than their low-risk counterparts. The authors then validated their findings by applying the 8 gene-based risk formula on the 536 GBM patients obtained from The Cancer Genome Atlas (TCGA) database. They were able to replicate their findings by revealing that high-risk patients did have a statistically significant lower OS than the low-risk patients. These findings were also replicated in low-grade gliomas. Furthermore, the authors analyzed the immune-related gene expression in low vs. high risk patients and found that low-risk patients had higher expression levels of the protective genes whereas high-risk patient had higher expression of high risk genes. To exclude the major confounding factors, the patients were then stratified by their IDH1 and MGMT status. The authors found that regardless of the IDH1 and MGMT status, high-risk patients still had significantly shorter OS and PFS than low-risk patients. This was again confirmed with a univariate and multivariate cox regression analysis. They noted that high-grade gliomas (GBM) had a distinct immune phenotype when compared to low-grade gliomas defined as grade II and grade III gliomas. In addition, they noted an enrichment of immune-related phenotypes in GBM patients revealing an intense local immune response.

While the findings in this paper are at the very least intriguing, many questions remain. This paper revealed an upregulated immune response in the GBM microenvironment. The real question though is what are the implications of this immune response? What role does it play, if any, in the pathogenesis of GBM? Are these immune-related genes implicated in the resistance to the various therapeutic agents? In addition to being a prognostic factor, can the immune signature be used as a therapeutic target? In other words, can the high-risk genes be targeted and have their expression blocked? And if so, would that have any effect on the OS and PFS? Determining the mechanism of action of these high-risk genes would go a long way towards a better understanding of the role that the immune system can play in GBM.
therapy. Whether these genes act directly or indirectly by activating secondary pathways will have repercussions on the therapeutic potential and resistance to treatment. Along with studying high-risk genes, perhaps even more important would be to discern the “protective” effect of the low-risk genes as well. Though many questions remain unanswered, with the advances in immunotherapy as well genetic profiling, GBM treatment is ready to evolve to the era of precision medicine.

**References:**

Fig 1. Prognostic significance of the immune risk signature in stratified cohorts

- IDH1: wild type
  - Low risk (n=46)
  - High risk (n=60)
  - P=0.0006

- IDH1: Mutation
  - Low risk (n=18)
  - High risk (n=3)
  - P=0.0498

- MGMT promoter
  - Low risk (n=24)
  - High risk (n=38)
  - P=0.0032

- MGMT promoter Methylation
  - Low risk (n=28)
  - High risk (n=17)
  - P=0.03

- Radiation Treated
  - Low risk (n=51)
  - High risk (n=47)
  - P=0.0001

- Chemotherapy: Treated
  - Low risk (n=40)
  - High risk (n=32)
  - P=0.0498