Hypothesis/Commentary

Genetic and Viral Etiology of Glioblastoma—a Unifying Hypothesis

Janardan P. Pandey

Abstract

Growing body of evidence implicates human cytomegalovirus (HCMV) in the etiology of glioblastoma (GBM). Although HCMV is a ubiquitous herpesvirus, only a minority of those infected develop GBM, suggesting the involvement of host genetic factors in susceptibility to HCMV-induced/spurred GBM. HCMV has evolved a large repertoire of strategies for decreasing the efficacy of the host immune response and interfering with viral clearance. One strategy involves the generation of proteins that have functional properties of the Fcgamma receptor (FcγR), which may enable the virus to evade host immunosurveillance by avoiding the effector consequences of antibody binding, such as antibody-dependent cellular cytotoxicity. Results of binding studies involving HCMV-encoded FcγR and genetically different immunoglobulin G proteins suggest that GM genes—genetic determinants of immunoglobulin γ chains—could modulate this viral strategy and thus serve as functional risk factors for the development of GBM, potentially unifying its seemingly disparate infectious, immune, and genetic etiologies. Cancer Epidemiol Biomarkers Prev; 20(6); 1061–3. ©2011 AACR.

Introduction

Glioblastoma (GBM) is a deadly brain cancer that kills more than 90% of the patients within 5 years of diagnosis, despite several modes of aggressive therapies. Therefore, there is an urgent need of novel ideas in GBM research that might lead to effective therapies in this malignancy. Although the exact mechanism(s) is not well understood, the findings by several investigators implicate human cytomegalovirus (HCMV) in GBM pathogenesis (1). The virus has been detected in a high percentage of malignant glioma cells in vivo, but not in adjacent normal brain cells (2–7). Furthermore, enhanced immune responses to HCMV proteins seem to be associated with enhanced survival of GBM patients (1, 8, 9). An infectious etiology would suggest that the genes of the host immune system might mediate the neoplastic process in GBM and contribute to the putative pathways toward the development of this disorder. However, immunity-related genes implicated thus far do not explain the highly significant interindividual differences in susceptibility to HCMV-induced/spurred GBM (10). Here, on the basis of the differential binding of HCMV-encoded FcγR to allelically different immunoglobulin G (IgG) proteins discussed below, I would like to hypothesize that immunoglobulin GM genes are functional risk/protective factors for GBM.

HCMV and immunosurveillance

As mentioned above, HCMV has evolved a large repertoire of strategies for evading host immunosurveillance (11). One of its immune-evasion strategies involves generating 2 proteins—encoded by genes TRL11/IRL11 and UL119-UL118—that have functional properties of the FcγR (12), which may enable the virus to evade host immunosurveillance by avoiding the effector consequences of antibody binding, such as antibody-dependent cellular cytotoxicity (ADCC), complement-dependent neutralization, and phagocytosis. The HCMV-encoded FcγRs may interfere with effector functions in a manner similar to that shown for the more thoroughly studied herpes simplex virus type 1 (HSV1)-encoded FcγR, which binds anti-HSV1 antibodies by bipolar bridging: the Fab part of antibody molecule (paratope) binds to its antigenic target (epitope) on the virus, whereas the Fc part of the antibody binds to the FcγR-like binding site on the viral protein, thus offering survival advantage to the virus by sterically hindering the access of FcγR-expressing effector cells to the HSV1-infected cells (13, 14).

HCMV-encoded FcγR and GM allotypes

Immunoglobulin GM allotypes are hereditary antigenic determinants on γ polypeptide chains. They are encoded by 3 very closely linked cistrons on human chromosome
14. Several population genetic properties of the GM genetic system—the marked differences in the frequencies of GM alleles among races, strong linkage disequilibrium within a race, and racially restricted occurrence of GM haplotypes—suggest that differential selection over many generations may have played an important role in the maintenance of polymorphism at these loci (15, 16). Infectious diseases caused by major pathogens are the most likely selective forces of natural selection in humans (17). GM genes could contribute to this evolutionary mechanism by modifying the strategies employed by infectious agents to evade host immunosurveillance. Results of the studies involving HCMV- and HSV1-encoded FcγRs provide support for this mechanism. In a recent study (18), we have shown that HCMV TRL11/IRL11-encoded FcγR has significantly higher affinity for IgG1 proteins expressing the GM 3+,1−,2− haplotype than for those expressing the allelic GM 17+,1+,2+ haplotype (P = 0.0005). These findings are reminiscent of those reported by Atherton and colleagues (19), who showed that HSV1-encoded FcγR binds much more strongly to the IgG molecule carrying the GM 1,17 allele than the one carrying the GM 3 allele, which differ by 3 amino acid residues at positions 214, 356, and 358 of the γ1 chain. The contrasting binding patterns of the 2 viral FcγRs shed light on the nature of the evolutionary mechanism that maintains genetic polymorphism at the γ1 locus. Because the Fc regions expressing both alleles/haplotypes would be expected to be protective factors due to their modulating effects against the immune-evasion strategies of HCMV and HSV1, the heterozygotes at this locus would have advantage over homozygotes, resulting in the persistence of both alleles/haplotypes in the population.

Anti-HCMV IgG antibodies and GM allotypes

In the inflammatory autoimmune disease scleroderma—in which HCMV seems to serve as an accelerating factor in the disparate pathologies associated with the disease (20)—we have presented evidence for a highly significant association between anti-HCMV IgG antibody responses and GM alleles at the γ1 locus (21). One mechanism underlying this association could involve GM determinants being part of the recognition structure for HCMV epitopes on B cells. Perhaps membrane-bound IgG molecules expressing certain GM determinants are more compatible receptors for HCMV epitopes and thus provoke a strong humoral immunity, whereas IgG molecules with other GM alleles form a less compatible receptor for the critical epitopes of this virus. In addition, and contrary to the prevalent belief in immunology, these constant-region determinants could directly influence anti-HCMV antibody specificity by causing conformational changes in the antigen-binding site in the immunoglobulin variable region (22). They could also influence the expression of idiotypes involved in HCMV immunity. Contribution of immunoglobulin variable and constant regions in the formation of idiotypic determinants has been clearly documented (23). Thus, it is tempting to speculate that the mechanism underlying the recently reported association between high anti-HCMV IgG antibody levels and prolonged survival of GBM patients (9) could involve the expression of high responder GM alleles in these patients.

Testable predictions

Because of their higher affinity to the HCMV-encoded FcγR, subjects with the GM 3+,1−,2− haplotype would be more likely to have their Fc domains scavenged, thereby reducing their immunologic competence to eliminate the virus and virally infected cells through ADCC and other Fc-mediated effector mechanisms. Thus, the hypothesis would predict a higher frequency of the GM 3+,1−,2− haplotype in subjects with GBM than in matched controls, and the reverse for the GM 17+,1+,2+ haplotype, which because of its lower affinity to the viral FcγR, would be expected to be protective. This would provide one explanation as to why not all HCMV-exposed individuals are equally likely to develop HCMV-induced/spurred GBM. Because the GM 3 allele is in significant linkage disequilibrium with the γ2 allele GM 23 and the γ3 allele GM 5, the immune (anti-HCMV) IgG molecules carrying the latter would also be expected to have higher affinity for the viral FcγR than those carrying their allelic counterparts (GM 23− and GM 21) and consequently would be expected to have higher prevalence in GBM subjects than in controls. These allelic predictions are for a Caucasian population; distinct racially associated alleles/haplotypes would be expected to be involved in other groups.

If GM genes contribute to the etiopathogenesis of GBM, as hypothesized here, why have they not been detected by the genome-wide association studies (GWAS) of this malignancy? A likely reason is the absence of these genes in current genotyping platforms. Certain regions of the genome are technologically difficult to type and are not included in the HapMap panel (24). The genes encoding IgG subclasses, which express GM alleles, are highly homologous (>95%) and apparently not amenable to the high-throughput genotyping technology used in GWAS. Therefore, a candidate gene approach would be necessary to test the predictions from this hypothesis.

If large-scale linkage and association studies in diverse racial groups show that GM genes confer susceptibility to GBM, and if the differential binding of viral FcγR to allelically disparate nonimmune IgG is confirmed with immune (anti-HCMV) IgG from GBM patients, it would suggest possible active (vaccine) and passive (antibody based) immunotherapeutic intervention in HCMV-associated GBM.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Received March 8, 2011; revised April 14, 2011; accepted April 16, 2011; published OnlineFirst May 17, 2011.
References

Genetic and Viral Etiology of Glioblastoma—a Unifying Hypothesis

Janardan P. Pandey


Updated version
Access the most recent version of this article at:
doi:10.1158/1055-9965.EPI-11-0247

Cited articles
This article cites 23 articles, 8 of which you can access for free at:
http://cebp.aacrjournals.org/content/20/6/1061.full#ref-list-1

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, use this link http://cebp.aacrjournals.org/content/20/6/1061.
Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.