Immunoglobulin GM Allotypes as Effect Modifiers of Cytomegalovirus-Spurred Neuroblastoma

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Abstract
An uncommon immunoglobulin GM (γ marker) genotype has been reported to be strongly associated with susceptibility to neuroblastoma, but the mechanism(s) underlying this association is not known. Increasing evidence implicates human cytomegalovirus (HCMV) in the pathogenesis of neuroblastoma. HCMV has evolved a large repertoire of sophisticated strategies to evade host immunosurveillance. Particular GM alleles modulate an immunoevasion strategy of HCMV and contribute to humoral immunity to HCMV epitopes, attributes that provide possible mechanistic explanations for their involvement in the etiopathogenesis of neuroblastoma and explain, at least partially, why a common virus causes/spurs an uncommon cancer. Cancer Epidemiol Biomarkers Prev; 22(11); 1927–30. ©2013 AACR.

Introduction
GM allotypes are encoded by 3 very closely linked genes—immunoglobulin heavy chain G1 (IGHG1), IGHG2, and IGHG3—on chromosome 14q32. They are localized on the constant regions of γ1, γ2, and γ3 chains (1). Using hypothesis-driven candidate gene approaches, several studies have identified particular GM genes/genotypes as risk factors for many malignant diseases (2–6). In neuroblastoma, a study involving 68 patients with neuroblastoma and 2,773 normal blood donors as controls, reported a highly significant association (P < 0.001) between a GM genotype (GM 1/a, 3/f, 5/b) and susceptibility to neuroblastoma (7). Although this association is very strong, it nonetheless needs to be replicated by independent investigations. It is noteworthy that it has not been confirmed or refuted by genome-wide association studies (GWAS) of this malignancy. One contributing factor for this omission might be the absence of GM gene probes in most genotyping platforms. GWAS are assumed to be able to detect/tag all single-nucleotide polymorphisms (SNPs) in the genome whose frequency is at least 5% or less (using newer arrays). This, however, is not true. Most GM alleles are common within a racial group (some typed in the HapMap or the 1000 Genomes projects, they cannot be imputed or tagged (through linkage disequilibrium) by any SNPs that are included in the genotyping platforms (8, 9). SNPs responsible for most of the 18 serologically detectable GM specificities have not yet been identified.

HCMV and Neuroblastoma
Although HCMV is not considered an oncogenic virus at present, several features of HCMV biology overlap with the essential alterations of cell physiology, including tumor microenvironment, that are hallmarks of cancer, as enunciated by Hanahan and Weinberg (10). Several HCMV proteins—US2, UL16, IE2—and HCMV-encoded homologs to immunosuppressive cytokines [e.g., interleukin (IL)-10] are involved in the evasion of host immunosurveillance. HCMV proteins IE1, IE2, and others inhibit apoptosis, thus resisting cell death (11). Increasing evidence implicates HCMV in the pathogenesis of neuroblastoma (12–15). A recent report documented the expression of early and late HCMV proteins in primary neuroblastomas, in neuroblastoma cell lines, and in neuroblastoma xenografts. The antiviral drug valganciclovir, which is specific for HCMV, significantly reduced both the viral protein expression and the tumor cell growth (16). Thus, although HCMV infection has not yet been shown to directly result in tumor formation, and additional functional studies providing evidence for its involvement in cancer development are clearly warranted, the observations cited above do suggest a role for this virus in the pathogenesis of neuroblastoma. But the question arises: How could a common virus (seroprevalence 80%) cause an uncommon (0.01%) disease? Understanding the contribution of certain host genetic factors, which influence immunity to HCMV and modulate particular viral immunoevasion strategies, may shed light on this vast discrepancy.

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HCMV Immunevasion and GM Allotypes

As mentioned above, HCMV has evolved a large repertoire of strategies for evading host immunosurveillance (17, 18). One strategy involves encoding proteins with functional properties of the Fcγ receptor (FcγR; ref. 19), 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. Interestingly, one of the GM alleles (GM 3) in the uncommon genotype (GM 1, 3, 5) associated with neuroblastoma modulates this viral strategy, which provides a mechanistic explanation for its involvement in susceptibility to this malignancy. The HCMV TRL11/IRL11-encoded FcγR (gp34) has significantly higher affinity for IgG1 proteins expressing the GM 3+, 1+−, 2−-allotypes than for those expressing the allelic GM 17+, 1+, 2+− allotypes (20). Because of their higher affinity to the viral FcγR, subjects with the GM 3+, 1+−, 2−-alleles would be more likely to have their Fc domains scavenged, thereby reducing their immunologic competence to eliminate the virally infected cells through ADCC and other Fc-mediated effector mechanisms and consequently would be at an increased risk of developing HCMV-associated diseases. Similar studies involving the other HCMV-encoded FcγRs (gp68 and RL13), as well as the GM markers expressed by IgG2 and IgG3 proteins, are warranted to further delineate the mechanisms underlying the GM gene involvement in HCMV-spurred neuroblastoma. Furthermore, to be truly relevant to neuroblastoma, the HCMV FcγR-IgG binding studies need to use affinity-purified anti-HCMV antibodies isolated from the sera/plasma of patients with neuroblastoma. For the measurement of affinities between the HCMV-encoded FcγRs and allotypically disparate IgG proteins, surface plasmon resonance, which provides an absolute quantitative measure of binding affinity between 2 molecules, would be preferable.

HCMV Antibodies and GM Allotypes

GM allotypes could also mediate the pathogenesis of HCMV-spurred neuroblastoma by contributing to immunity to this virus. GM allotypes 3 and 17 are associated with humoral immunity to HCMV in scleroderma, an inflammatory autoimmune disease with suspected HCMV etiology (21–23). Similar studies in neuroblastoma are warranted. Although GM 3 and 17 are constant-region determinants, they could directly influence anti-HCMV antibody specificity by causing conformational changes in the antigen-binding site in the immunoglobulin variable region. It is noteworthy that amino acid sequence polymorphism in the CH1 domain of the γ1 chain—where the allelic determinants GM 3 and GM 17 are located—has been shown to modulate the kinetic competence of antigen-binding sites (24, 25). Constant-region GM allotypes could also influence the expression of idiotypes involved in HCMV immunity. Contribution of both variable and constant regions in the formation of idiotypic determinants has been clearly documented for the T15 system in mice (26). Similar studies on the control of idiootype expression in humans are warranted.

Herpesvirus Immunevasion and the Maintenance of Allelic Diversity at GM Loci

There are striking qualitative and quantitative differences in the distribution of immunoglobulin GM allotypes among different racial groups (1). In addition, there is almost complete linkage disequilibrium between particular GM determinants within a race, and every major racial group is characterized by a distinct array of GM haplotypes. These population genetic properties suggest that differential selection may have played an important role in the maintenance of polymorphism at these loci, but the nature of putative evolutionary selective forces is not understood. As first suggested by J.B.S. Haldane, major infectious diseases have been the principal selective forces of natural selection (27). One mechanism as to how GM determinants could contribute to the outcome of infection with various agents may be through their modulating influence on the immune evasion strategies used by these pathogens, resulting in differential immunity to infectious diseases. A clue to one such mechanism is provided by the contrasting contribution of GM 3 and 17 alleles to the immune evasion strategies used by HCMV and herpes simplex virus type 1 (HSV1). Like HCMV, the HSV1-encoded FcγR also discriminates between GM 3 and 17 alleles; however, in contrast to the former, it binds much more strongly to the IgG molecule carrying the GM 1, 17 allele than the one carrying the GM 3 allele (28). 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. As the constant 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.

Racial Disparity in Neuroblastoma Outcomes and GM Allotypes

A higher proportion of black children than white children present with high-risk neuroblastoma and have worse survival (29). However, it is relevant to note that this topic is controversial and a study using subjects at a research hospital did not find disparities in neuroblastoma outcome (30). A trans-population analysis, which focused on SNPs identified in GWAS of this malignancy, identified a common SNP (within sperm-associated antigen 16) to be responsible for the ethnic disparities in survival (31). By selecting only the genes identified by GWAS, however, this study might have excluded some genetic variants relevant to ethnic disparities in neuroblastoma. Common GM alleles, which are usually not evaluated by GWAS, are one of the most powerful tools for genetic characterization of human
GM Allotypes and Neuroblastoma

populations; for instance, unless there is genetic admixture, GM 3 is not found in African Americans; GM 6 is present only in people of African ancestry; GM 1 is polymorphic only in people of European ancestry (1). Thus, for instance, anti-HCMV IgG3 antibodies expressing the GM 6 allele in the Fcγ region could have a high affinity for the HCMV-encoded FcγR, which would hinder their ability to eliminate the virus by Fc-mediated effector mechanisms, resulting in an enhanced risk of developing HCMV-spurred neuroblastoma in individuals expressing this determinant. Similarly, GM 6–expressing IgG3 antibodies against tumor-associated antigens relevant to neuroblastoma (e.g., GD2) could have a low affinity (which usually translates into low cytotoxicity) to the cellular FcγRs expressed on effector cells (natural killer cells and neutrophils), resulting in reduced ADCC against tumors. Either or both of these possibilities would lead to worse outcome in African American children with neuroblastoma.

The shortcomings of the hypothesis that GM genes are effect modifiers of HCMV-neuroblastoma association include (i) the GM gene–neuroblastoma association reported by Morell and colleagues has not been confirmed by independent investigations; (ii) supporting HCMV FcγR-IgG binding studies used nonimmune IgG proteins. Although it is unlikely to affect the outcome, to be truly relevant to neuroblastoma, anti-HCMV anti-

bodies isolated from patients with neuroblastoma would be preferable for these experiments; (iii) a lack of studies involving GM genes and antibody responsiveness to HCMV epitopes and neuroblastoma-associated antigens (e.g., GD2), using specimens from patients with neuroblastoma. Despite these shortcomings, the author hopes that the ideas and observations presented here would inspire large-scale investigations of immunoglobulin GM genes and immunity to HCMV in neuroblastoma that could provide additional insights into (i) the mechanisms underlying the association of an uncommon GM genotype with neuroblastoma; (ii) the vast discrepancy between HCMV seroprevalence and the prevalence of neuroblastoma; (iii) the "missing" (unexplained by the SNPs identified by the GWAS) heritability in neuroblastoma; (iv) the possible reasons behind the racial disparity in neuroblastoma survival; (v) the putative evolutionary selective mechanisms responsible for the maintenance of extensive polymorphism in the GM gene complex; and (vi) the putative factors that influence the HCMV-host co-evolution.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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