Significance of FçγRIIIa-V158F Polymorphism—Letter

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Cartron and colleagues in their commentary (CCR Translations) present an informative discussion of several putative host and tumor factors that may explain the conflicting reports of correlation between FçγRIIIa-V158F polymorphism and response to rituximab and other mAbs (1). To their list of possible variables influencing the outcome of mAb therapy, I would like to add the extensive genetic polymorphism in the Fc region of IgG. Most presentations on this topic have treated the constant region of human IgG as if it were naturally monomorphic. The constant region of IgG heavy chains is highly polymorphic with at least 18 testable specificities, γ marker (GM) allotypes, segregating at differing frequencies in different population groups (2).

There are several mechanisms through which GM polymorphisms could contribute to the efficacy of mAbs. For instance, mAbs expressing different GM allotypes in the Fc region bind differentially to the neonatal Fc receptor (FcRn), thereby influencing the half-lives of infused mAbs (3). An mAb expressing the GM 1,3 haplotype has higher affinity to FcRn, and is transcytosed better, than the commercial mAbs expressing other allotypic combinations, including rituximab, which expresses GM 1,17 allotypes (3). Antibodies to GM allotypes could also contribute to the decrease and acquired resistance to mAb therapy. Most GM determinants are highly immunogenic. Thus, anti-allotype antibodies, generated through infusion of mAbs, allotype-incompatible blood transfusion, or preexisting because of maternal-fetal incompatibility, could reduce the effectiveness of infused mAbs.

Through their epistatic interactions with the FçγRIIIa alleles expressed on natural killer cells, GM allotypes have been shown to contribute to the magnitude of antibody-dependent cellular cytotoxicity (ADCC), a leading mechanism underlying the clinical efficacy of mAb therapy (4, 5).

There is another factor that could contribute to the inconsistent correlation between FçγRIIIa-V158F polymorphism and the efficacy of mAb therapy. In addition to killing the tumor cells by engaging the Fc-mediated effector mechanisms, infused mAb “immunizes” the patients via the antigen-processing/presenting pathway and thus augments the endogenous antibody responses to the tumor antigen complexed with the mAb. These endogenous antibodies will express the patient’s Fc (GM) genotype, whose affinity to the FçγR alleles might be different from that of the infused mAb, resulting in differences in the magnitude of ADCC and in the efficacy of mAb therapy.

These mechanisms suggest that in the construction of mAbs and in the evaluation of their clinical efficacy, natural genetic variability in both FçγR and Fc (GM) should be taken into consideration.

Disclosure of Potential Conflicts of Interest

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