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# Consideration of C1q and FcRn binding to allotypically disparate IgG3 could aid in engineering more efficacious anti-SARS-CoV-2 mAbs

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Izadi et al. (1) have added to the increasing body of evidence that IgG3 monoclonal antibodies (mAbs) are more potent than their IgG1 counterparts in mediating Fc-mediated effector functions. They also show that immunoglobulin constant domains influence variable-region binding. Although evidence of constant-region contribution to the expression of variable-region determinants was presented 40 y ago by one of the founders of modern immunology (2), it has been largely overlooked by the immunology community.

Izadi et al. have shown that IgG3 mAbs induce more potent complement activation, resulting in complement receptor–mediated phagocytosis. Since the C1q complex, which triggers the complement cascade, binds differentially to IgG3 antibodies expressing different GM (γ marker) alleles (3), it is conceivable that an IgG3 mAb expressing a higher affinity (to C1q) GM allele would be an even more potent complement activator. It appears that all subclass-switched IgG3 mAbs investigated by Izadi and colleagues express the GM 11/b0 allele of the *IGHG3* gene located on human chromosome 14q32. GM 11 is in linkage disequilibrium with GM 5/b1, which has a slightly lower affinity to C1q than its allelic counterpart, GM 21/g (3).

Izadi et al. state that IgG3 has short half-life due to its lower affinity to the neonatal Fc receptor (FcRn), limiting its biological utility. However, not all IgG3 antibodies are the same in terms of their binding affinity to the FcRn; rather, IgG3–FcRn binding is GM allotype restricted (4). In fact, the short half-life of IgG3 can be overcome by introducing histidine (H) at position 435 of IgG3, which is naturally present in people with the GM 15/s,16/t haplotype (5). The half-life of H435-expressing IgG3 is comparable to that of IgG1 (4, 5).

With 13 GM alleles segregating at different frequencies in different populations, IgG3 is the most polymorphic IgG subclass (6), which may be a result of selective pressure from infectious diseases during our evolutionary history. In sum, taking into account the extensive allelic diversity of IgG3—and its allotypically differential binding to C1q and FcRn—could help engineer IgG3 mAbs with more potent effector functions and longer half-life.

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