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A Multivalent Binding Model Predicts FcγR Regulation and Effector Cell-Elicited Killing

Immunoglobulin (Ig)G proteins are crucial regulators of the immune response and particularly versatile therapeutic agents. These capabilities are due to their high-affinity antigen binding and their ability to direct immune effector cell-elicited responses via the Fcγ receptors. IgGs elicit effector response through the multiple members of the FcγR family, cell types (e.g., macrophages, monocytes) and processes (e.g., ADCC, ADCP). Many possible design parameters—FcγR binding affinities, responder cell populations, and antigen binding properties—make precisely predicting and manipulating effector response an elusive goal. Here, we show that a model of multivalent receptor-ligand binding accurately accounts for the contribution of IgG-FcγR affinity and immune complex (antibody-antigen complex) valency [1]. Modeling the binding of various effector cell types based on their FcγR expression is better able to predict effector-elicited disease clearance in mouse models of melanoma, ITP, B cell cancer, and HIV infection than the receptor affinities directly. Moreover, the model accurately identifies and weights binding to experimentally verified critical effector populations. Building upon this model, we explore the predicted effects of IgG Fc combinations, and under which regimes two IgG isotopes or glycosylation forms might operate synergistically or antagonistically. In total, these results enable both rational immune complex design for a desired IgG effector function and the deconvolution of effector cell-elicited responses.

[1] Ryan A. Robinett, Ning Guan, Anja Lux, Markus Biburger, Falk Nimmerjahn, Aaron S. Meyer. Dissecting FcγR Regulation through a Multivalent Binding Model. Cell Systems. 2018.