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The impact of Fc receptors and host characteristics on myeloid phagocytic response to rituximab-treated 3D-cultured B-cell lymphoma

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Antibody-based immunotherapy is successful in treating cancer, however its effectiveness varies among patients. To improve treatment outcome in each patient we need to understand what factors affect biological activities of therapeutic antibodies. Antibodies depend very much on the functional properties of immune cells that express Fc receptors (FcR). In this study, we explored FcR expression as well as host characteristics of monocytes in the capacity to phagocyte 3D-cultured human $CD20^+$ B-cell lymphoma (spheroids) treated with isotype variants of anti-CD20 rituximab (RTX) monoclonal antibody. The monocytes were obtained from healthy donors of different ages and sexes and their FcR for IgG (FcγRI, FcγRIIa, FcγRIIIa) and IgA (FcαRI) were determined, as well as FcR gene polymorphisms. Antibody-dependent phagocytosis was assessed using flow cytometry, confocal imaging, and Fc receptor blocking. Different RTX isotypes showed varying efficacy in stimulating phagocytosis of lymphoma spheroids. RTX-IgG3 proved to be most efficient, followed by RTX-IgG1, while moderate efficacy was observed by RTX-IgA1, RTX-IgA2, RTX-IgG4, and RTX-IgG2 had minor effect. RTX-stimulated monocytes infiltrated lymphoma spheroids predominantly at the periphery, but monocytes could also be identified in the spheroid core. Blocking FcγRI or FcγRIIa, but not FcγRIIIa, with antibodies inhibited RTX-IgG1 and RTX-IgG3-mediated phagocytosis. Monocytes derived from younger women exhibited elevated levels of FcγRI and FcγRIIa in comparison to their older counterparts. Conversely, in older men, there was a notable rise in FcγRI and FcγRIIIa levels when contrasted with younger men. This pattern was further supported by the observation that monocytes isolated from younger women displayed heightened phagocytic activity compared to those from older women. Similarly, older men demonstrated superior IgG-mediated phagocytosis relative to younger men. Single Fc receptor levels, or FcγRIIa and FcγRIIIa genetic variants, had low correlation with phagocytic intensity, possibly due to the involvement of multiple Fc receptors in IgG-mediated phagocytosis. In conclusion, the interplay of antibody isotype, Fc receptors, age, and sex significantly affects tumor phagocytosis. This study unveils a critical connection between host characteristics and the effectiveness of therapeutic antibodies, offering invaluable insights for advancing cancer immunotherapy treatments.