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

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The effectiveness of antibody-based immunotherapy in treating cancer varies among patients, making it crucial to understand the role of myeloid phagocytic responses to therapeutic antibodies. This study sheds light on the role of immunoglobulin Fc receptors (FcR) and host characteristics in antibody-dependent cellular phagocytosis (ADCP).

Using primary monocytes from healthy blood donors of different ages and sexes, the study assessed ADCP of 3D-cultured $CD20^+$ B-cell lymphoma (spheroids) treated with anti-CD20 rituximab (RTX) monoclonal antibodies (mAb) of different isotypes. The isotypes displayed different efficacy to stimulate donor monocytes to phagocytose spheroid cells, with RTX-IgG3 being most efficient followed by RTX-IgG1. Monocytes infiltrated RTX-treated spheroids predominantly at the periphery, but migrated also into the core when stimulated with RTX-IgG3. Blocking monocytes with antibodies to FcγRI or FcγRIIa, but not FcγRIIIa, prior co-culture with RTX-opsonized spheroids inhibited RTX-IgG1 and RTX-IgG3 stimulated ADCP.

The study demonstrates further that a combination of age and sex have a significant impact on monocytic capacity to phagocytose multicellular tumors. Specifically, younger women demonstrated higher ADCP than older women, while older men demonstrated higher ADCP than younger men. Interestingly, single FcR expression levels, or FcγRIIa and FcγRIIIa gene variants had low correlation with ADCP intensity, likely due to multiple FcγR engagement for IgG isotypes.

In conclusion, specific mAb isotypes, sex and age can be taken into consideration to improve monocytic capacity to phagocytose multicellular tumors. Understanding ADCP is essential for improving antibody treatment of individual cancer patients, and this study provides valuable insights towards that goal. Overall, this research brings us one step closer to achieving more personalized and effective antibody-based cancer immunotherapy.