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Blood 142 (2023) 5796

The 65th ASH Annual Meeting Abstracts

ONLINE PUBLICATION ONLY

605.MOLECULAR PHARMACOLOGY AND DRUG RESISTANCE: LYMPHOID NEOPLASMS

The KIR-HLA-CD16a Immunogenetic Profile Influences NK Cell-Mediated ADCC and Response to Rituximab Therapy in B-Cell Lymphomas

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Rituximab-based chemoimmunotherapy (R-CHOP) is the standard of care in most B-cell lymphomas, however there is marked interpatient heterogeneity in treatment response. An important mechanism of Rituximab (anti-CD20) action is through natural killer (NK) cell-mediated antibody-dependent cellular cytotoxicity (ADCC), but the factors influencing this are poorly understood. Here, we present findings from a preclinical study investigating the role of NK cell receptor polymorphisms and HLA allelic variation on ADCC against aggressive B-cell lymphoma cell lines. Genotyping was conducted using Luminex-based SSO and Sanger sequencing. Multicolor flow cytometry was used to assess the response of activated NK cells from healthy donors against 8 lymphoma cell lines. Individuals carrying the GG or GT allele in CD16a were found to have a 3-8 fold greater NK cell response compared to individuals with a TT allele and rituximab-mediated ADCC was significantly greater in individuals with a KIR-3DL1 allele when tested against B-cell lymphomas lacking the HLA-Bw4 allele. An additive effect was observed when considering both CD16a and KIR-HLA together. As expected, CD20 expression was a strong correlate of NK cell response. In summary, NK cell-mediated ADCC in response to ADCC appears to be influenced by the KIR-HLA-CD16a genotype. These findings suggest a potential role for immunogenotyping in B-cell lymphomas treated with Rituximab. Additionally, the presence of the shared F_c receptor domain opens the possibility of applying this framework towards predicting NK cell responses to antibody therapies in other diseases.

Disclosures Storek: *Sanofi-Pasteur:* Research Funding.

https://doi.org/10.1182/blood-2023-190062