Tipo	Periódico
Título	G protein-coupled receptor 183 mediates the sensitization of Burkitt lymphoma tumors to CD47 immune checkpoint blockade by anti-CD20/PI3Kδi dual therapy
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Programa/Curso (s)	Programa de Pós-Graduação Stricto Sensu em Ciências da Saúde
DOI	10.3389/fimmu.2023.1130052
Assunto (palavras chaves)	D spheroid; ADCP; B-NHL; CAM assay; M1 macrophage; drug combination; immune checkpoint blockade; inflammatory receptor
Idioma	Ingles
Fonte	Título do periódico: Front Immunol ISSN: 1664-3224 Volume/Número/Paginação/Ano: 2023 Apr 21:14:1130052
Data da publicação	April 2023
Formato da produção	Impressa ou digital
Resumo	Background: Immunotherapy-based regimens have considerably improved the survival rate of B-cell non-Hodgkin lymphoma (B-NHL) patients in the last decades; however, most disease subtypes remain almost incurable. TG-1801, a bispecific antibody that targets CD47 selectively on CD19+ B-cells, is under clinical evaluation in relapsed/refractory (R/R) B-NHL patients either as a single-agent or in combination with ublituximab, a new generation CD20 antibody. Methods: A set of eight B-NHL cell lines and primary samples were cultured in vitro in the presence of bone marrow-derived stromal cells, M2-polarized primary macrophages, and primary circulating PBMCs as a source of effector cells. Cell response to TG-1801 alone or combined with the U2 regimen associating ublituximab to the PI3Kδ inhibitor umbralisib, was analyzed by proliferation assay, western blot, transcriptomic analysis (qPCR array and RNA sequencing followed by gene set enrichment analysis) and/or quantification of antibody-dependent cell death (ADCC) and antibody-dependent cell phagocytosis (ADCP). CRISPR-Cas9 gene edition was used to selectively abrogate GPR183 gene expression in B-NHL cells. In vivo, drug efficacy was determined in immunodeficient (NSG mice) or immune-competent (chicken embryo chorioallantoic membrane (CAM)) B-NHL xenograft models. Results: Using a panel of B-NHL co-cultures, we show that TG-1801, by disrupting the CD47-SIRPα axis, potentiates anti-CD20-mediated ADCC and ADCP. This led to a remarkable and durable antitumor effect of the triplet therapy composed by TG-1801 and U2 regimen, in vitro, as well as in mice and CAM xenograft models of B-NHL. Transcriptomic analysis also uncovered the upregulation of the G protein-coupled and inflammatory receptor, GPR183, as a crucial event associated with the efficacy of the

	triplet combination. Genetic depletion and pharmacological inhibition of GPR183 impaired ADCP initiation, cytoskeleton remodeling and cell migration in 2D and 3D spheroid B-NHL co-cultures, and disrupted macrophage-mediated control of tumor growth in B-NHL CAM xenografts. Conclusions: Altogether, our results support a crucial role for GPR183 in the recognition and elimination of malignant B cells upon concomitant targeting of CD20, CD47 and PI3Kδ, and warrant further clinical evaluation of this triplet regimen in B-NHL.
Fomento	