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MYELOID CELLS CONTRIBUTION IS KEY TO REPRODUCE CRS PATHOPHYSIOLOGY INDUCED BY T CELL ENGAGERS IN BRGSF-HIS MODEL

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Background T cell engagers show high efficacy in B cells malignancies. High risk of immune-related adverse events, including cytokine release syndrome (CRS), is reported in patients treated with T cell engagers due to on-target off-site effects. Thus, reliable and translational mouse models are required to predict potential safety issues and investigate their rescue. PBMC reconstituted models are the most currently used as preclinical models to investigate CRS induction while CD34⁺ reconstituted ones are more rarely described for this application. BRGSF-HIS mice (CD34⁺ based model) develop all major human hematopoietic cell subsets, such as B, T, natural killer (NK), dendritic cells (cDCs and pDCs), and monocytes/macrophages, while BRGSF-PBMC mice develop mainly T and B cells, as described for other PBMC-engrafted models. Myeloid cells are thought to be critical to mimic CRS.

Methods Here, we investigated the cytokine release profile and clinical signs induced by OKT3 (2 mg/kg, iv) in BRGSF mice reconstituted with CD34⁺ cells (BRGFS-HIS) and BRGSF mice reconstituted with hPBMC (BRGSF-PBMC).

Results We previously demonstrated that OKT3 (anti-CD3 mAb) administration in BRGSF-HIS mice induced a rapid release of human cytokines (i.e., IL-6, TNF- α , IFN- γ , IL-2) in serum. CRS clinical signs (hypothermia and body weight loss) were reproduced in OKT3-injected BRGSF-HIS mice. Pretreatment with Infliximab reduced cytokine production and clinical signs, suggesting that BRGSF-HIS mice enable both the development of CRS and test of agents with potential activity in clinical management of CRS.

BRGSF-PBMC could have an advantage in personalized medicine, where patient's PBMC could be used to reconstitute mice and assess patient-specific safety response to a given therapy. While IFN- γ release was drastically increased upon OKT3 administration, its basal level was already around 2 ng/mL in serum from non-treated mice. Despite the absence of clinical signs of GvHD during the study, IFN- γ basal levels suggest a state of pre-activation of T cells, which is not physiological. Furthermore, almost no cytokines secreted by myeloid cells were detected in OKT3-injected BRGSF-PBMC mice contrary to BRGSF-HIS ones. In addition, CRS clinical signs detected in BRGSF-HIS mice were absent in OKT3-treated BRGSF-PBMC mice.

Conclusions In summary, these data suggest that BRGSF-HIS mice enable a more translatable assessment of CRS induction by T cell engagers than BRGSF-PBMC, mainly due to the presence of myeloid cells, which contribute to the physiopathology of CRS.

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