836 RELEASING THE RESTRAINTS OF Vγ9Vδ2 T-CELLS IN CANCER IMMUNOTHERAPY

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Background Vγ9Vδ2 T-cells are a subset of cells with a crucial role in immunosurveillance which can be activated and expanded by multiple means to stimulate effector responses, often exploited in cancer immunotherapy. Little is known about the expression of checkpoint molecules on this cell population and whether the ligation of these molecules can regulate their activity. The aim of this study was to assess the expression of activatory and inhibitory markers on Vγ9Vδ2 T-cells to assess potential avenues of regulation to target with immunotherapy.

Methods PBMCs were isolated from healthy donors and the expression of activatory and inhibitory receptors was assessed on Vγ9Vδ2 T-cells by flow cytometry at baseline, following 24 hours activation and 14 days expansion using zoledronic acid (ZA) and Bacillus Calmette-Guerin (BCG), both with IL-2. Activation and expansion of Vδ2 cells was assessed by expression of CD69 and by frequency of Vδ2 cells, respectively. Production of effector molecules was also assessed following coculture with various tumour cell targets. The effect of immune checkpoint blockade on Vγ9Vδ2 T-cells was also assessed.

Results Vγ9Vδ2 T-cells constitutively expressed high levels of NK-associated activatory markers NKG2D and DNAM1 which remained high following stimulation with ZA and BCG. Vγ9Vδ2 T-cells expressed variable levels of checkpoint inhibitor molecules at baseline with high levels of BTLA, KLRG1 and NKG2A and intermediate levels of PD1, TIGIT and VISTA. Expression of checkpoint receptors were modulated following activation and expansion with ZA and BCG with decreased expression of BTLA and upregulation of numerous markers including PD1, TIGIT, TIM3, LAG3 and VISTA. Expression of these markers is further modulated upon coculture with tumour cell lines with changes reflecting activation of these cells with Vγ9Vδ2 T-cells expressing inhibitory receptors PD1 and NKG2A producing the highest level of TNF.

Conclusions Our data reveals unique characteristics of Vδ2 in terms of their expression of immune checkpoints, which provide a mechanism which may be utilised by tumour cells to subvert Vγ9Vδ2 T-cell cytotoxicity. Our work suggests different profiles of immune checkpoints dependent on the method of stimulation. This highlights importance of expansion method in the function of Vγ9Vδ2 T-cells. Furthermore, this work suggests important candidates for blockade by immune checkpoint therapy in order to increase the successful use of Vγ9Vδ2 T-cells in cancer immunotherapy.

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