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NK CELLS SEIZE PD1 FROM LEUKAEMIA CELLS

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PD1 is an inhibitory immune checkpoint receptor expressed by exhausted T cells; PD1 blockade renders T cells able to effectively target tumour cells for death and is a leading immunotherapy for cancer in the clinic. Although the function of PD1 in T cells is well understood, deciphering its role in natural killer (NK) cells has proven more challenging.

In a recent non-peer-reviewed preprint, Hasim et al. sought to determine whether trogocytosis — the process of plasma membrane exchange during cell–cell interaction — could lead to the acquisition of surface receptors from tumour cells by NK cells. Hasim et al. observed that PD1 was acquired by NK cells co-cultured with two PD1-expressing leukaemia cell lines. Trogocytosis of PD1 was mediated by SLAM receptors, adhesion molecules that are implicated in cell–cell interactions. In vitro findings were corroborated in vivo by demonstrating that PD1 is acquired by NK cells from leukaemia cells in mice. Importantly, NK cells isolated from the bone marrow of patients with multiple myeloma were shown to have acquired PD1 from tumour cells.

Hasim et al. further evaluated whether tumour-derived PD1 acquired by NK cells was functional. PD1 blockade significantly slowed the growth of PD1-expressing tumours in PD1-deficient mice; however, upon concomitant NK cell depletion, this reduction in tumour growth was completely abrogated. The authors used a Fc-silent antibody to PD1 to show that the efficacy of PD1 blockade is not attributable to antibody-dependent cellular cytotoxicity and instead is likely owing to the reversal of PD1-induced dampening of anti-tumour NK cell effector function.

These data represent an important advance in our understanding of how trogocytosis may shape the surface receptor milieu of immune cells; knowledge of the full range of inhibitory receptors acquired by immune cells will be important when designing next-generation immunotherapy regimens. Furthermore, Hasim et al. have contributed to the contradictory reports of PD1 expression by NK cells, with some studies suggesting that NK cells do not endogenously express PD1. This preprint supports the notion that NK cells acquire PD1 exogenously, at least in the context of PD1-expressing haematological malignancies. Together, these data contribute to our knowledge of potential immunotherapy resistance in cancer, although their clinical significance has yet to be determined.

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ORIGINAL ARTICLE

Hasim MS et al. When killers become thieves: trogocytosed PD-1 inhibits NK cells in cancer. Preprint at bioRxiv 10.1101/2020.06.26.174342 (2021)

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