NK cell recognition of malignant cells

– a CRISPR approach to define novel mediators

Natural killer (NK) cells are cytotoxic lymphocytes of the innate immune system, capable of eliminating malignant cells. Their activity is intricately regulated through a balanced interplay between activating and inhibitory receptors that interact with molecules on their prospective target cells. A loss-of-function genome-wide CRISPR/Cas9 screen using NK cell cytotoxicity as selective pressure, unveiled genes impacting target cell susceptibility. *TMEM30A* depletion rendered target cells more resistant, and subsequent investigations elucidated its role in phospholipid transportation within the plasma membrane, influencing the interaction with the inhibitory receptor TIM-3 (paper I). *BAP1* was found to support MHC class I expression through involvement in interferon-γ signalling, making the cells more sensitive upon gene depletion (paper II). The CRISPR/Cas9 technique was further employed to suppress the expression of crucial ligands for activating NK cell receptors, which provided a model to study the impact of a single nucleotide polymorphism (SNP) in the receptor NKG2D gene on NK cell function (paper III). Notably, the identified SNP in the linked gene for NKG2A emerged as the key driver, influencing the outcome of immunotherapeutic treatment HDC/IL-2 in acute myeloid leukemia. Leveraging this established model cell line, dominantly killed via NKp46, a subsequent genome-wide CRISPR/Cas9 screen was conducted to identify potential ligand candidates for the NKp46 receptor (paper IV). In conclusion, CRISPR/Cas9 technology has been instrumental in uncovering key genes and molecular mechanisms that intricately regulate the dynamic interaction between NK cells and target cells, shedding light on potential targets for therapeutic interventions in cancer.

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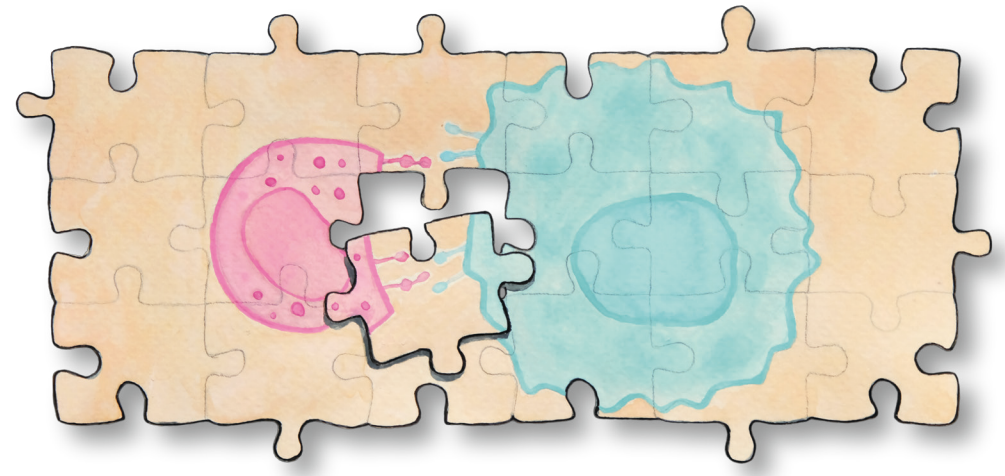

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