995 MODULATION OF THE INFLAMMATORY RESPONSE WITHIN THE TUMOR MICROENVIRONMENT BY INTRAEPITHELIAL ILC1-LIKE NATURAL KILLER CELLS

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Background Natural killer (NK) cells are innate immune cells that generate inflammatory responses important for anti-tumor responses. NK cell therapies have been increasingly explored and tested as a novel approach to cancer immunotherapy in recent years. In contrast to currently approved CAR-T technologies, NK cell therapy can potentially be administered off-the-shelf with low risk of graft-versus-host disease compared to T cells.[1] Recently, we identified intraepithelial ILC1-like (ieILC1-like) NK cells as the subset of NK cells within the tumor microenvironment (TME) of head and neck squamous cell carcinoma (HNSCC) with the highest cytotoxicity.[2] Here, we explore how these cells may modulate the TME and interact with other immune cells in the anti-tumor response.

Methods We used various methods to assess the range of cytokine production by ieILC1-like NK cells in the context of cancer. Co-culture of activated conventional NK (cNK) cells (CD56+CD49a+CD103-CD3-CD14-CD19-CD20-) or ieILC1-like NK cells (CD56+CD49a+CD103+CD3-CD14-CD19-CD20-) with K562 chronic myelogenous leukemia (CML) cells was performed and cytokines were analyzed via Luminex immunoassay of cultured supernatants, evaluating a panel of 80 cytokines and chemokines. Validation was performed by intracellular flow cytometry of the cells in this co-culture system.

Results Luminex analysis revealed that the co-culture of ieILC1-like NK cells with K562 cells resulted in elevated levels of CXCL10 in cultured supernatants compared to that of K562 cells alone, ieILC1-like NK cells alone, or cNKs co-cultured with K562. Similarly, cultured supernatants of ieILC1-like NK cells with K562 had elevated levels of IL-13 compared to that of K562 alone, ieILC1-like NK cells alone, or cNKs co-cultured with K562. To determine the source of these cytokines, we performed intracellular flow cytometry. We found that the K562 cells were the primary source of CXCL10 when co-cultured with ieILC1-like NK cells. Unexpectedly, however, IL-13 was uniquely produced by a subset of IFN-gamma-producing ieILC1-like NK cells following stimulation by tumor cells.

Conclusions The ieILC1-like NK cells induce CXCL10 production by K562, most likely via IFN-gamma. CXCL10 is a pro-inflammatory chemokine involved in immune cell recruitment to the TME.[3] Unexpectedly, we identified a subset of ieILC1-like NK cells that produce IL-13, a Th2-type cytokine that has the potential to dampen anti-tumor immune responses and possibly promote tumor survival and proliferation.[4] Thus, the CD49a+CD103+ ieILC1-like NK cell population is heterogeneous, and further studies to understand the functional differences of these distinct subsets are necessary.

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