INVESTIGATING THE IMMUNOMODULATORY ROLE OF INNATE LYMPHOID CELLS IN EPITHELIAL OVARIAN CARCINOMA

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Background Innate lymphoid cells (ILCs) are an emerging family of effector cells that mostly reside within non-lymphoid peripheral tissues and orchestrate innate and adaptive immunity in response to infections.1 ILCs play an important role in cancer including its ability to directly kill cancer cells and promote anti-tumour immunity within the tumour microenvironment (TME).2 In addition to these classical pro-inflammatory functions of ILCs, our group and others have identified a subset of immunoregulatory ILCs (ILCregs) in various diseases including cancer.3 We previously found a CD56+ ILCreg population that suppressed T cells in slow growing ex vivo tumour-infiltrating lymphocyte (TIL) cultures.4 The objective of this study is to identify markers that distinguish immunoregulatory and non-immunoregulatory ILCs straight from primary tumours and uncover its role within the TME of epithelial ovarian carcinoma (EOC).

Methods Women with suspected EOC were recruited and consented pre-operatively at the Gynecology Cancer Clinic at Princess Margaret Hospital. Surgical resections were processed and analyzed by flow cytometry and single-cell RNA sequencing (scRNA-seq). In vitro stimulation of peripheral blood CD56+ ILCs were performed over 7 days in IL-15 with 50% ascites supernatant.

Results We identified subsets of intratumoural ILCs including ILC1s, ILC2s, ILC3s, and CD56+ ILCs within lineage negative populations. Interestingly, a population of CD56+ GZMB+ ILCs exhibited distinct tissue-resident-like properties including expression of tissue-retention marker CD69 and reduced expression of tissue-egress marker CD49e. Interestingly, transcriptomic profile of CD56+GZMB+CD49e- ILCs from our scRNA-seq dataset (n=3) had similar gene expression as intra-epithelial ILC1s (ieILC1) from other studies.5 These ieILC1-like cells were associated with poor recurrent free survival and reduced granzyme B expression in CD8+ TILs. Moreover, ieILC1-like phenotypes can be induced from peripheral blood CD56+ cells using ascites supernatant from patients with EOC. Finally, ieILC1-like cells from primary tumours expressed gene signatures that have been previously upregulated in ILCregs and regulatory T cells (Tregs), suggesting that these populations may have immunoregulatory properties. Ongoing work is being done to identify whether ieILC1-like cells directly suppress T cells in vitro, and uncover mechanisms of immunosuppression.

Conclusions Our findings suggest that ieILC1-like CD56+ cells are negatively associated with prognosis of EOC and may play a unique role in modulating the tumour microenvironment. Further investigation into the biology of ILCs in human tumours may provide novel therapeutic targets for ovarian carcinoma and beyond.

REFERENCES