Background Immunotherapy has been regarded as the most promising strategy for eradicating malignancies especially solid tumors. However, tumor immune escape mechanisms strongly hamper the efficacy of immunotherapy. Thus, adaptive (a)NK cells capable of establishing immune memory against specific antigens and resisting the suppression tumor microenvironment (TME) can become an ideal alternative. But the role of aNK cells was rarely reported in solid tumors. Therefore, we sought to investigate whether aNK cells had the specific immune memory against solid tumor and the underlying related mechanism.

Methods We used ex vivo tumor samples to obtain the primary tumor cells and infiltrated NK cells. Flow cytometry was used to detect the immune cell frequency and functionality. Multiparametric immunofluorescence was used to map the cell distribution and evaluate the cell-cell interaction. In addition, single cell RNA sequencing (scRNA-seq) was operated for thorough insights into the novel molecular architecture of aNK cells from primary and secondary stimulations. Eventually, multiple bioinformatic methods were utilized to validate in bigger cohorts of public data to establish the correlation between aNK cells and cancer patient prognosis.

Results Here we found that aNK cells expanded from ovarian tumor biopsies presented a strong correlation with the enhanced tumor reactivity in form of degranulation and cytokine production, in contrast to conventional (c)NK cells when encountering the autologous primary tumor cells. Interestingly, following culture with dendritic cells (DCs) loaded with a specific tumor lysate, aNK cells elicited recall responses only against the tumor cells which were previously presented by DCs in form of degranulation (CD107a), proliferation (Ki67) as well as pro-inflammatory cytokine production, compared with their counterpart cNK cells.

Furthermore, we found aNK cells at close proximity to tumor cells in whole ovarian tumor tissue sections compared to cNK cells that were located in the stroma. Data from publicly available database have shown that high aNK cells gene signature was associated with improved survival in ovarian cancer patients. Lastly, from the scRNAseq, a distinct cluster with corresponding markers was found, which was enriched in multiple immune pathways including immune memory, NK cell activation and cytotoxicity. Following pseudo-time analysis, this cluster located at the terminal stage, which fit the developmental feature of memory cells.

Conclusions Intratumoral aNK cells positively correlate with better tumor killing. aNK cells can form immune memory against solid tumor. Moreover, based on our scRNAseq analysis, intratumoral and educated aNK cells also constitute characteristics which contain the intrinsic mechanism related to the memory formation.

Acknowledgements We would like to thank Dr. Ian Moore at NIH/NIAID/Infectious Disease Pathogenesis Section for providing guidance in immune fluorescence staining of the paraffin embedded tumor tissues. And our study is funded by the following funding: KI Stiftelser och Fonder, 2020–01829 (DS); Swedish Cancer Society 200169F (DS); Swedish Cancer Society 201128Pj (DS); China Scholarship Council 201906280459 (YS); Stiftelsen Clas Groschinsky Minnesfond M2258 (DS)

Trial Registration The high-grade serous ovarian tumor samples were collected from the patients participating in a Phase III clinical trial (Intra-Peritoneal Local Anesthetics in Ovarian Cancer trial (IPLA-OVCA), whose registry is www.clinicaltrials.gov (https://clinicaltrials.gov/ct2/show/NCT04065009).

Ethics Approval The high-grade serous ovarian tumor samples were collected from the patients participating in a Phase III clinical trial (Intra-Peritoneal Local Anesthetics in Ovarian Cancer trial (IPLA-OVCA) (https://clinicaltrials.gov/ct2/show/NCT04065009). Written and informed consents were obtained from all patients before inclusion in the trial in accordance with the Declaration of Helsinki. The protocol for patient participation was approved by the local Ethics Committee and the Institutional Review Board (Dr’s, 2019–05149 and 2015/1862-32).

Consent Written informed consent was obtained from the patient for publication of this abstract and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

http://dx.doi.org/10.1136/jitc-2023-SITC2023.1000

Abstracts

1000 ADAPTIVE NK CELLS WITH DISTINCT FEATURES POSSESS IMMUNE MEMORY TOWARDS OVARIAN TUMORS

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http://dx.doi.org/10.1136/jitc-2023-SITC2023.1000

J Immunother Cancer 2023;11(Suppl 1):A1–A1686