371 DISTINCT PREDICTIVE VALUE OF CD137 AS A TUMOR REACTIVE MARKER AMONG DIFFERENT CANCER TYPES AND TIL EXPANSION STAGE

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Background TIL therapy has demonstrated promising therapeutic effects in multiple types of solid tumors. Although the positive correlation between frequency of tumor reactive subsets within TIL products and beneficial clinical outcomes is well accepted, identification and enrichment of these tumor specific TILs from the entire group represents a major challenge to cell-based cancer immunotherapies. CD137 was reported as a biomarker of endogenous tumor reactive TILs in primary ovarian cancer and malignant melanoma. However, whether the predictive value of CD137 is applicable in other cancers has yet to be investigated.

Methods Fresh tumor tissues were collected from patients with cervical cancer, non-small cell lung cancer (NSCLC) and metastatic ovarian cancer for nanobeads-based CD137 sorting after tumor digestion and cytokine cocktail pre-treatment for 24–48 hours. CD137 expression on TILs was analyzed at timepoint 0, 24 and 48 hours as well as the end of pre-rapid expansion (preREP) stage before sorting. CD137+ sorted and unsorted TILs were able to expand to $10^8 \sim 10^9$ within 4 weeks. Tumor specific response including 4–1BB and CD69 expression on CD8+ and CD4+TILs, respectively and IFN-γ production of sorted versus unsorted TIL groups was examined against autologous tumor cells.

Results Within tumor specimens derived from all cancer types, CD137 on TILs were significantly increased after cytokine cocktail pre-treatment for 24 hours and then declined at 48 hours. CD137+ sorted TILs either from 24 hours after pre-treatment or the end of preREP could be expanded successfully to clinical relevant scale. It is notable that the salient performance of CD137+Sorted TILs is consistently observed in different samples derived from cervical cancer and NSCLC patients compared with unsorted TILs as demonstrated by enhanced IFN-γ release and 4–1BB and/or CD69 expression, but not in metastatic ovarian cancer samples .

Conclusions Our finding reveals that CD137 might not be a bona fide biomarker of tumor reactive TILs in all solid tumor types. Enrichment and expansion of CD137+ TIL in cervical cancer and NSCLC provides a feasible manufacture process to produce TIL product with high tumor specific reactivity. In metastatic ovarian cancer where CD137 didn't demonstrate good predictive value in our study, it might be necessary to tease out tumor reactive TILs based on multiple impact factors, such as lesion location, histology stage and other biomarker(s) rather than CD137 expression only.

http://dx.doi.org/10.1136/jitc-2023-SITC2023.0371