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Editorial: Next generation $\gamma\delta$ T cell-based tumor immunotherapy

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Editorial on the Research Topic

Next generation $\gamma\delta$ T cell-based tumor immunotherapy

The discovery of the $\gamma\delta$ T-cell receptor (TCR) and its ability to confer potent cytotoxic activity in CD3+ cells some 35 years ago sparked the initial proliferation in research that garnered widespread interest in the biology and function of $\gamma\delta$ T cells. The identification of major human $\gamma\delta$ TCR clonotypes, their tissue distributions as well as dynamic changes throughout ontogeny and in disease states have contributed to the appreciation of human $\gamma\delta$ T cell diversity. Despite this, incomplete understanding of mechanisms underlying the complexity of various $\gamma\delta$ T cell subsets in homeostasis, inflammation and malignancy restricted the focus of most early studies to blood circulating V γ 9V δ 2 T cells which could be robustly activated and expanded *ex vivo* using aminobisphosphonates such as zoledronate compared with other $\gamma\delta$ T cell subsets for which activating ligands were then largely unknown. This galvanized attempts to harness the tumoricidal potential of V γ 9V δ 2 T cells in clinical trials. Although these cells exhibited highly promising safety profiles in patients, early trial data revealed suboptimal anti-tumor efficacy. Despite these setbacks, recent breakthroughs in deciphering the unique antigen (Ag) binding modes of $\gamma\delta$ TCR coupled with high dimensional analyses of tissue- and disease-specific $\gamma\delta$ T cell subsets at single cell resolution led to renewed excitement in the development of $\gamma\delta$ T cell-based therapeutics. This Research Topic has compiled a series of nine articles of which five review our hitherto understanding of the multifaceted nature of $\gamma\delta$ T cells and four report original research providing new insights into the molecular and cellular regulation of a diverse repertoire of $\gamma\delta$ T cells, paving the way for next generation $\gamma\delta$ T cell-based tumor immunotherapies.

Despite extensive use of phosphoantigens (pAgs) to activate and expand V γ 9+V δ 2+ T cells, the role of butyrophilins (BTNs) in mediating V γ 9V δ 2 TCR-dependent activation is only gaining recent appreciation. Expression of BTN3A1 and BTN2A1 heterodimers, in complex with pAgs, on the surface of accessory innate immune, infected or tumor cells is an absolute requirement for interaction with the V γ 9V δ 2 TCR. Other BTN and BTN-like (BTNL) molecules are involved in the ontogeny and homeostasis of non-V γ 9+V δ 2+ T cell subtypes as noted by Herrmann and Karunakaran. Their review also emphasized dissection of BTN-associated mechanisms that enhance the effector function to broaden the therapeutic applications of $\gamma\delta$ T cells in disease settings. Extending the role of TCR δ complementarity-determining region 3 (CDR3 δ) in V γ 9V δ 2 TCR-mediated responses, Vyborova et al. adduced evidence for CDR3 δ determinants in pAg sensing that are significantly correlated with V γ 9V δ 2 TCR affinity and signal strength, contributing to V γ 9V δ 2 T cell repertoire focusing. Furthermore, surface expression of the inhibitory natural killer receptor (NKR) CD94/NKG2A is biased toward while that of activating NKR NKG2D is independent of these CDR3 δ traits, findings which may impact design of high-affinity V γ 9V δ 2 TCR-based therapies.

$\gamma\delta$ T cells manifest substantial plasticity and can be polarised to different cell states in response to environmental stimuli. It is thus not uncommon to identify $\gamma\delta$ T cells with opposing functional properties in different biological contexts. The mini review by Bhat et al. provides a comprehensive summary of studies highlighting the dichotomous nature of $\gamma\delta$ T cells influenced by diverse pathological milieus, leading to beneficial or detrimental outcomes in the host. For example, IL-17 production by $\gamma\delta$ T cells has been shown to aggravate autoimmune conditions (1, 2) and also be associated with immunosuppression that exacerbate tumour growth (3, 4). Such phenomena attributable to the varied cellular interactions of $\gamma\delta$ T cells can be addressed by appropriate considerations of systems immunology and personalized approaches. In this regard, Chan et al. provided an updated account of crosstalk between $\gamma\delta$ T cells and a variety of immune cells which collectively coordinates anti-tumor responses. Additionally, the cytokine milieu plays a major role in shaping the fate commitment of $\gamma\delta$ T cells. Consistent with this, Song et al. discussed how cytokines and their combinations differentially direct the polarization of tissue-resident and tumour-infiltrating $\gamma\delta$ T cells. Such experimental insights will inform strategies to manipulate the cytokine dependencies of $\gamma\delta$ T cells to improve the cytotoxic function and *in vivo* persistence of administered T cells against tumors. Pei et al. elegantly showed that CD137 costimulation of V γ 9+V δ 2+ T cells using CD137L agonist diminished IL-10 receptor expression and alleviated exhaustion in these cells by mitigating the immunosuppressive tumor microenvironment (TME) mediated by IL-10. This increased V γ 9+V δ 2+ T cell efficacy against Epstein Barr virus (EBV)-transformed B lymphoma in a humanized mouse

model. Hu et al. examined the immunosuppressive TME of hepatocellular carcinoma (HCC) which the authors showed close correlation with high expression of inhibitory checkpoint molecules, presence of tumor-promoting immune cells and various types of programmed cell death. This is associated with $\gamma\delta$ T cell subtype imbalance characterized by selective depletion of cytotoxic V δ 2+ T cells and enrichment of Treg-like V δ 1+ T cells as well as poorer patient prognosis. These studies underscore the importance of performing greater in-depth analyses of the cellular networks and interplay of cytokines in the TME to accelerate the clinical translation of $\gamma\delta$ T cell therapies.

Over the years, translating $\gamma\delta$ T cell therapies from bench to bedside has encountered tremendous challenges. Saura-Esteller et al. expertly summarized the evolution of $\gamma\delta$ T cell therapeutic strategies assessed in clinical trials that signifies past progress in $\gamma\delta$ T cell research. With a growing list of companies developing $\gamma\delta$ T cell-based or engaging therapies, the authors noted the high cost of manufacturing $\gamma\delta$ T cell-based products due in part to requirement for multiple cytokines and prolonged *ex vivo* expansion process. Exemplifying continual efforts to reduce $\gamma\delta$ T cell production cost, Ferry et al. described a one-step protocol utilizing a single cytokine to expand V δ 1+ T cells. In addition, the authors demonstrated that these cells were amenable to high efficiency transduction of chimeric antigen receptors (CARs). Going forward, development of other ways that harness the anti-tumor potency of $\gamma\delta$ T cells, namely bispecific $\gamma\delta$ T cell engagers and advanced $\gamma\delta$ T cell genome-editing, is expected to widen the immuno-oncological applications of these cells.

Author contributions

AT and AC discussed findings of various articles of the Research Topic in broader context of tumor immunotherapy. AT collated contributions and prepared final version of editorial by taking into account suggestions from AC and DK.

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