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Tumour antigen-induced T cell exhaustion — the archenemy of immune-hot malignancies

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Abstract

Two recent studies addressed the functional properties and clinical significance of tumour antigen-specific effector T cells in human melanomas and lung carcinomas using single-cell strategies. Herein, we discuss their findings, which expand our understanding of T cell alterations in the tumour microenvironment and demonstrate that $CD8^+$ T cell exhaustion is mediated by exposure to tumour cell-specific antigens and is associated with a tissue-resident memory phenotype.

Despite prominent clinical success of immune-checkpoint inhibitors (ICIs) targeting the PD-1–PD-L1 axis in multiple cancer types, questions remain regarding their mechanism of action, biomarkers to guide treatment, determinants of sensitivity and resistance, and treatment combinations to enhance clinical responses. Solid tumours develop and progress in the context of a complex tumour microenvironment (TME). High levels of tumour-infiltrating lymphocytes (TILs) are generally associated with favourable outcomes[1]; however, effector T (T_{eff}) cells can be exposed to immunoregulatory signals from the TME and to continuous antigen stimulation that can affect transcriptional and epigenetic programmes. This exposure can limit their activity and result in a form of dysfunction referred to as T cell exhaustion[2].

The T_{eff} cell dysfunction programme can encompass multiple T cell profiles characterized by altered differentiation and cytolytic properties, deregulated proliferation and/or death programmes, and increased expression of multiple immune-inhibitory signals (such as PD-1, LAG3, TIM3, TIGIT and CD39)[2,3]. Exhausted T_{eff} cells have been described in chronic viral infections and cancer, although their biological properties, disease context dependency and clinical relevance remain poorly understood. Developments in multimodal high-throughput single-cell analysis strategies coupled to computational models have

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Competing interests

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enabled detailed and unsupervised functional studies of immune populations in tumour specimens.

Oliveira et al.[4] evaluated single-cell transcriptomic profiles, T cell receptor (TCR) repertoires and selected surface proteins in tumour antigen-specific $CD8^+$ T_{eff} TILs from four patients with surgically resected melanoma. Using previously defined signatures, $CD8^+$ TILs were classified into 13 subpopulations, which were ultimately grouped into two functional categories on the basis of the distribution of dominant T_{eff} clonotypes: exhausted cells and non-exhausted memory cells. $CD8^+$ T_{eff} cells of the most-expanded TCR clonotypes predominantly had an exhausted profile and expressed transcripts associated with tissue-resident memory (T_{RM}) cells (such as *ITGAE* (encoding CD103) and *ZNF683*). Furthermore, when transducted into T cells from individuals without cancer, the majority (83%) of TCR clones from exhausted $CD8^+$ T_{eff} cells but only a small fraction (10%) of TCRs from non-exhausted cells had autologous reactivity against cancer cells. In addition, the specificity of TCRs isolated from TILs was established through co-culturing with non-transformed cells pulsed with a variety of melanoma and viral antigens; most of them recognized one or more tumour-specific antigens with shared HLA restriction. Antigenic peptide-specific stimulation of T_{eff} cells with both patient-specific mutant neopeptides or shared melanoma antigens was associated with an exhausted transcriptional profile, which was not seen in $CD8^+$ T_{eff} cells containing viral TCR clonotypes. Finally, in a cohort of 14 patients with melanoma, exhausted tumour antigen-specific $CD8^+$ T_{eff} cells were rare in peripheral blood samples, but higher numbers were detected in patients with progression after treatment with ICIs. Of note, these exhausted cells characteristically expressed high levels of PD-1 and CD39, as previously reported[5].

Together, their results demonstrate that tumour antigen-specific T_{eff} cells have exhausted functional profiles and that acquisition of this state is driven by continuous exposure to tumour antigens. These results are consistent with previous studies showing a strong association between tumour antigen specificity and T_{eff} cell exhaustion in TILs from patients with other malignancies[5,6], although these studies reported a high abundance and, in some cases, predominance of non-exhausted viral-specific bystander cells that did not seem to contribute to antitumour responses.

Caushi et al.[7] analysed the single-cell transcriptomic profiles and TCR sequences of in vitro-expanded tumour antigen-specific $CD8^+$ T_{eff} cells from 20 patients with resectable non-small-cell lung cancer treated with neoadjuvant nivolumab. Specificity was assessed using MANAFEST, a peptide stimulation-based assay that included mutant neoantigenic peptides and MHC class I-restricted viral antigens. Based on transcriptomic profiles, 15 T cell clusters were identified, 6 of which had expression programmes consistent with T_{RM} cells. Most neoantigen-specific $CD8^+$ T_{eff} cell clonotypes were allocated to discrete T_{RM} cell clusters characterized by an incomplete effector programme, increased immune inhibitory signals, upregulation of T_{RM} markers and expression of transcription factors associated with T cell exhaustion (*PRDM1* and *TOX2*). These features were not seen in viral-specific bystander T cells. Together, these results are consistent with the findings from Oliveira et al.[4] and with previous studies indicating that tumour antigen-specific cells display a T_{RM} phenotype and show exhausted and/or dysfunctional profiles[5,6]. Of note, peptide-stimulation

dose–response curves showed higher TCR–peptide avidity in $CD8^+$ T_{eff} cells from patients with major pathological responses after anti-PD-1 treatment, suggesting a role in treatment sensitivity. A preliminary comparative analysis of single-cell transcriptomic profiles between $CD8^+$ T_{eff} cells from patients with versus without major pathological responses showed upregulation of numerous exhaustion markers in the latter group, supporting a potential biomarker role. Neoantigen-specific $CD8^+$ T_{eff} cells also had reduced expression of IL-7R and sensitivity to IL-7 stimulation compared to influenza-specific T cells.

Together, both studies expand our understanding of T cell alterations in immune-'hot' human tumours containing MHC-presented tumour antigens and TILs. They unambiguously demonstrate that $CD8^+$ T_{eff} cell exhaustion is mediated by exposure to tumour-cell antigens and is prominently associated with a T_{RM} phenotype. These studies also indicate a role for T cell exhaustion in resistance to anti-PD-1/PD-L1 antibodies and evidence the presence of variable levels of non-exhausted bystander cells with limited tumour reactivity and uncertain biological function. The presence of large numbers of these bystander cells might create 'pseudo-immune-hot' tumours with reduced sensitivity to ICIs (FIG. 1).

These results also suggest a potential role for $CD8^+$ T_{eff} cell dysfunction and particularly of CD39 expression as biomarkers to identify exhausted cells and thus potentially spare treatment in patients who would derive limited benefit from anti-PD-1/PD-L1 ICIs. This role is also supported by previous studies from our group showing association between baseline TIL activation and proliferation, or expression of immune checkpoints with resistance to anti-PD-1/PD-L1 ICIs in patients with non-small-cell lung cancer[3,8,9].

Possible therapeutic options to reduce or control the negative impact of T cell dysfunction in the TME include the use of combination therapies simultaneously targeting multiple co-inhibitory signals or receptors, adoptive cell therapies with genetically modified (for example, exhaustion resistant) tumour antigen-specific T cells, or modulation of the IL-7 pathway. Studies including larger patient cohorts and additional experimental approaches are required to confirm the clinical implications of these findings, expand understanding of the role of T_{RM} cells in response to ICIs and reveal the specific molecular mechanisms by which tumour-specific T cells become dysfunctional. In this regard, the possible role of ligands for key immune checkpoints expressed in the TME, such as PD-L1, galectin-9, MHC class II and FGL1 in the acquisition or progression of the T cell exhaustion phenotype will need to be determined[10]. Finally, additional studies addressing dominant mechanisms of immune evasion and candidate therapeutic options in immune-cold tumours, such as those with low T cell infiltration and/or defective antigen presentation, are needed.

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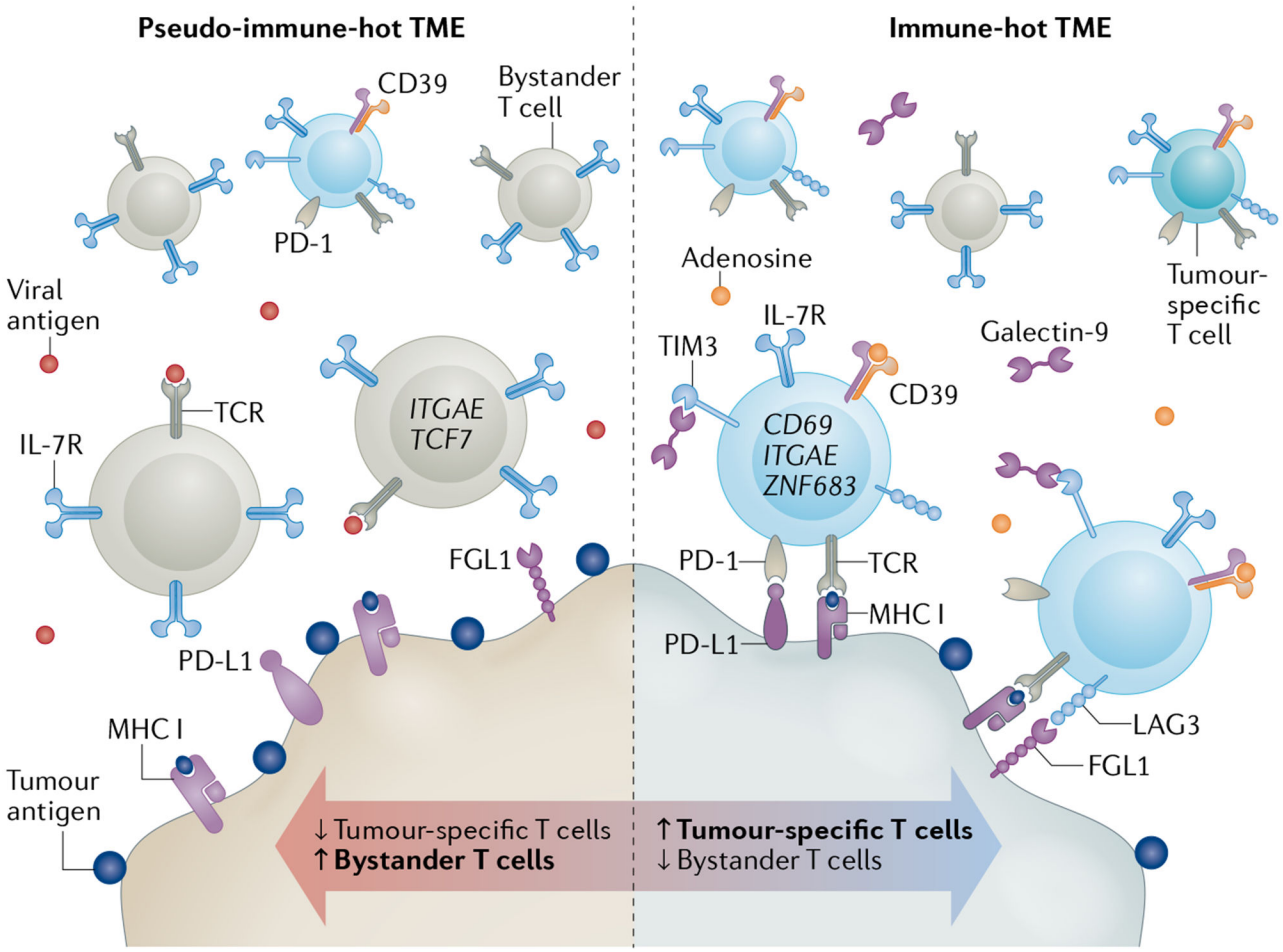

Fig. 1 |. Functional profile of tumour-infiltrating CD8$^+$ T_{eff} cells in human solid tumours. Tumours can contain variable levels of bystander effector T (T_{eff}) cells targeting non-tumour epitopes, which lack features of exhaustion and are not expected to mediate cancer cell elimination. Tumours with a high number of these cells could be considered as‘pseudo-hot’ (left) and are likely to be insensitive to immune-checkpoint inhibitors (ICIs). By contrast, immune-hot tumours preferentially contain tumour antigen-specific T_{eff} cells (right). Continuous antigen stimulation and regulatory signals in the tumour microenvironment (TME) can favour an exhausted T cell phenotype and acquisition of a tissue-resident memory profile.Their accumulation in the TME is associated with reduced sensitivity to ICIs. Therapeutic interventions aiming to achieve and/or maintain a TME with a predominance of tumour antigen-specific non-exhausted T_{eff} cells would lead to improved clinical responses to ICIs. TCR,T cell receptor. Created with BioRender.com.