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Tissue-resident memory T cells in immune-related adverse events: friend or foe?

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ABSTRACT

Many cancer patients experience toxicity during checkpoint blockade immunotherapy, which often leads to treatment discontinuation. To this end, understanding the mechanisms mediating immune-related adverse events (irAE) should ultimately enable improvement in clinical outcomes. Recent work has revealed that tissue-resident memory T (T_{RM}) cells are locally expanded in irAE-dermatitis and -colitis.

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Introduction

Checkpoint blockade immunotherapy (monoclonal antibodies targeting the negative regulatory receptors CTLA-4, PD-1, or LAG-3) has revolutionized cancer medicine. One limiting factor, however, is immune-mediated toxicity to normal tissues. IrAEs can affect virtually every organ system and sometimes become irreversible or even lethal[1]. One of the earliest characterized irAEs is vitiligo, which is immune-mediated destruction of melanocytes that occurs in melanoma patients treated with a variety of immunotherapies. Vitiligo is mediated by T cells and antibodies against melanoma-expressed antigens that cross-react with normal melanocytes[2]. In this context, it was presumed that other irAEs might similarly be due to antigen cross-reactivity. However, the majority of irAEs are tumor-type agnostic, raising doubt about this hypothesis. In addition to being expressed on activated T cells within the tumor microenvironment, PD-1 and other immune checkpoint molecules are also expressed in two other major T cell differentiation states: T follicular helper cells (T_{FH} cells) that reside in lymph nodes and provide help to B cells to produce antibodies, and tissue-resident memory cells (T_{RM} cells) that reside in peripheral tissues and maintain protection against infection by repeated challenge with extrinsic pathogens and commensals. T_{RM} cells remain in a tissue through the expression of retention molecules such as CD103, CD69 or CD49a, and express PD-1 and other inhibitory receptors that control their re-activation[3]. Therefore, recent work has examined whether checkpoint blockade immunotherapy might lead to irAEs through expansion and activation of locally present T_{RM} cells (Figure 1).

T_{RM} cells and immune related adverse events

Particularly in barrier organs such as the gastrointestinal tract or the skin, T_{RM} cells are found in abundance[3]. This might be explained by the regular occurrence of microbial antigens in barrier sites. When mice were challenged with immunotherapy and *Staph. epidermidis* colonization, researchers found that the majority of the bacteria-specific T cells were actually T_{RM} cells[4]. Additionally, those bacteria-specific T_{RM} cells expanded during immunotherapy. In our recent publication we reported that T_{RM} cells dominated in the inflammatory reactions associated with irAE-dermatitis and -colitis following checkpoint blockade immunotherapy. Biopsies showed and expansion of CD4+ and CD8+ T_{RM} cells in percentage and numbers as assessed by multispectral immune fluorescence staining[5]. Spatial transcriptomics and confirmatory RNAscope were utilized to examine the transcriptional signatures of these expanded T_{RM} cells. In terms of lineage differentiation state, IFN-γ and TNF-α were expressed, as well as IFN-γ-stimulated genes such as HLA-DRA, CD74 and GBP5, collectively indicating a Th1/Tc1 phenotype. In contrast, T_{RM} cells identified in psoriasis control samples were more Th17/Tc17-polarized. Spatial transcriptomics data also revealed the upregulation of checkpoint molecules such as PD-1, CTLA-4, TIM-3, LAG-3 and TIGIT in spots containing T_{RM} cells, arguing for a re-invigoration of these T_{RM} cells during immunotherapy. Furthermore, we found that IFN-γ induced chemokines (CXCL9–11) were strongly upregulated in situ as well. CXCL9–11 can recruit additional T cells from the circulation that could expand further the local inflammatory response. In patients with irAE-arthritis, IFN-γ producing CD8+ T cells have been reported to be increased in the blood during the irAE[6]. The

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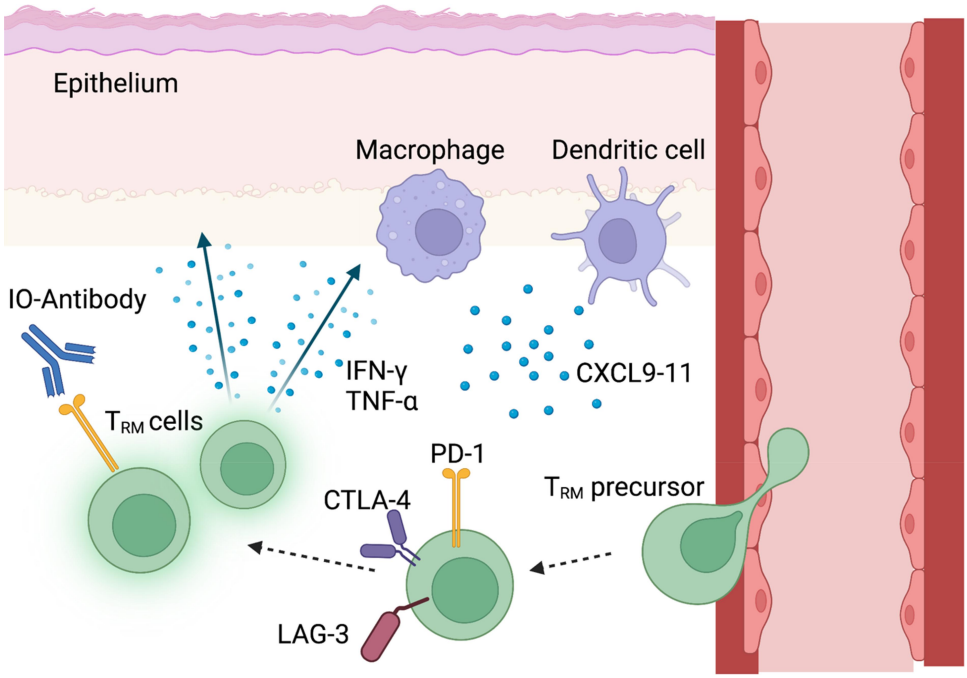

Figure 1. Model of immunotherapy-driven toxicity in a barrier organ. T_{RM} cells upregulate inhibitory checkpoint molecules. Checkpoint blocking antibodies can bind and re-invigorate T_{RM} cells (here a skin model). They expand and produce Th1/Tc1 cytokines such as IFN-γ or TNF-α and active myeloid cells downstream. Macrophages and dendritic cells can produce CXCL9–11 which recruits additional T cells from the circulation (figure created with biorender).

same CXCR3^{hi} CD8+ T cell clones were found in the synovial fluid, arguing for recruitment via CXCL9–11. The relevance of T_{RM} cells for irAEs has also been shown in other studies. During checkpoint inhibition in mice, myosin-specific T_{RM} cells developed during irAE-myocarditis[7]. In patients with irAE-colitis, CD8+ T_{RM} cells producing IFN-γ were reported to be causal[8]. The majority of CD8+ cells were represented by CD8+ T_{RM} cells, which showed expression of activation markers including HLA-DR and CD38. One patient with steroid-refractory irAE-colitis was treated with tofacitinib, a systemic Jak-inhibitor. After 5 weeks he achieved histologic and endoscopic remission, reflected in a significant shrinkage of the CD8+ T_{RM} cell compartment. An independent cohort of irAE colitis patients from another center studied irAE colitis using scRNAseq. T_{RM} cell clusters clonally expanded in irAE colitis cases compared to healthy controls. These cells expressed cytotoxicity genes GZMB and GNLY (CD8+ T cells) and GZMA (CD4+ T cells) and had a strong IFNG signature[9]. Myeloid cells expressed high levels of CXCL9/10/16, and TNF-α, ITGA4 and ITGB7 were upregulated. In our samples as well, Integrin alpha 4 (ITGA4) was also highly expressed across irAE dermatitis and colitis cases, suggesting a potential opportunity for therapeutic intervention blocking this integrin.

Treatment challenges with irAes

Systemic corticosteroids are regularly used to treat irAEs. More recently, systemic JAKi have been used anecdotally for steroid-refractory irAE colitis[8]. Both approaches suppress T cell function globally. One avenue for more selective immune suppression could be based on homing molecules such as integrins, such as ITGA4 which has been seen to be upregulated in multiple irAE studies. In one case report an antibody targeting ITGA4 (natalizumab) was successfully utilized for irAE-meningoencephalomyelitis[10]. An antibody targeting ITGA4 and ITGB7 called vedolizumab has been used successfully for steroid-refractory irAE colitis[9], which spared effects on anti-tumor immunity during checkpoint blockade. Based on the strong upregulation of TNF-α we have seen in our irAE-dermatitis cases, it might be plausible to not only treat severe steroid-refractory irAE-colitis but also irAE-dermatitis with TNF-α -blockade. The skin offers another attractive treatment avenue because it can be treated locally without systemic effects on anti-tumor immunity. To inhibit the IFN-γ pathway locally, it is conceivable to utilize topical JAKi therapy as a corticosteroid-sparing agent for treatment of rashes.

Conclusions

It is crucial to understand immunopathology of irAEs across organ-systems better to allow a more personalized immune suppression therapy and to spare negative effects on anti-tumor immunity. T_{RM} cells are associated with irAEs across different organ systems. Potential treatment targets that are more selective include integrins, TNF-α, and locally produced IFN-γ. Some irAEs are known to be antibody-mediated, such as hemolytic anemia. Future work should examine whether activation of T_{FH} cells by checkpoint blockade is operational in those instances, providing help for autoreactive B cells.

Disclosure statement

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