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Spotlight

TAM-tastic: from resistance to resilience in cancer

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Overcoming resistance to immunotherapy in cancer is challenging due, in part, to tumor-associated macrophages (TAMs) co-expressing T cell immunoglobulin and mucin domain-containing 3 (TIM3) and V-domain immunoglobulin suppressor of T cell activation (VISTA) in tumor microenvironments (TME) with sparse T cell infiltration. In a recent article, Vanmeerbeek *et al*. found that blocking TIM3 or VISTA on IL-4-supported TAMs, in combination with paclitaxel (PTX), reprogrammed TAMs to attack cancer cells, highlighting a potential new therapeutic strategy.

Cancer immunotherapy has emerged as a promising and rapidly advancing treatment approach. Among the most effective forms of antitumor immunotherapy is immune checkpoint blockade (ICB), which targets molecules, such as cytotoxic T lymphocyte-associated protein-4 (CTLA-4), programmed cell death-1 (PD-1), and programmed death ligand-1 (PD-L1) [1]. The successful application of ICB across various cancer types has significantly improved patient outcomes, providing a viable treatment option for those with advanced cancers. However, despite its success, some patients do not respond to ICB due to low tumor immunogenicity and poor T cell infiltration. These immunoresistant tumors remain a significant challenge for cancer immunotherapy, because the suppression of the antitumor responses is often driven by factors beyond tumor cells, including suppressive immune cells and other inhibitory molecules.

The presence of TAMs within the TME can limit the efficacy of anti-PD-1 treatment by sequestering anti-PD-1 antibodies from T cells [2]. Macrophages are tissue-resident innate immune cells with a crucial role in the host defense system and maintenance of tissue homeostasis under steady-state conditions [3]. Recent advances in single cell resolution analyses revealed that TAMs exhibit phenotypic plasticity and heterogeneity, demonstrating both immunostimulatory and immunosuppressive functions [4,5]. Clinical studies have linked a higher infiltration of TAMs with poorer prognosis in many human tumors [6]. Therefore, targeting TAMs to shift their protumorigenic responses to elicit tumoricidal activity could contribute to tumor regression and a favorable outcome for patients.

Current TAM-based immunotherapies target TAM recruitment, differentiation, or polarization to activate antitumorigenic functions [6]. For example, monoclonal antibodies against triggering receptor expressed on myeloid cells 2 (TREM2) have been shown to dampen tumor growth, enhance T cell activation, and improve anti-PD-1 therapy [7]. Similarly, colony-stimulating factor 1 receptor (CSF-1R) antibody therapy was shown to reduce TAM infiltration to various TMEs, boost T cell antitumor immunity, and contribute to more favorable outcome for patients [8]. Despite advances in TAM-based immunotherapy, the translation of preclinical treatment strategies into clinically effective therapeutics has shown limited efficacy [6].

In a recent paper published in *Science Advances*, Vanmeerbeek and colleagues preformed an unbiased analysis of human single cell RNA sequencing (scRNA-seq) data sets from multiple cancers to identify unique gene expression profiles enriched in TAMs [9]. The authors detected a subset of TAMs in human ICB-nonresponsive tumors that co-expressed the inhibitory receptors TIM3 and VISTA. This co-expression was conserved from humans to mice and found exclusively on TAMs. $TIM3^{+}VISTA^{+}$ TAMs were preferentially enriched in type 2 cytokine IL-4-enriched immunoresistant tumors with low antigenicity and exhibited an anti-inflammatory phenotype across multiple human tumor types. The presence of these cells further correlated with shorter survival as well as with unfavorable response to ICBs against PD1, CTLA4, or PD-L1, suggesting that the $TIM3^{+}$ $VISTA^{+}$ TAM signature could serve as a prognostic and predictive indicator in patients with cancer.

The researchers explored TIM3 and VISTA as potential therapeutic targets to modulate TAM polarization. Although blocking TIM3 or VISTA individually, or together with PD-1, proved ineffective, a combination therapy of TIM3 or VISTA blockade with the immunogenic cell death (ICD) inducer PTX demonstrated TAM-dependent tumor control. This synergetic co-blockade shifted TAM function from an anti-inflammatory to a proinflammatory phenotype, triggering antitumor cytotoxicity through TNF-related apoptosis-inducing ligand (TRAIL)-mediated apoptosis, thereby suppressing non-immunogenic tumors.

The type I interferon (IFN) response is a key mediator of ICD-induced antitumor efficacy, activated through the recognition of nucleic acids from dying cells [10]. The authors found that, while non-immunogenic murine tumors exposed to PTX induced autocrine type I IFN secretion, the presence of macrophages suppressed the IFN-stimulated gene (ISG) response. This suppression could be reverted by blocking TIM3 or VISTA. These findings suggest that $TIM3^{+}$ $VISTA^{+}$ TAMs in immunoresistant tumors inhibit type I IFN-driven antitumor immunity by dampening the ISG response. Furthermore, the authors identified that

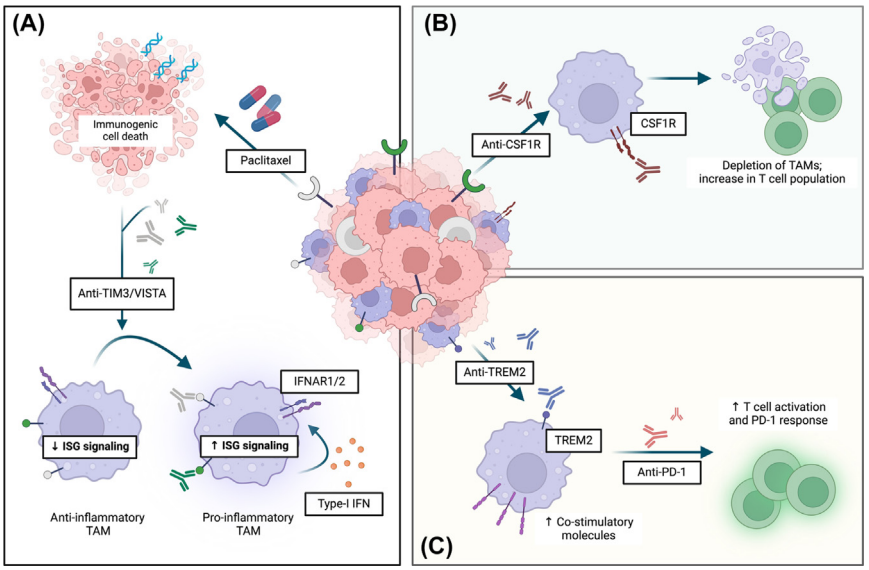

Figure 1. Current insights on tumor-associated macrophages (TAM)-based immunotherapy. (A) Paclitaxel treatment induces immunogenic cell death, leading to increased type I interferon (IFN) signaling, but this is not sensed properly by TAMs due to suppressive signaling mediated by T cell immunoglobulin and mucin domain-containing 3 (TIM3) and V-domain immunoglobulin suppressor of T cell activation (VISTA) [9]. Subsequent treatment with anti-TIM3 or anti-VISTA antibodies shifts TAMs from an anti-inflammatory to a proinflammatory phenotype, characterized by increased sensing of type I IFNs leading to IFN-stimulated gene (ISG) signaling. (B) Inhibition of colony-stimulating factor 1 receptor (CSF1R) through anti-CSF1R antibodies depletes TAMs from the tumor microenvironment while increasing the T cell population [8]. (C) Anti-triggering receptor expressed on myeloid cells 2 (TREM2) treatment enhances co-stimulatory molecule expression on TAMs and, when combined with anti-PD-1 antibodies, promotes T cell activation and an enhanced PD-1 response, strengthening antitumor immune activity [7]. Figure created with BioRender (biorender.com).

HMGB1 and VISTA on dying cancer cells served as ligands that engage TIM3 and VISTA on TAMs, respectively.

In summary, the authors identified a subset of immunosuppressive TAMs in T cell-depleted, ICB-resistant tumors that have a central role in therapy resistance. They also explored the potential of targeting TIM3$^+$VISTA$^+$ TAMs for TAM-based immunotherapy (Figure 1). It would be valuable to investigate whether co-treatment with ICB induction and TIM3 or VISTA blockade could be effective in human tumors. Niche-specific signals are crucial in determining the function of activated TAMs [4], making it important to understand the spatial localization of TIM3$^+$VISTA$^+$ TAMs within the TME to gain deeper insights into its complexity. Further studies would be beneficial to elucidate the role of TIM3$^+$VISTA$^+$ TAMs in disease progression and late-stage carcinogenesis. Additionally, investigating the metabolic basis of these TAM subsets could reveal other potential metabolic targets for reprogramming. Overall, gaining a more in-depth understanding of the mechanisms driving TAM polarization within the TME could lead to improved treatment strategies, particularly through the combination of PTX and anti-TIM3/VISTA therapy for immunoresistant tumors.

Declaration of interests

None declared by authors.

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