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PERSPECTIVE

From dichotomy to diversity: deciphering the multifaceted roles of tumor-associated macrophages in cancer progression and therapy

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Macrophages are innate immune cells that are ubiquitously distributed throughout the vertebrate body. Macrophages orchestrate sophisticated processes in development, homeostasis, immunity, and disease[1]. Macrophages residing in tumor tissues are commonly known as tumor-associated macrophages (TAMs) and promote or inhibit tumor growth depending on the activation state[2]. TAMs often predominantly display pro-tumorigenic properties that promote inflammation, angiogenesis, metastasis, and immunosuppression. Nevertheless, TAMs also have the potential to serve as anti-tumor effectors and boost anti-tumor immunity. Thus, targeting TAMs is a promising therapeutic strategy[3]. Antibody-mediated depletion of TAMs has shown promise in preclinical models. Numerous clinical trials are now evaluating macrophage-targeting strategies, often in combination with other immunotherapies[4]. Furthermore, harnessing the anti-tumor functions of macrophages, especially by enhancing M1 polarization and concurrently inhibiting M2 polarization, also represents a promising therapeutic strategy[5].

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The paradigm shift from the M1/M2 dichotomous model to TAM diversity

The M1/M2 macrophage polarization model was proposed in the early 2000s to describe the two extremes of macrophage activation and function[6]. M1 (classically activated macrophages) are pro-inflammatory and involved in host defense, while M2 (alternatively activated macrophages) are anti-inflammatory and involved in wound healing and tissue repair. The M1/M2 model was initially based on *in vitro* studies showing that IFN-γ and lipopolysaccharide (LPS) stimulate macrophages to the M1 phenotype, while IL-4 stimulates the M2 phenotype. M1 macrophages produce pro-inflammatory cytokines, such as TNF and IL-12, as well as reactive oxygen and nitrogen species (ROS and RNS, respectively). In contrast, M2 macrophages produce anti-inflammatory cytokines, such as IL-10 and TGFβ, and express markers, including Arg1. M2-like TAMs are thought to facilitate angiogenesis, matrix remodeling, and immunosuppression, while M1-like TAMs have anti-tumor activity. Over the years, the M1/M2 model has been particularly influential in studies involving TAMs and the role of TAMs in promoting tumor progression[7].

While useful as a conceptual framework, this dichotomous model is now recognized as an oversimplification due to the significant diversity in cell morphology, function, and cell surface marker expression in macrophages, suggesting that macrophage activation is a continuum *in vivo*[8,9]. TAMs display a diverse range of phenotypes *in vivo* that do not fit neatly into the M1/M2 categories[10]. Indeed, TAM polarization depends on the integration of multiple environmental signals.

In addition, the model does not fully capture the plasticity and reversibility of macrophage polarization. Hence, the development of new tools to characterize macrophage phenotypes is critical to better understand the diverse roles of macrophages in health and disease.

Redefining TAM subpopulations in the single cell era

Recent breakthroughs in single cell omics methods, especially single-cell RNA sequencing (scRNA-seq), have transformed our comprehension of cell diversity by offering detailed transcriptomic data for individual cells[11]. Unlike traditional methods that often rely on pre-existing knowledge or a limited set of genes, scRNA-seq operates without any prior assumptions[12]. Specifically, scRNA-seq classifies cell subpopulations based solely on the transcriptional profiles, eliminating the potential for subjective biases and arbitrary categorizations. This method harnesses the power of large amounts of data, offering a more comprehensive and unbiased view. Thus, scRNA-seq provides insight that goes beyond what can be gained from idealized laboratory models by presenting a more accurate representation of real-world biological complexities. Due to major progress in experimental methods and bioinformatics workflow, scRNA-seq is now commonly utilized to study cell diversity in nearly all types of cancer. Notably, the unbiased analysis from clinical samples using scRNA-seq has offered a powerful tool to dissect the intrinsic heterogeneity of macrophages in the tumor microenvironment[13].

Since the application of commercialized high-throughput single-cell sequencing technology on clinical samples, there has been a marked increase in studies using scRNA-seq on various cancer types and macrophages, which uncovered diverse subpopulations of TAMs. Indeed, two recent large-scale pan-cancer scRNA-seq studies provided valuable insight into TAM diversity[14,15]. For example, Cheng et al.[15] identified several tumor-enriched macrophage subsets, including $SPP1^+$, $C1QC^+$, $ISG15^+$, and $FN1^+$ TAMs. $ISG15^+$ TAMs are characterized by the upregulation of multiple interferon-inducible genes. In contrast, $SPP1^+$ and $C1QC^+$ TAMs resemble the recently described dichotomous functional phenotypes of TAMs in colorectal cancer. These findings, along with other single-cell profiling studies involving immune cells undertaken by various laboratories with different tumors, have been comprehensively summarized in recent reviews[16,17]. Based on these results, Ma et al.[17] proposed a new classification of TAMs. These subsets include interferon-primed TAMs (IFN-TAMs), immune regulatory TAMs (Reg-TAMs), inflammatory cytokine-enriched TAMs (Inflam-TAMs), lipid-associated TAMs (LA-TAMs), pro-angiogenic TAMs (Angio-TAMs), RTM-like TAMs (RTM-TAMs), and proliferating TAMs (Prolif-TAMs). In another summary, TAMs were simply categorized into 5 subgroups: $IL4I1^+$; $TREM2^+$; $FOLR2^+$; FTL^+; and proliferating[18]. Each of these TAM subpopulations is distinguished by unique surface markers and is linked to particular cancer types. The roles of TAM subpopulations include various functions (antigen presentation, lipid metabolism, matrix remodeling, angiogenesis, and cell proliferation).

It is worth noting that these TAM subgroups are not distinct but rather form a continuous range across various forms of cancer. Additionally, some marker genes may shift or co-exist between these TAM subgroups. The existence of intermediate groups also implies that the diversity of TAMs in cancer could be more accurately described as a continuous spectrum rather than as separate categories[13,15]. While some of these TAMs resemble traditional macrophage classifications, such as M1-like macrophages, TAM functions in the tumor environment can be more complex and even paradoxical, with some potentially having immunosuppressive roles[19].

Revisiting the origination and plasticity of TAM subpopulations defined by scRNA-seq

The redefinition of these TAM subpopulations raises several critical questions: (1) What are the origins of these subgroups? (2) Are these subpopulations stable or can a single subpopulation differentiate into another, and do the subpopulations have the capability to interconvert (a phenomenon often referred to as "plasticity")? If this is the case, how is such plasticity regulated? (3) How reliable are the subpopulations, as defined by scRNA-seq, and how can this data be better aligned with experimental findings? (4) Are there subpopulations specific to certain types of tumors? (5) Is it feasible to target specific subpopulations more precisely for cancer immunotherapy? Delving into these questions promises not only to enrich our understanding of TAM biology but also to pave the way for more refined and potent therapeutic approaches for cancer (**Figure 1**).

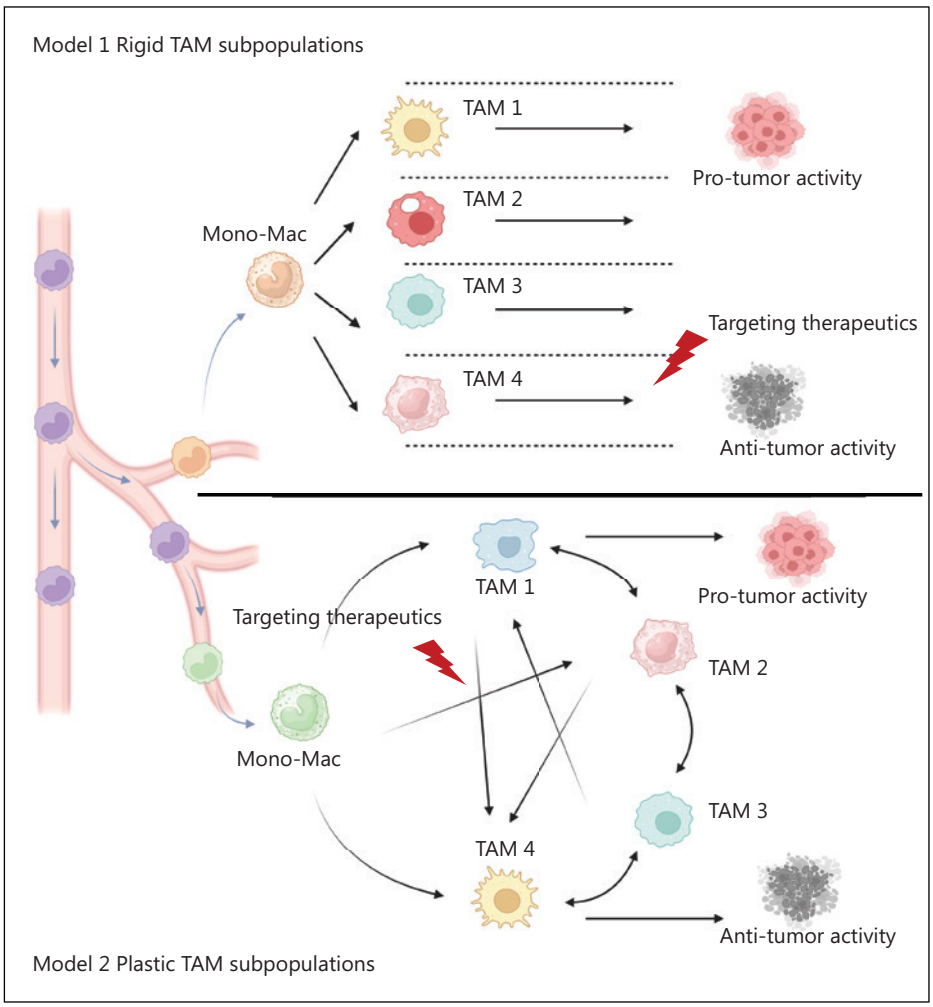

Figure 1 The relationships between subpopulations of tumor-associated macrophages (TAMs). Macrophages, originating from circulating monocytes, infiltrate tumor tissues and differentiate into TAMs. Model 1 suggests that TAM subgroups are rigid in nature, with each subpopulation developing independently. Targeting specific subpopulations could serve as potential immune therapeutic targets for tumor treatment. Model 2 proposes that TAM subpopulations exhibit plasticity, allowing for interconversion between subgroups. When targeting a particular subpopulation as a therapeutic strategy, the potential to transform into another subpopulation upon treatment must be considered.

Macrophages, as tissue-specific immune cells, originate from various stages of hematopoiesis during embryogenesis to populate and reside in their respective organs[20]. Most TAMs, in contrast, are derived from circulating monocytes. Notably, a minor group of original embryonic macrophages can remain in the tumor tissues, exhibiting functions different from TAMs. One such unique role involves remodeling of the extracellular matrix[18]. Distinct positioning within the tumor microenvironment is evident between pre-existing tumor-linked resident tissue macrophages (RTMs) and TAMs originating from monocytes in multiple cancers. For example, in conditions like lung cancer and glioblastomas, RTMs derived from the embryonic stage predominantly reside on the outskirts of tumors, while TAMs from monocytes penetrate the tumor core[21-23]. Consequently, these insights indicate the pressing need to differentiate between tumor-linked RTMs and TAMs stemming from monocytes when evaluating TAM characteristics and roles.

The coexistence of marker genes among the newly defined TAM subpopulations coupled with the paradoxical presence of subpopulations across different cancer types and the common origin of most TAMs all underscore the remarkable plasticity observed in TAMs[15,17,19]. TAM plasticity suggests the potential for interconversion between distinct subpopulations,

highlighting the dynamic nature of TAMs. This ability to transition between states is not arbitrary but is likely governed by intrinsic regulatory mechanisms. Factors, such as cytokine signaling, interactions with other immune cells, and cues from the tumor milieu, are essential in directing the fate of TAMs[17]. Additionally, epigenetic modifications influenced by the tumor environment might serve as molecular switches that determine the differentiation trajectory of these cells[24,25]. In light of these findings, the characterization of the epigenomes in monocytes and *in vitro*-differentiated macrophages has facilitated the identification of cell type-specific epigenetic loci and revealed differentiation and treatment-specific repertoires[24]. Furthermore, the combination of single-cell assay for transposase-accessible chromatin using sequencing (scATAC-seq) with scRNA-seq has been applied in defining the epigenetic features of TAM subsets. For example, *de novo* motif analysis revealed key transcription factors, such as TEAD1 and CEBP, that bind and act at open chromatin sites, indicating potential epigenetic regulation of TAM plasticity[26]. Pan-cancer scRNA-seq studies that identified various TAM clusters across multiple cancer types also suggest potential lineage relationships and interconversion possibilities among these subsets[15]. Therefore, elucidating the regulatory networks that underpin TAM plasticity is crucial in determining the diverse roles of TAMs in tumor progression and potential therapeutic interventions.

The current scRNA-seq methodologies present some technical challenges that can impede the precise characterization of cell subpopulations, adding an additional layer of complexity to the heterogeneity of TAMs. One concern is the possibility of obtaining limited and non-representative cell samples due to cell loss that occurs during the tissue digestion process of scRNA-seq sample preparation. For example, the yield of macrophages following tissue digestion is much less than the number of macrophages *in situ*[27]. Furthermore, the procedure of tissue dissociation, essential for obtaining individual cells, can inadvertently lead to the activation of macrophages[28]. This activation can subsequently induce alterations in the transcriptional profiles, thereby introducing bias into the data. The tissue digestion procedures can result in cell debris attached to other cells, which may lead to experimental artifact.[27] Additionally, the application of unsupervised machine learning for clustering can introduce overfitting, which may result in misclassification of cell types or states[29]. To address the challenges and overcome the technical limitations, several approaches can be adopted[30]. Myeloid-specific transgenic reporter mouse lines, when combined with scRNA-seq, enable researchers to trace the origins of specific TAM subgroups[31]. This tracing assists in confirming whether a particular group genuinely represents a cellular subpopulation[32,33]. Another strategy involves single-cell multi-omics, such as cellular indexing of transcriptomes and epitopes by sequencing (CITE-seq)[34]. This method uses oligo-conjugated antibodies to link cell surface markers to single-cell transcriptomes. Consequently, CITE-seq can organize information about cell surface proteins, facilitating comparisons with extensive data previously acquired through flow cytometry. Additionally, scATAC-seq allows for high-resolution mapping of open chromatin regions at the single-cell level to provide insight into the chromatin landscape[35]. Unlike the pronounced changes observed in transcriptomes, chromatin modifications are more stable, making chromatin modifications robust markers. When integrated with scRNA-seq, it is feasible to determine if a detected subpopulation is authentic or merely an artifact. Lastly, spatial transcriptomics techniques present a more intuitive method, allowing researchers to visualize cellular distribution *in situ*, thus offering a holistic view of cell locations and cell interactions within the tissue[36].

Harnessing the plasticity of TAMs in cancer therapeutics

Strategies targeting macrophages for tumor therapy have been under investigation for a long time to complement existing T cell-focused immunotherapies[3]. One primary method has focused on inhibiting the recruitment of macrophages. Essential molecules present on monocytes/macrophages, such as CCR2, CCR5, VEGFR, CSF1R, ITGA4 and C5a, have a crucial role in guiding macrophage infiltration into tumor tissues[37]. Utilizing inhibitors or antibodies against these molecules or their associated ligands, such as CCL2, CCL5, VEGF, and CSF1, can effectively suppress macrophage infiltration. Moreover, by focusing on reducing angiogenesis, especially through targeting molecules, like Nrp1 and ANG2, macrophage recruitment can be further limited[38,39].

Another strategy focuses on diminishing macrophage longevity. For example, CSF1, a key factor in macrophage differentiation, can be targeted to limit the development and growth of these cells[40]. Despite the potential of these strategies, targeting immunomodulators in macrophages, such as SIRPa-CD47 or CSF1R-CSF1/IL34 interactions, to boost anti-tumor immunity has shown limited success in clinical trials due to various

compensatory mechanisms[41]. As a result, we can now comprehend why pan-TAM targeting approaches have shown limited efficacy in clinical settings. Recognizing the multifaceted roles of TAMs in hindering anti-tumor immunity and promoting cancer progression, there is a pressing need for innovative techniques and methods. Specifically, we could harness these roles to develop therapeutic strategies that mitigate the immunosuppressive attributes of TAMs (**Figure 1**).

Therefore, combining new and comprehensive translational knowledge from unbiased scRNA-seq profiling, patient samples, mouse models, and *in vitro* functional assays should be synchronized with rational clinical study design that consider the diverse nature of TAMs[42]. Recent studies have shown that novel TAM subpopulations and their plasticity can be characterized using unbiased single-cell sequencing combined with clinical samples. For instance, through scRNA-seq of clinical samples, a study identified two distinct subsets of macrophages in malignant breast tissues (TREM2+ and FOLR2+ TAMs). FOLR2+ TAMs are located in the perivascular niche of the tumor stroma and interact with tumor-infiltrating CD8+ T cells, showing a positive correlation with T cell infiltration. This finding highlights the distinction between two primary macrophage populations in breast cancer. The effectiveness of this approach has also been demonstrated in studies involving the Siglec-sialic acid family protein, Siglec-9, on macrophages in glioblastomas (GBMs)[19,43]. One study investigated the role of the Siglec-sialic acid axis immunosuppressive tumor environment of GBMs[43]. High abundance of SIGLEC9$^+$ macrophages in patients was linked to worse clinical outcomes. This finding suggests that targeting the Siglec-sialic acid axis could offer a potential therapeutic approach for GBM patients. In another scRNA-seq profiling study, we used single-cell transcriptomic and spatial analysis to show that SIGLEC9$^+$ monocyte-derived macrophages are prominent in GBMs of patients unresponsive to neoadjuvant immune checkpoint inhibitors (ICIs)[19]. By systematically analyzing the gene transcriptional profile of this cellular subset, these macrophages were shown to be highly plastic and immunosuppressive, harboring pro-tumorigenic and anti-tumorigenic activity programs. Hence, these macrophages have dual roles, displaying both immunosuppressive functions (enriched for angiogenesis and cellular response to hypoxia signatures) and intrinsic anti-tumor functions (enriched for antigen presentation, inflammatory responses, and IFN-induced pathways). This dual expression within the same TAM further illustrates the complexity and plasticity of these cells. In the current study we underscored the significance of selectively targeting macrophage subpopulations by demonstrating using a Siglece-knockout mouse model that removing SiglecE from TAMs hindered tumor growth and extended survival, an effect amplified with ICI treatment. Further, treatment with a recombinant protein combining the extracellular domain of SIGLECE with the mouse IgG1 Fc domain showcased the potential in boosting anti-tumor immunity, a finding also supported in a humanized melanoma mouse model[44]. Taken together, bridging single-cell profiling of human samples with mouse studies supports the adoption of novel ICI-based therapies and underscores the potential of targeting the plastic and immunosuppressive TAM subpopulation in clinical settings.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

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