RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

Tumour-Associated Macrophages and Cancer Metastasis

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Abstract

Tumour-associated macrophages (TAMs) play an important role in cancer metastasis by creating a favourable microenvironment for cancer cell survival, growth, and spread. These pathways ultimately affect the immune system and the development of cancer in the tumour microenvironment by enhancing macrophages' plasticity and their capacity to transition between distinct activation states. Because of their diverse functions and ability to switch between different activation states (M1 and M2) and their ability to polarize various immune cells in the tumour microenvironment, influencing the immune response to cancer, TAMs are appealing targets for cancer therapy and treatment, with ongoing research focusing on the development of new strategies to target and modulate TAM functions in the context of cancer metastasis. Despite these obstacles, targeting TAMs remains a promising area of research in cancer immunotherapy, with ongoing efforts to develop new strategies and therapies to harness the immune response, improve cancer treatment outcomes and save lives.

Keywords: Tumour-associated macrophages (TAMs); Metastasis; Cancer.

1. Introduction

Tumour-associated macrophages (TAMs) play a significant role in cancer metastasis, contributing to each stage of the metastatic process. Their involvement in creating pre-metastatic niches, intravasation, and the survival of circulating tumour cells has been well-documented. TAMs are known to orchestrate almost all the cascade steps of tumour metastasis, making them prominent promoters of metastasis in the tumour microenvironment (**Mantovani et al., 2017**).

TAMs promote cancer metastasis via a variety of mechanisms, including the release of cytokines, chemokines, and growth factors that alter the cellular microenvironment, eventually leading to the activation of various transcription factors that promote tumour progression and metastasis (**Tang et al., 2013**). Cancer increases the production and secretion of these pro-cancerous factors in TAMs, forming a positive feedback loop that ensures unstoppable cancer growth. TAMs also establish metabolic cross-talk with immune cells such as T helper 1 (TH1) cells, ultimately promoting the survival of newly lodged tumour cells via immunosuppression (**Bingle et al., 2002**). This immunosuppressive environment allows metastatic

cancer cells to survive and grow. In the tumour microenvironment, TAMs are predominantly M2-like anti-inflammatory immune cells and are associated with malignant disease, drug resistance, and poor prognosis. Their ability to switch between different activation states, particularly the M2 phenotype, contributes to their tumour-promoting effects, which include angiogenesis promotion, immune suppression, and the support of tumour growth and metastasis (**Mantovani et al., 2004; Cook & Hagemann, 2013**).

Tumour-associated macrophages (TAMs) can polarize various immune cells in the tumour microenvironment, influencing the immune response to cancer. The different types of immune cells that can be polarized by TAMs include:

• **T cells:** TAMs can influence the polarization of T cells, which are key players in the adaptive immune response. This polarization can impact the anti-tumour immune response and the regulation of immune tolerance (**Cook & Hagemann, 2013**).

• **B cells:** TAMs have been shown to induce M2b macrophage polarization in human hepatocellular carcinoma (HCC), which can suppress other immune cells, such as CD8+ T cells and M1 macrophages (**Tokunaga et al., 2019**).

• **Macrophages:** TAMs can also influence the polarization of other macrophages in the tumour microenvironment, contributing to the overall immune response to cancer. The plasticity of macrophages and their ability to switch between different activation states make them a key player in shaping the immune landscape within tumours (**Boutilier & Elsawa, 2021**).

These interactions highlight the complex and dynamic nature of the immune response in the tumour microenvironment, with TAMs playing a central role in shaping the polarization of various immune cells (**Xu et al., 2021**).

2. Classification of TAMs

Tumour-associated macrophages (TAMs) can undergo different activation states, primarily classified into two main groups: classically activated macrophages (M1) and alternatively activated macrophages (M2) (**Rhee, 2016**). These activation states have distinct functions and mechanisms in the context of cancer:

• **M1 macrophages:** These macrophages are

involved in the direct mediation of cytotoxicity and antibody-dependent cell-mediated cytotoxicity (ADCC), exerting anti-tumour functions. M1 macrophages are further divided into three subtypes based on their functions: M1a (tumouricidal), M1c (inflammatory), and M1d (wound healing) (**Italiani & Boraschi, 2014; Kapellos et al., 2019**).

• **M2 macrophages:** These macrophages promote the occurrence and metastasis of tumour cells, and are often associated with tumour-promoting activities, such as angiogenesis and neovascularization. M2 macrophages are further classified as M2a (pro-tumour) and M2c (regulatory). Aside from these primary activation states, macrophages can also undergo phenotypic polarisation in response to tumour-derived or microenvironmental signals, resulting in a diverse set of activation states. Macrophage plasticity contributes to their diverse functions in the tumour microenvironment, which can affect cancer progression and metastasis (**Jablonski et al., 2015; Fujisaka et al., 2016**).

3. Mechanisms of TAMs in metastasis

Tumour-associated macrophages (TAMs) are macrophages that are involved in the formation of the tumour microenvironment and play a crucial role in cancer development, progression, and metastasis. They can promote tumour growth, invasion, metastasis, and drug resistance. TAMs are divided into two main subtypes: M1 macrophages, which have anti-tumour functions, and M2 macrophages, which promote tumour growth and invasion (**Yin et al., 2019; Dallavalasa et al., 2021**). TAMs contribute to cancer through a variety of mechanisms including:

• **Activation of cell-stimulating growth factors and cytokines:** TAMs secrete various cytokines, chemokines, and growth factors, which can alter the cellular microenvironment and promote tumour progression and metastasis (**Wang et al., 2024; Zhou et al., 2024**).

• **Immune suppression:** TAMs can suppress the immune system by interacting with tumour cells and other immune cells, leading to immunosuppression and facilitating tumour growth (**Li et al., 2024**).

• **Angiogenesis:** TAMs play a role in the modulation of neoangiogenesis, which is the formation of new blood vessels in the tumour microenvironment, promoting tumour growth and

metastasis (**Zhang et al., 2024**).

• **Tumour microenvironment remodelling:** TAMs contribute to the remodelling of the extracellular matrix in the tumour microenvironment, which can affect cancer cell proliferation, metastasis, and drug resistance (**Winkler et al., 2020; Neophytou et al., 2021**).

• **Resistance to chemotherapeutic agents and checkpoint blockade immunotherapy:** TAMs can form a positive feedback loop with cancer cells, enhancing the generation and secretion of pro-cancerous factors, which can lead to resistance to various anticancer therapies (**Basak et al., 2023**).

TAMs have become an appealing target for cancer immunotherapies due to their critical role in cancer development and progression. Strategies that inhibit macrophage recruitment, polarization, or function have shown promise in improving the efficacy of cancer treatments. More research is needed, however, to better understand the complex interactions between TAMs and cancer cells and to develop effective therapies that target these macrophages (**Samadi et al., 2015; Morein et al., 2020**).

4. Signalling pathways involved in the polarization of macrophages in the tumour microenvironment

The signalling pathways involved in the polarization of M1 and M2 macrophages in the tumour microenvironment include:

• **IRF/STAT Signaling:** This pathway is a central mechanism in controlling macrophage M1–M2 polarization. Toll-like receptor signalling, particularly TLR4 stimulated by lipopolysaccharide (LPS) and other microbial ligands, drives macrophages to a preferentially M1 phenotype (**Chiang & Liu, 2019; Mogensen, 2019**).

• **Chemokine/Cytokine Receptor Signaling:** This pathway is involved in the interaction of chemokine/cytokine receptors with their ligands, leading to the polarization of M2-like macrophages, which are associated with tumour progression, angiogenesis, and immune suppression (**Haddad, 2002; Kuhn et al., 2024; Lan et al., 2024**).

• **Notch Signaling:** Notch signalling has been shown to determine the M1 versus M2 polarization

of macrophages in the antitumour immune response (**Yan et al., 2023**).

• **Tumour Microenvironment (TME) Signaling:** Stimuli from the TME can give rise to different macrophage polarization outcomes, leading to the predominant polarization of M2-like macrophages, which play a tumour-promoting role in the TME (**Malak et al., 2024; Sharma & Otto, 2024**).

5. TAMs and the immune response against cancer cells

Tumour-associated macrophages (TAMs) affect the immune response against cancer cells through various mechanisms, including:

• **Activation of immune cells:** TAMs play a crucial role in stimulating the immune system by secreting various cytokines and activating immune cells, such as T cells and NK cells, which can exert anti-tumour functions (**Xi et al., 2024**).

• **Immune suppression:** TAMs can contribute to an immunosuppressive environment by interacting with tumour cells and other immune cells, leading to the suppression of cytotoxic T-cell activity and facilitating tumour growth (**Alim et al., 2024; Trivanović et al., 2024**).

• **Influence on tumour cells:** TAMs can influence tumour cells through the secretion of cytokines and growth factors, which can lead to the production of reactive substances, oxidative DNA damage, and reduced DNA repair, contributing to cancer progression (**Solinas et al., 2009; Farajzadeh Valilou et al., 2018**).

• **Modulation of macrophage polarization:** TAMs can be classified into two main subtypes: M1 macrophages, which exert anti-tumour functions, and M2 macrophages, which promote tumour growth and invasion (**Malfitano et al., 2020; Tan et al., 2021**).

Depending on the tumour microenvironment, TAMs can switch between these subtypes, which may impact their immune response against cancer cells. Furthermore, the creation of T cells with the chimeric antigen receptor (CAR) that can specifically target macrophages has demonstrated promise in the field of cancer immunotherapy (**Jung et al., 2024**).

Downstream targets of the signalling pathways

involved in the polarization of. The downstream targets of the signalling pathways involved in the polarization of M1 and M2 macrophages in the tumour microenvironment include:

• **Proinflammatory factors:** M1 macrophages are associated with the secretion of proinflammatory factors, such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumour necrosis factor-alpha (TNF-α), which contribute to their anti-tumour effects (**Kung et al., 2020; Czajka-Francuz et al., 2021**).

• **Immunosuppressive factors:** M2 macrophages are prone to promoting angiogenesis and neovascularization, and they secrete immunosuppressive factors, such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β), which contribute to their tumour-promoting effects (**Yeo et al., 2021**).

• **Angiogenic factors:** M2 macrophages are also involved in the promotion of angiogenesis through the secretion of factors such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), which support tumour growth and metastasis (**Lamagna et al., 2006; Fu et al., 2020**).

• **Matrix metalloproteases:** Both M1 and M2 macrophages are involved in the expression of matrix metalloproteases, which play a role in tissue remodelling and the progression of cancer (**Mantovani et al., 2006; Allavena et al., 2008**).

These downstream targets reflect the distinct roles of M1 and M2 macrophages in the tumour microenvironment, with M1 macrophages exerting anti-tumour effects and M2 macrophages promoting tumour progression and metastasis. macrophages in the tumour microenvironment (**Braga et al., 2015**).

6. Challenges in targeting TAMs in cancer therapy

Challenges in targeting tumour-associated macrophages (TAMs) in cancer therapy include:

• **Complex roles of TAMs:** TAMs can have both tumour-supportive and tumour-suppressive functions, making it difficult to develop therapies that specifically target only the tumour-suppressive aspects of TAMs (**Gacche, 2023; Higginbottom et al., 2023**).

• **Macrophage plasticity:** TAMs can undergo various activation states and switch between different subtypes, depending on the tumour microenvironment. This plasticity makes it challenging to develop therapies that can consistently target TAMs in a specific state (**Wu et al., 2020; Ricketts et al., 2021**).

• **Immune evasion:** TAMs can contribute to immune evasion by interacting with tumour cells and other immune cells, leading to immunosuppression and facilitating tumour growth. This makes it difficult for therapies targeting TAMs to effectively restore anti-tumour immune responses (**Muenst et al., 2016; Yang et al., 2020**).

• **Limited success in clinical trials:** Some clinical trials targeting TAMs have shown suboptimal therapeutic responses and varying results among patients. This highlights the need for further research and development of more effective strategies to target TAMs in cancer therapy (**Fukumura et al., 2018; Aehnlich et al., 2021**).

• **Combination therapies:** Combining TAM-targeting therapies with other immunotherapies or cancer treatments may be necessary to achieve optimal therapeutic outcomes. This requires a deeper understanding of the complex roles of TAMs in the tumour microenvironment and the development of new strategies to harness the immune response and combat cancer progression (**Dang et al., 2024; Wei et al., 2024**).

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