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The role of macrophages in cancer progression: M1, M2 subtypes, and their impact on tumor microenvironment

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Abstract

Macrophages are key players in the immune system, exhibiting remarkable plasticity that allows them to influence cancer progression in opposing ways. Their polarization into M1 or M2 subtypes dictates their impact on the tumor microenvironment (TME). M1 macrophages, characterized by pro-inflammatory and anti-tumor functions, release cytokines that enhance immune responses and promote tumor destruction. Conversely, M2 macrophages support tumor growth by facilitating angiogenesis, immune suppression, and tissue remodeling, thereby creating a favorable environment for cancer progression. Further classification of M2 macrophages into subtypes M2a, M2b, M2c, and M2d underscores their diverse roles in tumor development, metastasis, and immune evasion. Given their crucial role in shaping the TME, macrophages have become a major focus in cancer research. Recent therapeutic strategies aim to reprogram macrophages, shifting their phenotype from tumor-promoting to tumor-suppressive. By targeting macrophage polarization, researchers seek to develop novel immunotherapies that enhance treatment efficacy, improve patient outcomes, and combat therapy resistance in cancer.

Keywords: Cancer, M1, M2a, M2b, M2c, M2d macrophages, TAM.

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1. Introduction

Macrophages, as professional phagocytes, are central players in immune homeostasis, pathogen defense, and tissue repair. However, their functions can be highly influenced by the local environment. In tumors, macrophages undergo polarization into distinct phenotypes that significantly impact cancer progression. M1 macrophages, often termed "classically

activated" or "pro-inflammatory" macrophages, play a crucial role in tumor suppression. They are characterized by their ability to produce pro-inflammatory cytokines, present antigens, and exhibit cytotoxic effects against tumor cells. In contrast, M2 macrophages, referred to as "alternatively activated" or "anti-inflammatory," are generally associated with tumor progression due to their roles in immunosuppression, angiogenesis, and tissue remodeling [1-7]. M1 and M2 macrophages are considered not as separate species, but as a spectrum with different degrees of M1- or M2-like properties. Macrophages represent a dynamic cellular population capable of plasticity, which allows them to transition between pro-inflammatory (M1) and anti-inflammatory (M2) states depending on the cytokines they encounter. The M2 subset has further been subdivided into M2a, M2b, M2c, and M2d, each contributing uniquely to tumor progression. Understanding these macrophage subsets and their specific contributions to the TME is essential for developing new therapeutic approaches to treat cancer [3, 8].

2. Macrophage Polarization: M1 and M2 Macrophages

2.1. M1 Macrophages and Tumor Suppression

M1 macrophages are activated by IFN-γ and microbial products such as LPS. These macrophages are characterized by the production of pro-inflammatory cytokines like CCL2, Type IIFN, IFN-γ, TNF-α, IL-1, 6, 12; CXCL1-3, CXCL-5, CXCL8-10, STAT1, iNOS, LPS, M-CSF, NF-κB, IRF5, miR-155, miR-125b, DNMT1, DNMT3b, HDAC3, and are potent producers of reactive oxygen species (ROS) and nitric oxide (NO), which exhibit direct cytotoxic effects on tumor cells.

By enhancing the cytotoxic effect of NK cells and the formation of cytotoxic T-lymphocytes, IL-12 affects the production of certain cytokines, such as tumor necrosis factor alpha (TNF-alpha) and IFN-gamma, which contribute to the destruction of tumor cells. M1 macrophages not only directly attack tumor cells but also engage in the removal of apoptotic cells, debris, and pathogens. Their role in tumor suppression is well-documented, as they support the activation of adaptive immune responses that prevent tumor escape. However, tumors can subvert M1 macrophages through the secretion of immunosuppressive cytokines, thereby shifting macrophage polarization toward an M2 phenotype [9, 10]. M1 macrophages are tumor-resistant, exhibiting intrinsic phagocytosis and enhanced antitumor inflammatory reactions [11]. Furthermore, research on "Cell therapy using ex vivo reprogrammed macrophages enhances antitumor effects" demonstrates that reprogramming macrophages towards the M1 phenotype ex vivo, followed by adoptive cell therapy, can enhance antitumor responses. This approach involves treating macrophages with HDAC6 inhibitors to promote M1 polarization, thereby improving their tumor-suppressive functions [12].

Recent research has shed light on the multifaceted roles of M1 macrophages in tumor suppression, highlighting their potential as therapeutic targets in cancer treatment. For example, exosomal miR-29c-3p derived from M1 macrophages suppresses melanoma cell aggressiveness by targeting ectonucleotide pyrophosphatase/phosphodiesterase 2 (ENPP2) in melanoma cells, leading to reduced migration and invasion. The mechanism involves alterations in cholesterol metabolism and extracellular matrix remodeling, collectively diminishing tumor aggressiveness and invasion [13]. In colorectal cancer, M1 macrophages have been shown to suppress tumor growth by promoting a pro-inflammatory environment. They achieve this by enhancing T cell activation, leading to a self-reinforcing cycle that reduces tumor growth. This interplay underscores the importance of both innate and adaptive immune responses in limiting tumor progression [14]. Tumor cells secrete Pros1, which dampens macrophage M1-associated gene expression through receptors like Mer and Tyro3. This mechanism reduces macrophage p38α activity, promoting a shift towards the M2 phenotype and facilitating tumor progression by inhibiting their M1 polarization and promoting an immunosuppressive environment conducive to tumor progression [15].

Computational models have been developed to simulate macrophage interactions within the tumor microenvironment, providing insights into how repolarizing M2 macrophages to the M1 phenotype can influence tumor invasion dynamics [16].

These findings underscore the complex interactions between macrophages and tumors, highlighting both the tumor-suppressive functions of M1 macrophages and the mechanisms tumors employ to modulate macrophage activity. Understanding these dynamics offers promising avenues for developing macrophage-based therapeutic strategies in cancer treatment.

2.2. M2 Macrophages and Tumor Progression

M2 macrophages are typically activated by IL-4, IL-13, and other Th2 cytokines. They are primarily involved in immune regulation, tissue repair, and the resolution of inflammation. However, within the TME, M2 macrophages promote tumor growth, angiogenesis, and metastasis. They achieve this by secreting IL-10, TGF-β, VEGF, and PDGF, which contribute to the suppression of anti-tumor immune responses, stimulate tumor cell proliferation, and promote angiogenesis [17]. The polarization of macrophages to the M2 phenotype is often linked to poor prognosis in various cancers, including breast, lung, and colon cancer. The transition from M1 to M2 macrophages is regulated by various factors, including hypoxia, tumor-derived exosomes, and signaling through immune checkpoints like PD-1/PD-L1 [18, 19].

3. Subtypes of M2 Macrophages: M2a, M2b, M2c, and M2d

3.1. M2a Macrophages

M2a macrophages induced by IL-4 or IL-13 are characterized by their role in Th2 responses, tissue repair, and fibrosis. M2a macrophages are involved in the resolution of inflammation and tissue repair. These macrophages

participate in tissue remodeling after injury, particularly by secreting enzymes like matrix metalloproteinases (MMPs), which degrade extracellular matrix components to aid in wound healing. M2a macrophages also contribute to fibrosis formation, aiding in the deposition of extracellular matrix components such as collagen. They produce cytokines such as IL-10, TGF-β (transforming growth factor beta), and IL-1 receptor antagonists (IL-1ra), which act to suppress inflammation. IL-10, in particular, is a key cytokine produced by M2a macrophages and is known for its anti-inflammatory properties, contributing to the regulation of immune responses and limiting excessive tissue damage. By secreting cytokines such as IL-10 and TGF-β, they inhibit the activation of CD8+ T-cells and NK cells, providing tumors with an opportunity to evade immune surveillance [16, 20, 21].

In the context of cancer, M2a macrophages contribute to the formation of a fibrotic tumor stroma, which provides structural support to the tumor and protects it from immune attack. This fibrotic tissue can also facilitate tumor cell survival by creating a niche that is resistant to oxidative stress and cytotoxic agents. They can promote tumor growth by suppressing anti-tumor immunity, facilitating angiogenesis (the formation of new blood vessels), and inducing a pro-tumorigenic microenvironment. M2a macrophages may contribute to the creation of an immunosuppressive environment within the tumor, which can impair the body's ability to recognize and attack cancer cells. In several cancer types, such as breast cancer, colorectal cancer, and lung cancer, M2a macrophages are often recruited to the tumor microenvironment (TME). There, they play a role in tumor progression by promoting immune evasion, angiogenesis, and tissue remodeling. Tumor cells secrete factors such as IL-4, IL-13, and other signaling molecules that can induce macrophages to polarize towards the M2a phenotype [22]. M2a macrophages play an important role in promoting an immunosuppressive microenvironment. They suppress the activity of cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells, which are key players in anti-tumor immunity. By doing so, they help tumors evade immune surveillance. Studies have shown that the M2a macrophages in breast cancer tumors contribute to immune evasion and metastasis. These macrophages secrete high levels of IL-10 and TGF-β, which promote immune suppression and increase the tumor's ability to spread. A promising strategy involves targeting the pathways that induce M2 polarization, such as IL-4 and IL-13 signaling, to prevent tumor progression [23]. In lung cancer, M2a macrophages are found in the tumor stroma, where they support tumor growth through the production of cytokines like IL-10 and TGF-β. These cytokines are involved in suppressing the cytotoxic T-cell response and promoting the angiogenic process that facilitates tumor growth. Modulating the M2 macrophage phenotype through immune checkpoint inhibitors or other immunotherapies is explored as a potential treatment for lung cancer. [24]. In colorectal cancer, M2a macrophages are implicated in creating an immunosuppressive environment that supports tumor growth and metastasis. They may also contribute to the development of fibrosis, which is associated with poor prognosis in colorectal cancer patients [25].

3.2. M2b Macrophages

M2b macrophages are activated by immune complexes and Toll-like receptor (TLR) ligands, including lipopolysaccharides (LPS) and immune complexes containing antibodies. This activation leads to the production of pro-inflammatory cytokines, including IL-6, IL-10, and TNF-α, which are key mediators in immune modulation. They express markers such as CD206 (mannose receptor), CD163, and Arginase-1, which are shared with other M2 macrophages but differ in their cytokine production profiles. M2b macrophages are known for having a dual nature—they can promote inflammation, but they are also involved in tissue repair. Their role in cancer is complex, as they can either contribute to anti-tumor immunity or facilitate tumor growth depending on the tumor microenvironment (TME) [26, 27].

In cancer, M2b macrophages can produce a mix of IL-10, IL-12, and IL-6, which can both suppress immune responses and enhance immune surveillance. Their dual function complicates their role in the TME, and their influence on cancer progression is context-dependent. M2b macrophages can support tumor progression by creating an immunosuppressive environment. M2b suppresses inflammation by producing IL-10, IL-10 and TGF-β, both of which are anti-inflammatory cytokines that dampen the immune system's ability to recognize and attack tumor cells. By producing IL-10, M2b macrophages can suppress the activity of cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells, critical players in the immune response against tumors. M2b macrophages may contribute to tumor growth by promoting immune tolerance and suppressing anti-tumor immunity. This immune suppression allows tumor cells to evade detection and metastasize [28].

M2b macrophages can contribute to a chronic inflammatory environment, which is often observed in cancers. Inflammation in the TME can fuel cancer progression through the release of growth factors, cytokines, and extracellular matrix remodeling enzymes, which help in tumor cell survival, proliferation, and metastasis. IL-6 and TNF-α, produced by M2b macrophages, can promote tumor cell growth and survival, contributing to the pro-inflammatory nature of many cancers, including breast, colorectal, and lung cancers. They secrete high levels of PDGF, which is involved in angiogenesis. Angiogenesis, the formation of new blood vessels, is essential for tumor growth and metastasis. M2b macrophages can produce factors like VEGF (vascular endothelial growth factor), which promote angiogenesis and help tumors develop the vascular network needed to sustain their growth. M2b macrophages, like other M2 subtypes, can contribute to fibrosis in the TME by secreting collagen and other extracellular matrix (ECM) components. This fibrosis can create a desmoplastic tumor stroma, which can hinder drug delivery and facilitate the development of a barrier to the immune system, thus promoting tumor progression. They can also release enzymes such as matrix metalloproteinases (MMPs), which break down ECM components, facilitating tumor invasion and metastasis [29-31].

The immune-modulating effects of M2b macrophages are associated with resistance to therapies. Their immunosuppressive cytokine production, particularly IL-10, can contribute to resistance to checkpoint inhibitors,

chemotherapy, and radiation. By skewing the immune system toward tolerance, M2b macrophages can render tumors less susceptible to immune checkpoint blockade therapies, making them a key target for potential immunotherapy strategies [32]. In breast cancer, M2b macrophages are often found in the tumor stroma. They secrete IL-6 and TNF-α, contributing to the inflammatory environment. This promotes tumor progression and can increase the risk of metastasis to other organs. These macrophages also support immune escape by suppressing the activity of T-cells and promoting the expression of immune checkpoints. In lung cancer, M2b macrophages contribute to the chronic inflammation observed in the tumor microenvironment. The presence of IL-6 and TNF-α can foster the tumor's ability to grow and resist treatment. Moreover, M2b macrophages contribute to tumor-associated fibrosis, a hallmark of non-small cell lung cancer (NSCLC). This fibrosis complicates the delivery of therapeutic agents to the tumor site and impairs the anti-tumor immune response. In colorectal cancer, M2b macrophages also contribute to the pro-inflammatory environment in the TME. Their secretion of cytokines such as IL-6 and TNF-α promotes inflammation, tumor growth, and metastasis to distant organs like the liver and lungs. The immune suppression caused by M2b macrophages further supports tumor survival and progression. Studies have shown that M2b macrophages are recruited to head and neck cancer sites, where they aid in the development of an immunosuppressive TME. By secreting IL-10, M2b macrophages limit the activity of CD8+ T-cells and NK cells, promoting tumor immune escape. These macrophages may also contribute to the angiogenesis and fibrosis that support tumor growth and metastasis [5, 33].

3.3. M2c Macrophages

M2c macrophages are a subtype of alternatively activated macrophages (M2 macrophages)**,** which are generally associated with immune regulation, tissue repair, and anti-inflammatory functions. Among the various M2 macrophage subtypes (M2a, M2b, and M2c), M2c macrophages are specifically involved in tissue remodeling, immunosuppression, and the resolution of inflammation. These macrophages play a significant role in promoting cancer progression, creating an immunosuppressive tumor microenvironment (TME), and potentially contributing to metastasis. M2c macrophages are activated by IL-10, glucocorticoids, and other regulatory factors. They are primarily involved in immune suppression and tissue remodeling. They are characterized by the secretion of anti-inflammatory cytokines, like IL-10 and TGF-β, and they express markers like CD206**,** CD163**,** Arginase-1, and mannose receptor (MR). In cancer, M2c macrophages contribute to tumor progression by secreting TGF-β and IL-10, which foster an immunosuppressive microenvironment. These cytokines inhibit the activation of anti-tumor immune responses, promoting immune evasion and facilitating tumor cell metastasis [34].

Moreover, M2c macrophages are key players in extracellular matrix remodeling, a process that is critical for tumor cell migration and invasion. By modulating matrix composition and stiffness, they support the establishment of secondary tumors at distant sites. M2c macrophages are crucial for the resolution of inflammation, helping tissues return to homeostasis after an inflammatory response. However, in the context of cancer, this immunosuppressive effect can facilitate immune evasion and promote tumor growth. These macrophages suppress the activation and cytotoxic activity of immune cells such as T cells and natural killer (NK) cells, thus enabling tumors to evade immune detection. M2c macrophages are involved in tissue remodeling through the secretion of matrix metalloproteinases (MMPs), which degrade the extracellular matrix (ECM). This is critical for wound healing, but in cancer, it can contribute to tumor progression by facilitating tumor invasion and metastasis. M2c macrophages are associated with fibrosis in the tumor microenvironment, contributing to the desmoplastic response (the production of collagen and other ECM components) and creating a physical barrier that can hinder immune responses and drug delivery. They can also contribute to angiogenesis (the formation of new blood vessels), a critical process for tumor growth and metastasis, by secreting vascular endothelial growth factor (VEGF) and other factors [34-36].

M2c macrophages play a central role in promoting tumor progression, immunosuppression, and metastasis through a variety of mechanisms like IL-10 and TGF-β secretion: M2c macrophages secrete high levels of IL-10 and TGF-β, which dampen the immune response. IL-10 inhibits the function of cytotoxic T lymphocytes (CTLs) and NK cells, preventing them from effectively targeting and eliminating cancer cells. Similarly, TGF-β promotes immune suppression and tumor tolerance by inhibiting the activation of T-helper 1 (Th1) cells and cytotoxic T cells. These cytokines contribute to creating an immunosuppressive environment within the tumor, facilitating immune evasion by cancer cells. M2c macrophages are involved in creating a pro-tumorigenic microenvironment by secreting factors that stimulate tumor cell survival, proliferation, and migration. The immunosuppressive factors they release (such as IL-10 and TGF-β) also promote tumor growth by reducing the ability of the immune system to control the tumor. These macrophages can also promote angiogenesis, the growth of new blood vessels, which tumors rely on to receive nutrients and oxygen. By producing VEGF, M2c macrophages help tumors form the vascular networks necessary for growth and metastasis [37, 38].

M2c macrophages contribute to tumor-associated fibrosis by secreting collagen and other ECM proteins. This fibrotic tissue can act as a physical barrier, not only hindering immune cell infiltration but also impairing the delivery of therapeutic agents, thus contributing to therapy resistance. The fibrotic stroma also helps create a protective niche for tumor cells, allowing them to survive and invade surrounding tissues [32, 39].

By facilitating tissue remodeling and extracellular matrix (ECM) degradation, M2c macrophages enable tumor cells to invade surrounding tissues and metastasize to distant organs. The release of MMPs and other proteolytic enzymes by M2c macrophages breaks down the ECM, enabling tumor cells to migrate and invade other tissues. Additionally, the immunosuppressive environment created by M2c macrophages helps tumor cells evade immune surveillance during the metastatic process [40]. In breast cancer, M2c macrophages play a role in promoting tumor progression through

immunosuppression and fibrosis. High levels of IL-10 and TGF-β in the TME created by M2c macrophages lead to reduced T-cell activation and the inhibition of anti-tumor immunity. M2c macrophages also promote angiogenesis and fibrosis, both of which contribute to tumor growth, metastasis, and therapy resistance.M2c macrophages in lung cancer are involved in the promotion of an immunosuppressive microenvironment [41]. The secretion of IL-10 and TGF-β by M2c macrophages contributes to immune evasion, allowing lung cancer cells to avoid immune surveillance and continue to proliferate and metastasize. These macrophages also promote fibrosis in the tumor stroma, which contributes to poor prognosis and resistance to therapies. In colorectal cancer, M2c macrophages are found to contribute to tumor progression by secreting immunosuppressive cytokines that inhibit the activity of T-cells and NK cells. Their presence is associated with tumor metastasis and poor prognosis. M2c macrophages also promote the fibrotic response in the TME, creating a stroma that facilitates tumor cell migration and survival. In ovarian cancer, M2c macrophages contribute to tumor progression by promoting immune evasion and angiogenesis. M2c macrophages in the tumor microenvironment are associated with increased TGF-β and IL-10, which suppress immune cell function and enhance tumor cell proliferation. These macrophages also contribute to the formation of a fibrotic tumor stroma, which further promotes tumor metastasis and therapy resistance [3, 42].

3.4. M2d Macrophages

M2d macrophages represent one of the subtypes of alternatively activated macrophages (M2 macrophages), which are typically associated with immunosuppressive functions and tissue remodeling. While M2a, M2b, and M2c macrophages are more commonly studied, the M2d macrophage subset has been identified more recently and is emerging as an important player in various pathological conditions, including cancer. M2d macrophages are characterized by their role in immune regulation, inflammation, and promoting the tumor microenvironment (TME). Their actions are less well-defined compared to the other M2 subtypes, but they have been found to contribute to tumor progression, immune evasion, and angiogenesis.

The least characterized of the M2 subtypes, M2d macrophages produce high levels of VEGF, as well as IL-10 and TGF-β. They also suppress the pro-inflammatory TNF-α and IL-12. Macrophages activated by M2d under the influence of TLR agonists (via IL-6) and adenosine A2A receptors. The M2d macrophage phenotype can be induced by a combination of IL-6, IL-10, IL-4, and cyclic adenosine monophosphate (cAMP) signaling. M2d macrophages exhibit properties that make them distinct from other M2 subsets. M2d macrophages often secrete a range of cytokines and chemokines that include IL-10, IL-6, and TGF-β. These cytokines contribute to an anti-inflammatory and immune-suppressive environment, which is conducive to cancer progression and metastasis. Like other M2 subtypes, M2d macrophages contribute to the downregulation of immune responses. This involves suppressing the activity of T-cells and natural killer (NK) cells, which are typically responsible for targeting and eliminating cancer cells. Similar to other M2 macrophage subsets, M2d macrophages may enhance angiogenesis (the growth of new blood vessels), which is essential for tumor growth and metastasis. They do this by secreting VEGF, which promotes the formation of new blood vessels to supply the growing tumor. By producing low levels of IL-12 and high levels of IL-10, VEGF, and CCL5, they contribute to angiogenesis, immune suppression, and tumor progression. The role of M2d macrophages in tumors is particularly important in promoting tumor vascularization, thereby ensuring that the growing tumor receives adequate nutrients and oxygen. In addition to supporting angiogenesis, M2d macrophages also play a role in immune evasion by secreting factors that suppress the activity of effector T-cells and NK cells. They contribute to creating a tumor-friendly environment that supports continued tumor growth and spread [43-45].

Immunosuppressive Tumor Microenvironment: M2d macrophages contribute to the immunosuppressive TME by secreting anti-inflammatory cytokines such as IL-10 and TGF-β. These cytokines suppress the activation of cytotoxic T cells and NK cells, which normally target and kill cancer cells. As a result, tumors can escape immune surveillance, allowing them to grow unchecked. Chronic Inflammation: M2d macrophages contribute to chronic inflammation in the tumor microenvironment. This can promote tumor cell survival, proliferation, and metastasis by creating a supportive environment for cancer cells. VEGF Secretion: Like other M2 macrophages, M2d macrophages play a significant role in promoting angiogenesis by secreting VEGF. Angiogenesis is a crucial process for tumor growth, as it provides tumors with the necessary nutrients and oxygen for their expansion. Tumor Vascularization: The vascular network promoted by M2d macrophages helps tumors increase in size and facilitates the spread of cancer cells to distant organs (metastasis) [46, 47].

M2d macrophages, like other M2 subtypes, may be involved in the remodeling of the ECM, a process that can enhance tumor cell migration and invasion. This remodeling is often driven by the secretion of MMPs, which break down ECM components. The creation of a fibrotic stroma can further enhance tumor progression by providing both a physical barrier for immune cells and a scaffold for tumor cells to invade surrounding tissues [48, 49]. M2d macrophages are implicated in the process of metastasis, where they promote the invasion of tumor cells into adjacent tissues and the spread of cancer cells to other parts of the body. By aiding in angiogenesis and ECM remodeling, M2d macrophages enable tumor cells to detach from the primary tumor site, invade blood vessels, and migrate to distant organs. M2d macrophages contribute to therapy resistance by promoting an immunosuppressive environment that limits the effectiveness of chemotherapy, immunotherapy, and radiation therapy. The secretion of IL-10 and TGF-β by M2d macrophages suppresses the immune system's ability to respond to and eliminate cancer cells, potentially leading to tumor relapse after treatment [50-52]. In breast cancer, M2d macrophages contribute to tumor progression and metastasis by promoting immune evasion through cytokine production, such as IL-10 and TGF-β. They also assist in the formation of the vascular network and fibrotic tissue, which are crucial for tumor growth and spread. In lung cancer, M2d

macrophages are found to play a role in creating an immunosuppressive tumor microenvironment. They suppress T-cell function and promote angiogenesis, facilitating tumor growth and metastasis. In colorectal cancer, M2d macrophages help create a chronic inflammatory microenvironment, contributing to immune evasion and enhancing metastatic spread to distant organs. The cytokines they produce, such as IL-6 and TGF-β, contribute to tumor progression and resistance to treatment. M2d macrophages have been associated with the promotion of metastasis and the formation of a fibrotic stroma in ovarian cancer. Their secretion of immunosuppressive cytokines supports the establishment of a peritoneal niche for metastatic tumor cells (Figure 1) [27, 53, 54].

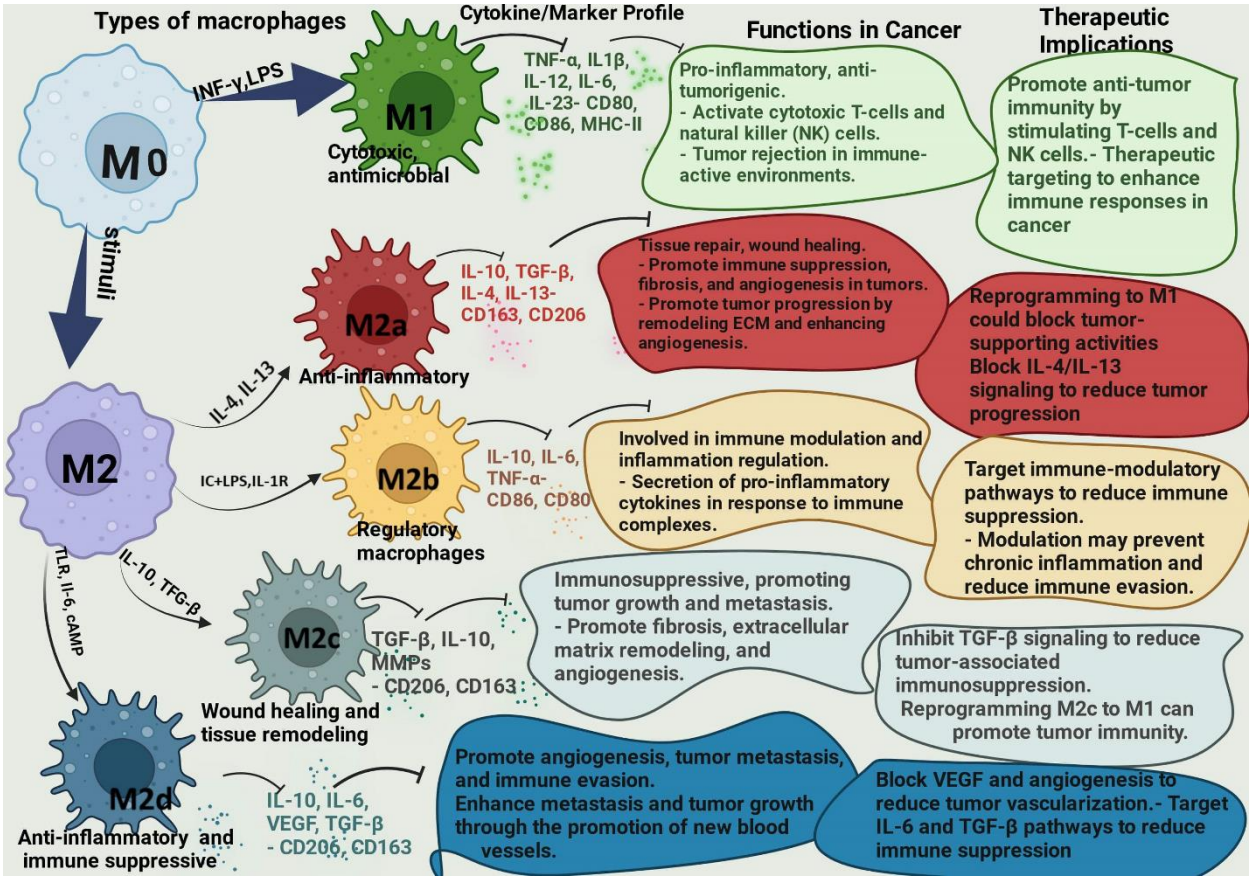

Figure 1.
The information related to macrophage subsets (M1, M2a, M2b, M2c, and M2d) and their roles in cancer, including key functions and therapeutic implications (Created in https://BioRender.com)

4. Macrophage Polarization and Cancer Immunotherapy

The plasticity of macrophages presents both a challenge and an opportunity for cancer immunotherapy. Inhibiting the conversion of M1 macrophages into M2 phenotypes or promoting the reprogramming of M2 macrophages into M1 macrophages could enhance the immune system's ability to target and eliminate tumors. Strategies to manipulate macrophage polarization include the use of cytokine-based therapies (e.g., IFN-γ for M1 polarization) and immune checkpoint inhibitors targeting PD-1/PD-L1 and CTLA-4 pathways, which modulate macrophage activity within the TME [54, 55].

There is growing interest in reprogramming M2 macrophages (including the M2a subtype) to an M1-like phenotype to enhance anti-tumor immunity. However, M2a macrophages are more challenging to reprogram than other M2 macrophage subtypes, as they are more strongly associated with tissue repair and immune regulation. Some studies suggest that blocking the IL-4/IL-13 signaling pathway or targeting specific receptors involved in M2a macrophage polarization may be a promising strategy to reduce the pro-tumorigenic effects of these macrophages in cancer.

Additionally, targeting macrophage-derived exosomes as delivery vehicles for therapeutic agents or using macrophage-targeted therapies to reduce VEGF or TGF-β secretion holds promise for improving cancer treatment outcomes.

Given the association of M2a macrophages with tumor progression and immune suppression, targeting M2 polarization or directly inhibiting M2a macrophages could be a potential therapeutic approach for cancer. Researchers are exploring drugs or small molecules that could reverse M2a polarization or block the signaling pathways involved in their activation.

Given their dual nature, M2b macrophages are an intriguing target for cancer therapy. Reprogramming M2b macrophages to a more anti-tumor (M1-like) phenotype is proposed as a potential therapeutic strategy. This can involve blocking the IL-4 and IL-13 signaling pathways or using specific drugs to reverse the polarization of M2b macrophages in the TME. Strategies to block pro-inflammatory cytokines such as IL-6, TNF-α, or IL-10 could reduce the immune suppression and inflammation induced by M2b macrophages, potentially enhancing the efficacy of immunotherapies like checkpoint inhibitors. TNF-α inhibitors and IL-6 receptor antagonists are explored in cancer treatments to reduce the tumor-promoting

effects of M2b macrophages. Drugs that target the fibrotic activity of M2b macrophages could be developed to disrupt the tumor stroma and enhance the delivery of chemotherapeutic agents or immune therapies to the tumor site [54, 56, 57].

Given the significant role of M2c macrophages in promoting tumor progression, immune suppression, and metastasis, targeting these cells or their activity represents a promising therapeutic strategy. Strategies to reprogram M2c macrophages into M1-like macrophages (which are pro-inflammatory and anti-tumorigenic) have the potential to enhance anti-tumor immunity. This could involve targeting the IL-10 and TGF-β signaling pathways that promote the M2c phenotype. Reversing the polarization of M2c macrophages could lead to improved immune responses against tumors. Since IL-10 and TGF-β are key cytokines secreted by M2c macrophages, therapeutic strategies that block these cytokines or their receptors could reduce the immunosuppressive effects of M2c macrophages. This could lead to enhanced T-cell responses and a more favorable tumor microenvironment for therapeutic interventions. Targeting fibrosis in the tumor microenvironment by inhibiting the activity of M2c macrophages and their ECM-degrading enzymes (like MMPs) could help improve the delivery of chemotherapies and immune-based therapies to the tumor. Since M2c macrophages promote angiogenesis, targeting VEGF or the pathways responsible for angiogenesis could reduce the blood supply to tumors and inhibit their growth [58].

Given their important role in promoting cancer progression, targeting M2d macrophages or their secreted cytokines represents a promising therapeutic strategy. Potential approaches include macrophage reprogramming strategies aimed at shifting M2d macrophages toward a more pro-inflammatory, anti-tumor M1 macrophage phenotype. This could enhance anti-tumor immunity and reduce the tumor-promoting effects of M2d macrophages. Therapeutic strategies that block the action of IL-10, TGF-β, or other cytokines secreted by M2d macrophages could reverse the immunosuppressive tumor microenvironment, enhancing the effectiveness of immunotherapy and other cancer treatments [59].

Inhibiting VEGF and other angiogenic factors secreted by M2d macrophages could restrict tumor growth by limiting the formation of new blood vessels and reducing the tumor's ability to metastasize. Targeting MMPs or other ECM-remodeling enzymes secreted by M2d macrophages could reduce tumor cell invasion and metastasis by preventing the breakdown of the extracellular matrix.

5. Conclusion and Future Directives

Macrophages, through their polarization into distinct M1 and M2 subtypes, are crucial regulators of tumor progression and immune evasion. While M1 macrophages enhance anti-tumor immunity, M2 macrophages particularly the M2a, M2b, M2c, and M2d subtypes contribute to tumor growth, metastasis, and immune suppression. Each M2 subtype has unique roles in promoting an immunosuppressive tumor microenvironment, fibrosis, angiogenesis, and immune evasion, all of which facilitate tumor progression and therapy resistance. Understanding the mechanisms underlying macrophage polarization in the tumor microenvironment is essential for developing targeted therapeutic strategies aimed at reprogramming these macrophages. Modulating macrophage function, particularly through shifting M2 macrophages toward a more pro-inflammatory, anti-tumor phenotype, holds promise for enhancing anti-tumor immunity, improving therapeutic efficacy, and ultimately improving patient outcomes in cancer treatment.

Table 1.
Glossary of Immunology Terms.

Glossary	
A2A	Adenosine receptor
cAMP	Cyclic adenosine monophosphate
CCL/R	Chemokine ligand/receptor
CD	Cluster of differentiation
CSC	Cancer stem cells
CSF	Colony-stimulating factor
CTL	Cytotoxic T cell
CTLA4	Cytotoxic T-lymphocyte-associated antigen 4
CXCL/R	Chemokine (C-X-C motif) ligand/receptor
DC	Dendritic cell
DNMT/R	ectonucleotide pyrophosphatase/phosphodiesterase
ECM	Extracellular matrix
EGF	Epidermal growth factor
EMT	Epithelial–mesenchymal transition
ENPP	ecto-nucleotide pyrophosphatase/phosphodiesterase
FGF	Fibroblast growth factor
HDAC	*Histone Deacetylase*
HIF	Hypoxia-induced transcription factor
IFN	Interferon
IL	Interleukin
IRF	Interferon regulatory factors
LPS	Lipopolysaccharide
miR	small non-coding RNA molecules
M-CSF	Macrophage colony-stimulating factor

Mer	Proto-oncogene tyrosine kinase
MMP	Matrix metalloproteinases
MR	Mannose receptor
NFκB	Nuclear factor kappa B
NK	Natural killer cell
NO	Nitric oxide
NOS	Nitric oxide synthase
NSCC	Non-stem cancer cell
NSCLC	Non-small cell lung cancer
PD1/PDL1	Programmed cell death protein 1/ ligand 1
PDGF	Platelet-derived growth factor
ROS	Reactive oxygen species
STAT	Signal transducer and activator of transcription
TAM	Tumor-associated macrophage
TGFβ	Transforming growth factor-β
TLR	Toll-like receptor
TME	Tumor microenvironment
TNFα	Tumor necrosis factor α
Tyro	Subfamily of receptor tyrosine kinases
VEGF	Vascular endothelial growth factor

References

[1] A. Mantovani and M. Locati, "Tumor-associated macrophages as a paradigm of macrophage plasticity, diversity, and polarization: Lessons and open questions," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 33, no. 7, pp. 1478-1483, 2013. https://doi.org/10.1161/ATVBAHA.113.300168

[2] S. Gordon and P. R. Taylor, "Monocyte and macrophage heterogeneity," *Nature Reviews Immunology*, vol. 5, no. 12, pp. 953-964, 2005. https://doi.org/10.1038/nri1733

[3] A. Sica and A. Mantovani, "Macrophage plasticity and polarization: In vivo veritas," *The Journal of Clinical Investigation*, vol. 122, no. 3, pp. 787-795, 2012. https://doi.org/10.1172/JCI59643

[4] S. K. Biswas and A. Mantovani, "Macrophage plasticity and interaction with lymphocyte subsets: Cancer as a paradigm," *Nature Immunology*, vol. 11, no. 10, pp. 889-896, 2010. https://doi.org/10.1038/ni.1937

[5] L. Cassetta and J. W. Pollard, "Targeting macrophages: Therapeutic approaches in cancer," *Nature Reviews Drug Discovery*, vol. 17, no. 12, pp. 887-904, 2018. https://doi.org/10.1038/nrd.2018.169

[6] P. Allavena, A. Sica, G. Solinas, C. Porta, and A. Mantovani, "The inflammatory micro-environment in tumor progression: The role of tumor-associated macrophages," *Critical Reviews in Oncology/hematology*, vol. 66, no. 1, pp. 1-9, 2008. https://doi.org/10.1016/j.critrevonc.2007.07.004

[7] S. S. Sedighzadeh, A. P. Khoshbin, S. Razi, M. Keshavarz-Fathi, and N. Rezaei, "A narrative review of tumor-associated macrophages in lung cancer: Regulation of macrophage polarization and therapeutic implications," *Translational Lung Cancer Research*, vol. 10, no. 4, p. 1889, 2021. https://doi.org/10.21037/tlcr-20-1241

[8] Z. Strizova *et al.*, "M1/M2 macrophages and their overlaps–myth or reality?," *Clinical Science*, vol. 137, no. 15, pp. 1067-1093, 2023. https://doi.org/10.1042/CS20220531

[9] C. Wang *et al.*, "The macrophage polarization by miRNAs and its potential role in the treatment of tumor and inflammation," *Oncology Reports*, vol. 50, no. 4, p. 190, 2023. https://doi.org/10.3892/or.2023.8627

[10] J. Liu, X. Geng, J. Hou, and G. Wu, "New insights into M1/M2 macrophages: Key modulators in cancer progression," *Cancer Cell International*, vol. 21, pp. 1-7, 2021. https://doi.org/10.1186/s12935-021-02089-2

[11] S. k. R. Noonepalle *et al.*, "Cell therapy using ex vivo reprogrammed macrophages enhances antitumor immune responses in melanoma," *Journal of Experimental & Clinical Cancer Research*, vol. 43, no. 1, p. 263, 2024. https://doi.org/10.1186/s13046-024-03182-w

[12] B. An *et al.*, "M1 macrophage-derived exosomal microRNA-29c-3p suppresses aggressiveness of melanoma cells via ENPP2," *Cancer Cell International*, vol. 24, no. 1, p. 325, 2024. https://doi.org/10.1186/s12935-024-03512-0

[13] T. D. Ricketts, N. Prieto-Dominguez, P. S. Gowda, and E. Ubil, "Mechanisms of macrophage plasticity in the tumor environment: Manipulating activation state to improve outcomes," *Frontiers in Immunology*, vol. 12, p. 642285, 2021. https://doi.org/10.3389/fimmu.2021.642285

[14] E. Ubil, L. Caskey, A. Holtzhausen, D. Hunter, C. Story, and H. S. Earp, "Tumor-secreted Pros1 inhibits macrophage M1 polarization to reduce antitumor immune response," *Journal of Clinical Investigation*, vol. 128, no. 6, pp. 2356-2369, 2018. https://doi.org/10.1172/JCI97354

[15] S. Suveges, R. Eftimie, and D. Trucu, "Directionality of macrophages movement in tumour invasion: A multiscale moving-boundary approach," *Bulletin of Mathematical Biology*, vol. 82, no. 12, p. 148, 2020. https://doi.org/10.1007/s11538-020-00819-7

[16] A. Shapouri-Moghaddam *et al.*, "Macrophage plasticity, polarization, and function in health and disease," *Journal of Cellular Physiology*, vol. 233, no. 9, pp. 6425-6440, 2018. https://doi.org/10.1002/jcp.26429

[17] J. Han, L. Dong, M. Wu, and F. Ma, "Dynamic polarization of tumor-associated macrophages and their interaction with intratumoral T cells in an inflamed tumor microenvironment: from mechanistic insights to therapeutic opportunities," *Frontiers in Immunology*, vol. 14, p. 1160340, 2023. https://doi.org/10.3389/fimmu.2023.1160340

[18] V. C. Brom, C. Burger, D. C. Wirtz, and F. A. Schildberg, "The role of immune checkpoint molecules on macrophages in cancer, infection, and autoimmune pathologies," *Frontiers in Immunology*, vol. 13, p. 837645, 2022. https://doi.org/10.3389/fimmu.2022.837645
[19] T. A. Wynn and K. M. Vannella, "Macrophages in tissue repair, regeneration, and fibrosis," *Immunity*, vol. 44, no. 3, pp. 450-462, 2016. https://doi.org/10.1016/j.immuni.2016.02.015
[20] A. M. Malfitano, S. Pisanti, F. Napolitano, S. Di Somma, R. Martinelli, and G. Portella, "Tumor-associated macrophage status in cancer treatment," *Cancers*, vol. 12, no. 7, p. 1987, 2020. https://doi.org/10.3390/cancers12071987
[21] R. Guo *et al.*, "Macrophage polarization in the tumor microenvironment: Recent research advances and therapeutic potential of different macrophage reprogramming," *Cancer Control*, vol. 32, p. 10732748251316604, 2025. https://doi.org/10.1177/10732748251316604
[22] C. E. Lewis and J. W. Pollard, "Distinct role of macrophages in different tumor microenvironments," *Cancer Research*, vol. 66, no. 2, pp. 605-612, 2006. https://doi.org/10.1158/0008-5472.CAN-05-4005
[23] R. Zhu, J. Huang, and F. Qian, "The role of tumor-associated macrophages in lung cancer," *Frontiers in Immunology*, vol. 16, p. 1556209, 2025. https://doi.org/10.3389/fimmu.2025.1556209
[24] Z. Zheng, T. Wieder, B. Mauerer, L. Schäfer, R. Kesselring, and H. Braumüller, "T cells in colorectal cancer: unravelling the function of different T cell subsets in the tumor microenvironment," *International Journal of Molecular Sciences*, vol. 24, no. 14, p. 11673, 2023. https://doi.org/10.3390/ijms241411673
[25] D. M. Mosser and J. P. Edwards, "Exploring the full spectrum of macrophage activation," *Nature Reviews Immunology*, vol. 8, no. 12, pp. 958-969, 2008. https://doi.org/10.1038/nri2448
[26] R. Noy and J. W. Pollard, "Tumor-associated macrophages: from mechanisms to therapy," *Immunity*, vol. 41, no. 1, pp. 49-61, 2014. https://doi.org/10.1016/j.immuni.2014.06.010
[27] L.-x. Wang, S.-x. Zhang, H.-j. Wu, X.-l. Rong, and J. Guo, "M2b macrophage polarization and its roles in diseases," *Journal of Leukocyte Biology*, vol. 106, no. 2, pp. 345-358, 2019.
[28] U. Basak *et al.*, "Tumor-associated macrophages: An effective player of the tumor microenvironment," *Frontiers in Immunology*, vol. 14, p. 1295257, 2023. https://doi.org/10.3389/fimmu.2023.1295257
[29] J. Kim and J.-S. Bae, "Tumor-associated macrophages and neutrophils in tumor microenvironment," *Mediators of Inflammation*, vol. 2016, no. 1, p. 6058147, 2016. https://doi.org/10.1155/2016/6058147
[30] B. Ruffell and L. M. Coussens, "Macrophages and therapeutic resistance in cancer," *Cancer Cell*, vol. 27, no. 4, pp. 462-472, 2015.
[31] A. Mantovani, A. Sica, S. Sozzani, P. Allavena, A. Vecchi, and M. Locati, "The chemokine system in diverse forms of macrophage activation and polarization," *Trends in Immunology*, vol. 25, no. 12, pp. 677-686, 2004.
[32] L. Chávez-Galán, M. L. Olleros, D. Vesin, and I. Garcia, "Much more than M1 and M2 macrophages, there are also CD169+ and TCR+ macrophages," *Frontiers in Immunology*, vol. 6, p. 263, 2015. https://doi.org/10.3389/fimmu.2015.00263
[33] R. Ostuni, F. Kratochvill, P. J. Murray, and G. Natoli, "Macrophages and cancer: from mechanisms to therapeutic implications," *Trends in Immunology*, vol. 36, no. 4, pp. 229-239, 2015. https://doi.org/10.1016/j.it.2015.02.004
[34] L. M. Coussens and Z. Werb, "Inflammation and cancer," *Nature*, vol. 420, no. 6917, pp. 860-867, 2002. https://doi.org/10.1038/nature01322
[35] J. Chen *et al.*, "CCL18 from tumor-associated macrophages promotes breast cancer metastasis via PITPNM3," *Cancer cell*, vol. 19, no. 4, pp. 541-555, 2011.
[36] L. Yang and Y. Zhang, "Tumor-associated macrophages: from basic research to clinical application," *Journal of hematology & oncology*, vol. 10, pp. 1-12, 2017.
[37] R. Kalluri, "The biology and function of fibroblasts in cancer," *Nature Reviews Cancer*, vol. 16, no. 9, pp. 582-598, 2016.
[38] D. V. Tauriello *et al.*, "TGFβ drives immune evasion in genetically reconstituted colon cancer metastasis," *Nature*, vol. 554, no. 7693, pp. 538-543, 2018.
[39] M. R. Galdiero, E. Bonavita, I. Barajon, C. Garlanda, A. Mantovani, and S. Jaillon, "Tumor associated macrophages and neutrophils in cancer," *Immunobiology*, vol. 218, no. 11, pp. 1402-1410, 2013.
[40] Q. Feng *et al.*, "Tumor-associated macrophages as prognostic and predictive biomarkers for postoperative adjuvant chemotherapy in patients with stage II colon cancer," *Clinical Cancer Research*, vol. 25, no. 13, pp. 3896-3907, 2019.
[41] H. Yang, H. Cheng, R. Dai, L. Shang, X. Zhang, and H. Wen, "Macrophage polarization in tissue fibrosis," *PeerJ*, vol. 11, p. e16092, 2023. https://doi.org/10.7717/peerj.16092
[42] M. G. Netea *et al.*, "Trained immunity: A program of innate immune memory in health and disease," *Science*, vol. 352, no. 6284, p. aaf1098, 2016. https://doi.org/10.1126/science.aaf1098
[43] E. Bonavita, M. R. Galdiero, S. Jaillon, and A. Mantovani, "Phagocytes as corrupted policemen in cancer-related inflammation," *Advances in Cancer Research*, vol. 128, pp. 141-171, 2015. https://doi.org/10.1016/bs.acr.2015.04.002
[44] S. B. Coffelt, M. D. Wellenstein, and K. E. de Visser, "Neutrophils in cancer: neutral no more," *Nature Reviews Cancer*, vol. 16, no. 7, pp. 431-446, 2016. https://doi.org/10.1038/nrc.2016.52
[45] B.-Z. Qian and J. W. Pollard, "Macrophage diversity enhances tumor progression and metastasis," *Cell*, vol. 141, no. 1, pp. 39-51, 2010. https://doi.org/10.1016/j.cell.2010.03.029
[46] D. I. Gabrilovich and S. Nagaraj, "Myeloid-derived suppressor cells as regulators of the immune system," *Nature Reviews Immunology*, vol. 9, no. 3, pp. 162-174, 2009. https://doi.org/10.1038/nri2496
[47] K. Kessenbrock, V. Plaks, and Z. Werb, "Matrix metalloproteinases: Regulators of the tumor microenvironment," *Cell*, vol. 141, no. 1, pp. 52-67, 2010.
[48] M. T. Chow, A. Möller, and M. J. Smyth, "Inflammation and immune surveillance in cancer," *Seminars in Cancer Biology*, vol. 22, no. 1, pp. 23–32, 2012. https://doi.org/10.1016/j.semcancer.2011.11.005
[49] G. P. Dunn, A. T. Bruce, H. Ikeda, L. J. Old, and R. D. Schreiber, "Cancer immunoediting: From immunosurveillance to tumor escape," *Nature Immunology*, vol. 3, no. 11, pp. 991-998, 2002.
[50] A. J. Boutilier and S. F. Elsawa, "Macrophage polarization states in the tumor microenvironment," *International Journal of Molecular Sciences*, vol. 22, no. 13, p. 6995, 2021. https://doi.org/10.3390/ijms22136995
[51] Q. Yang, N. Guo, Y. Zhou, J. Chen, Q. Wei, and M. Han, "The role of tumor-associated macrophages (TAMs) in tumor progression and relevant advance in targeted therapy," *Acta Pharmaceutica Sinica B*, vol. 10, no. 11, pp. 2156-2170, 2020.

[52] S.-Q. Qiu, S. J. Waaijer, M. C. Zwager, E. G. de Vries, B. van der Vegt, and C. P. Schröder, "Tumor-associated macrophages in breast cancer: Innocent bystander or important player?," *Cancer Treatment Reviews*, vol. 70, pp. 178-189, 2018. https://doi.org/10.1016/j.ctrv.2018.08.002

[53] D. Schweer, A. McAtee, K. Neupane, C. Richards, F. Ueland, and J. Kolesar, "Tumor-associated macrophages and ovarian cancer: implications for therapy," *Cancers*, vol. 14, no. 9, p. 2220, 2022. https://doi.org/10.3390/cancers14092220

[54] Y. Xu, X. Wang, L. Liu, J. Wang, J. Wu, and C. Sun, "Role of macrophages in tumor progression and therapy," *International Journal of Oncology*, vol. 60, no. 5, p. 57, 2022. https://doi.org/10.3892/ijo.2022.5369

[55] Y. Liu *et al.*, "Metabolic reprogramming in macrophage responses," *Biomarker Research*, vol. 9, pp. 1-17, 2021. https://doi.org/10.1186/s40364-020-00263-4

[56] J. Van Den Bossche, J. Baardman, and M. P. de Winther, "Metabolic characterization of polarized M1 and M2 bone marrow-derived macrophages using real-time extracellular flux analysis," *Journal of Visualized Experiments: JoVE*, no. 105, p. 53424, 2015. https://doi.org/10.3791/53424

[57] L. Chong, Y.-W. Jiang, D. Wang, P. Chang, K. Xu, and J. Li, "Targeting and repolarizing M2-like tumor-associated macrophage-mediated MR imaging and tumor immunotherapy by biomimetic nanoparticles," *Journal of Nanobiotechnology*, vol. 21, no. 1, p. 401, 2023. https://doi.org/10.1186/s12951-023-02044-9

[58] A. Shimabukuro-Vornhagen, A. Draube, T. M. Liebig, A. Rothe, M. Kochanek, and M. S. von Bergwelt-Baildon, "The immunosuppressive factors IL-10, TGF-β, and VEGF do not affect the antigen-presenting function of CD40-activated B cells," *Journal of Experimental & Clinical Cancer Research*, vol. 31, pp. 1-7, 2012.

[59] J. D. Smith and Y. Liu, "Targeting macrophage polarization in cancer therapy: A promising approach to enhancing anti-tumor immunity," *Journal of Cancer Research*, vol. 75, no. 3, pp. 1044-1059, 2021. https://doi.org/10.1016/j.jcr.2021.04.010