Macrophage

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Macrophages within solid tumors and metastatic sites are heterogenous populations with different developmental origins and substantially contribute to tumor progression. A number of tumor-promoting phenotypes associated with both tumor- and metastasis-associated macrophages are similar to innate programs of embryonic-derived tissue-resident macrophages. In contrast to recruited macrophages originating from marrow precursors, tissue-resident macrophages are seeded before birth and function to coordinate tissue remodeling and maintain tissue integrity and homeostasis. Both recruited and tissue-resident macrophage populations contribute to tumor growth and metastasis and are important mediators of resistance to chemotherapy, radiation therapy, and immune checkpoint blockade. Thus, targeting various macrophage populations and their tumor-promoting phenotypes holds therapeutic promise.

tumor-associated macrophages   tissue-resident macrophages   tumor microenvironment

monocyte   metastasis-associated macrophage   trained immunity   depletion   recruitment

repolarization   cancer   immune therapy

1. Introduction

The tumor microenvironment (TME) is a diverse niche in which tumor, stromal, and immune cells dynamically interact via secreted factors and physical engagement, all within a dynamic extracellular matrix (ECM) [1]. Though the composition of the TME varies between tumor types, macrophages are often abundant and play a key role in tumor progression through promotion of tumor survival pathways and suppression of cytotoxic T cell responses [2]. Perhaps unsurprisingly, tumor cells co-opt a number of known tissue regulatory programs orchestrated by macrophage populations, including regulation of ECM, cell motility, chemotaxis, angiogenesis, and immune signaling pathways, to increase their survival [3]. Targeting macrophages and their tumor promotional programs is a major area of research in the pursuit of successful therapy [4]. It is also increasingly clear that targeting macrophages may be a beneficial approach to enhance the efficacy of conventional cytotoxic therapies and immune checkpoint blockade (ICB) [5]. Encouraging results from pre-clinical murine models are now being translated to the clinic with a number of clinical trials currently under investigation [6].

2. Targeting Macrophages to Potentiate Anti-Cancer Therapy

Given the high propensity of macrophages as prognostic indicators of negative outcomes in solid tumors, it stands to reason that selective and targeted therapeutic approaches should benefit the patient. Indeed, over the past two decades, results from pre-clinical studies have largely established a tumor-promotional role of macrophages in solid tumors [4][7]. Thus, targeting either macrophages and/or these tumor-promoting phenotypes may be instrumental to developing therapeutic opportunities to alleviate cancer burden (Figure 1).
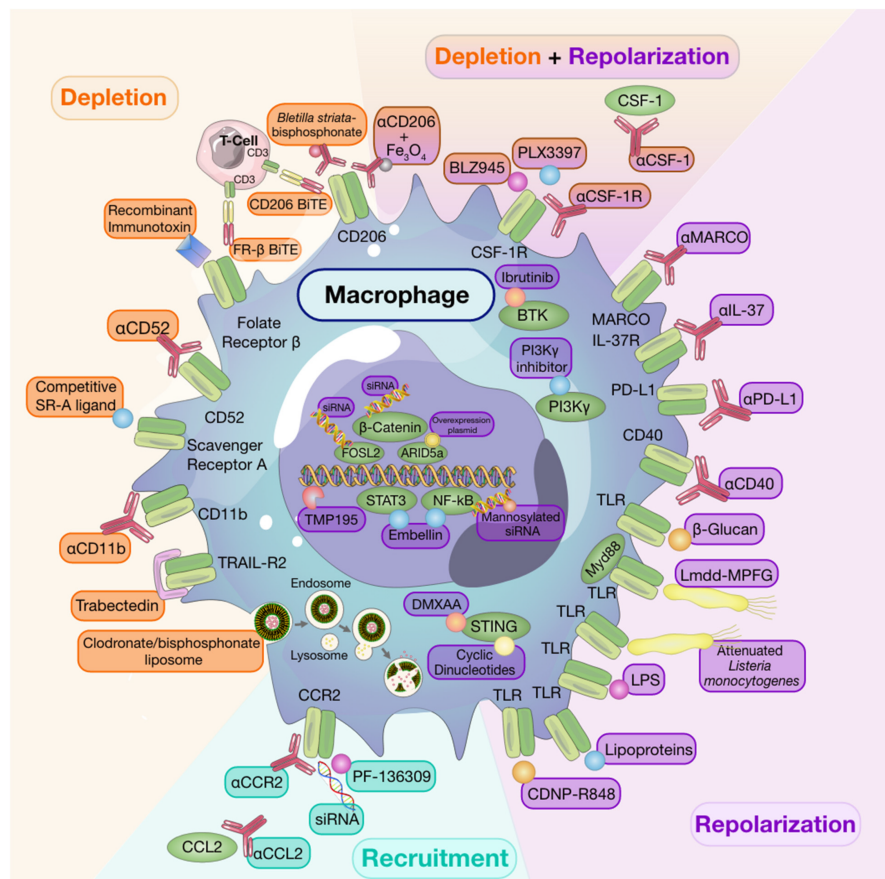
Figure 1. Therapeutic strategies targeting macrophages and their tumor-promoting phenotypes. Macrophage depletion, inhibiting macrophage recruitment, and/or promoting repolarization of macrophages towards anti-tumor phenotypes are the main strategies currently under investigation in the pursuit of developing macrophage-targeted therapies in cancer. These strategies include the use of antibodies (αCSF-1, αCSF-1R, αCCR2, αCCL2, αCD11b, αCD52, αCD206, αMARCO, αIL-37, αPD-L1, αCD40); small molecule inhibitors (PLX3397, BLZ945, embelin; ibrutinib); pharmacological inhibitors (PF-136309); recombinant immunotoxin; small-interfering RNAs; toll-like receptor (TLR) agonists (CDNP-R848; lipopolysaccharide [LPS]; lipoproteins); stimulator of interferon genes (STING) agonists (DMXAA; cyclic dinucleotides); trabectedin chemotherapy; clodronate or bisphosphonate-packed liposomes; microbe-derived products (β-glucan, attenuated listeria monocytogenes, attenuated hepatocellular carcinoma-specific Listeria vaccine [Lmdd-MPFG]); histone deacetylase inhibitors (TMP195); competitive inhibitors (competitive scavenger receptor A [SR-A] ligand); novel antibody-drug conjugates, such as bivalent T cell engagers (BiTE; folate receptor-β [FR-β] BiTE, CD206 BiTE); and antibody-conjugated iron oxide nanoparticles (αCD206 + Fe_3O_4) in the blockade of macrophage survival, recruitment, and repolarization pathways.

2.1. Macrophage Depletion

While targeted depletion of macrophages as monotherapy in preclinical models of established solid tumors is beneficial in some instances [8][9][10], other studies have revealed that, when used as a single agent, macrophage targeting strategies are minimally effective at slowing growth in established tumors [11]. It is interesting to note that for some studies wherein monotherapy was advantageous, depletion strategies targeted resident macrophage populations in addition to TAMs [9]. Despite limited evidence of efficacy for single-agent therapies to deplete macrophages in solid tumors, a number of clinical trials investigating macrophage depleting agents have been undertaken [12] and have also shown limited efficacy. However, it is worth noting that macrophage depletion following tumor resection in a spontaneous mouse model of melanoma reduced recurrence and metastasis [13], thus, highlighting timing of therapy as a consideration to achieve maximal therapeutic success [11].

Early monocyte and macrophage depletion methods relied on the use of bisphosphonate-packed and clodronate-loaded liposomes [14][15][16]. Clodronate-mediated TAM ablation demonstrated the crucial role of macrophages in orchestrating early tumor formation and progression in a mouse model of mammary cancer [17]. Depleting TAMs using clodronate-loaded liposomes was also shown to augment the anti-tumor effects of the protein kinase inhibitor, sorafenib, on tumor angiogenesis, growth, and metastasis in a hepatocellular carcinoma model [18]. Moreover, other studies have shown that clodronate liposomes enhance the anti-tumor and anti-angiogenic effects of anti-VEGF antibodies in subcutaneous tumor models [19][20].

2.2. Recruitment

The majority of monocyte recruitment inhibitors are monoclonal antibodies or pharmacological targets designed to block the interaction between monocyte-chemotactic cytokines and chemokines and their receptors. There are currently several clinical trials testing the safety and efficacy of such treatments as single agents or in combination with other therapies [6].

Much of the research investigating monocyte/macrophage recruitment strategies as targets for anti-cancer therapy have centered around the CCL2/CCR2 axis given that CCR2 is overexpressed by many tumors and enhances monocyte recruitment into the TME [21]. Indeed, use of anti-CCL2 antibodies have been associated with reduced macrophage infiltration and tumor growth [21][22]. However, in the clinic, completion of a Phase II clinical trial using anti-CCL2 antibodies in castration-resistant prostate cancer found that treatment neither blocked the signaling axis nor did it reduce tumor burden [23]. Therapeutic approaches targeting CCR2 by pharmacological inhibitors, such as PF-136309, anti-CCR2, or small-interfering RNA (siRNA) knockdown, are still under investigation [24][25][26]. As mentioned previously, many macrophage targeting therapies will be most efficacious when used in conjunction with others rather than when used alone. A recent study revealed that CCR2 antagonism sensitized tumors to anti-PD-1 ICB therapy in a number of murine tumor and metastasis models. In these models, tumor regression was associated with increased mobilization and activation of CD8+ T cells [27]. While single-agent strategies targeting monocyte recruitment may be beneficial in alleviating pro-tumorigenic effects of recruited macrophage populations, resident macrophage populations will remain undisturbed and may thwart attempts of regaining tumor control.

2.3. Repolarization

The abundance of macrophages, their contribution to the TME, and their plasticity make them attractive targets not only for depletion but also for repolarization strategies. As discussed below, many experimental therapies have focused on repolarizing these tumor-promoting cells towards a tumor-suppressive phenotype to improve patient outcomes.

Engagement of toll-like receptors (TLR) with their cognate ligands is a well-described method of inducing macrophage repolarization. TLR agonists, including lipopolysaccharides, and lipoproteins, stimulate NFκB, activator protein 1 (AP-1), and interferon regulatory factor signaling pathways. This results in activation of M1-associated genes and production of pro-inflammatory cytokines, including TNFα, IL-12, and IL-6 [28]. Indeed, Poly:IC-mediated activation of TLR-3 in a murine model of colon cancer led to M1 macrophage repolarization and reduced tumor growth through activation of IFN-α/β signaling pathways [29]. Despite successes in pre-clinical models, use of systemic TLR agonists as anti-cancer therapy is hindered by toxicity [30]. However, intratumoral TLR agonist therapy [31] or use of drug delivery systems to directly target TLRs expressed by TAMs can mitigate toxicity. For example, administration of β-cyclodextrin nanoparticles loaded with TLR7/8 agonists to tumor-bearing mice led to effective drug delivery to TAMs with limited off-target effects. These TLR7/8 agonist-loaded nanoparticles were potent inducers of M2-to-M1 macrophage repolarization and sensitized mice to anti-PD-1 therapy in PD-1 refractory tumors [32]. In addition, activation of the cytosolic stimulator of interferon genes (STING) pathway, which results in type-I interferon expression, has also been associated with macrophage polarization [33] and potentiation of ICB responses [34] in pre-clinical models.

3. Conclusions

There is accumulating evidence that macrophages are key players in cancer evolution and, consequently, patient outcomes. Therefore, macrophages are obvious candidates for therapeutic intervention strategies. However, a deeper understanding of the biological role of these cells is needed to design more effective treatment options for patients with cancer. Phenotypic and transcriptomic differences among macrophages of different origins provide a rationale to consider macrophage ontology when studying macrophage-mediated tumor promotional pathways and potential targeting options. Despite significant advancements in development and implementation of immune therapy approaches targeting macrophages, many obstacles still remain and continue to be a barrier to successful patient treatment. When should treatment begin? Which treatments or combinations thereof will achieve long-term tumor control? Will there be significant toxicities associated with combination therapy? How can we improve treatment delivery methods to induce a potent but tumor-localized therapy response? With advancing research, these outstanding questions, and many others, will hopefully be resolved.

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