Targeting Mononuclear Phagocyte Receptors

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Inflammatory cells are major players in the onset of cancer. The degree of inflammation and type of inflammatory cells in the tumor microenvironment (TME) are responsible for tilting the balance between tumor progression and regression. Cancer-related inflammation has also been shown to influence the efficacy of conventional therapy. Mononuclear phagocytes (MPs) represent a major component of the inflammatory circuit that promotes tumor progression. Despite their potential to activate immunosurveillance and exert anti-tumor responses, MPs are subverted by the tumor to support its growth, immune evasion, and spread. MP responses in the TME are dictated by a network of stimuli integrated through the cross-talk between activatory and inhibitory receptors. Alterations in receptor expression/signaling can create excessive inflammation and, when chronic, promote tumorigenesis. Research advances have led to the development of new therapeutic strategies aimed at receptor targeting to induce a tumor-infiltrating MP switch from a cancer-supportive toward an anti-tumor phenotype, demonstrating efficacy in different human cancers.

mononuclear phagocytes | tumor-associated macrophages and dendritic cells | tumor microenvironment | cancer immunotherapy | pattern recognition and immunoregulatory receptors | triggering receptor expressed on myeloid cells

1. Introduction

The onset of cancer involves a complex interplay among neoplastic, stromal, endothelial, and infiltrating inflammatory cells, which results in the establishment of a highly specialized tumor microenvironment (TME) [1][2][3][4][5][6][7][8][9][10]. Clinical and experimental evidence indicate that chronic inflammation is an indispensable participant in the neoplastic process, fostering genomic instability, epigenetic modifications, angiogenesis, cancer cell proliferation, survival, and dissemination [11][12][13][14][15][16]. Indeed, many cancers arise at sites of infection and chronic inflammation, and different inflammatory conditions, e.g., inflammatory bowel diseases (IBD), are highly correlated with the increased risk of neoplastic transformation [17][18][19]. Furthermore, cancer-related inflammation negatively affects the clinical efficacy of conventional therapies (chemotherapy and radiotherapy) and immunotherapy, antagonizing or hindering therapeutic responses [20].

The type of inflammatory cells present at tumor sites is responsible for tilting the balance between tumor progression and regression [2][3][4][5][6][7]. In particular, mononuclear phagocytes (MPs) have been recognized as major components of the inflammatory infiltrate in most solid human malignancies and crucial drivers of cancer-associated inflammation, being involved in every step of tumorigenesis from early transformation through to

metastatic progression [8][9][10][21][22][23]. They are highly versatile immune cells able to adapt to different environmental conditions and display distinct phenotypes and functional programs dictated by a network of signals, including cytokines, microbial pathogens (pathogen-associated molecular patterns, PAMPs), molecules released by damaged/stressed cells (damage-associated molecular patterns, DAMPs), and metabolites [24][25][26][27][28][29][30][31][32][33]. Environmental stimuli are integrated through the cross-talk between multiple activatory/inhibitory receptor families, whose dynamic equilibria finely tune MP responses in diseased tissues, regulating their inflammatory and effector functions [34]. Alterations in receptor expression/activation can create excessive inflammation and, when chronic, promote tumorigenesis[35][36][37][38][39]. Given their role in carcinogenesis and influence on the effectiveness of anti-tumor therapies, MPs have attracted a lot of interest as potential targets of immunotherapeutic strategies, a concept that has already been investigated in several tumors [40][41][42][43].

In this review, we provide a comprehensive overview of published studies on MP physiopathology in the TME and an update of the state of the art of MP-targeted immunotherapeutic approaches. We summarize the current knowledge on the role of MP receptors in inflammation-mediated carcinogenesis and discuss the most recent advances regarding the attempts to their therapeutic targeting. We focus in particular on the triggering receptor expressed on myeloid cells (TREM1)-1, a major player in the amplification of MP inflammatory responses [44][45][46], highlighting its relevance in the development of several inflammation-associated malignancies and the promises of its inhibition as a novel therapeutic strategy in cancer.

2. MPs in Tumors

2.1. MP Pro- and Anti-Cancer Activities

MPs are recruited from the circulation to tumor sites by tumor-derived factors as primary monocytes (Mn), differentiating into tumor-associated macrophages (TAMs) or dendritic cells (TADCs) [47][48][49][50][51][52][46].

Macrophages are a heterogeneous cell population and a key component of innate defense mechanisms, exerting microbicidal and immunostimulatory activities. In the TME, TAMs display a dual influence on tumor progression [53][54]. They have the potential to activate immunosurveillance and exert anti-tumor responses by destroying cancer cells or inhibiting their proliferation through the release of cytokines, reactive oxygen species (ROS), and nitric oxide (NO), complement components, and prostaglandins. However, they can be subverted by the tumor to support its progression, spread, and immune evasion through the production of pro-angiogenic, mitogenic, metastatic factors, and immunosuppressive cytokines and the upregulation of inhibitory receptors [55][56]. Preclinical and clinical studies demonstrated that the nature of the activating stimulus and the combination of different stimuli in the TME can profoundly impact upon the type of response that occurs, polarizing TAMs into specialized functional subsets [24,26,30]. In addition, TAMs can undergo a rapid and reversible shift among functional programs in response to changes in the activating stimulus, often exhibiting mixed phenotypes [57][58][59][60]. It is currently accepted that TAMs involved in the early tumor initiation process display a “M1-like” pro-inflammatory and tumoricidal phenotype, activating Th1-type immune responses and eliminating transformed cells, but, as the tumor grows, they are educated by the TME to switch to an “M2-like” immunosuppressive and tumor-promoting

phenotype, fostering tumor growth/metastatization and immune evasion [61][62]. High TAM infiltration in solid tumors is generally associated with poor prognosis and reduced overall survival in both experimental models and neoplastic patients [63][64][65][66][67], although a correlation with better prognosis has been suggested for some tumors [68].

DCs are professional antigen-presenting cells central to the orchestration of innate and acquired immunity and the maintenance of self-tolerance . Deregulated DC responses may result in the amplification of inflammation, loss of tolerance, or establishment of immune escape mechanisms [69][70][71]. TADCs were described in the TME of many cancer types, and their inactivation was reported as one of the main mechanisms of tumor escape [72]. Several evidence suggest that TADCs can exist in a multitude of functional states during the course of the disease [73], and that their immunogenic capacity may be strongly conditioned by the TME, ranging from immunostimulatory to immunosuppressive [74][75]. In established tumors, TADCs display mostly an immature phenotype, characterized by a low expression of T-cell costimulatory and high levels of inhibitory molecules, defective migration to lymph nodes, and tolerance to tumor antigens, promoting tumor progression, dissemination, and immune evasion [76]. However, TADCs can generate tumor-specific adaptive immune responses, a capacity that is enhanced via DC-targeted vaccines [77].

2.2. Tumor Hypoxia Contributes to MP Pro-Tumoral Phenotype

A critical hallmark of the TME, especially in advanced-stage tumors, is represented by low partial oxygen tension (pO_2, 0–20 mm·Hg), referred to as hypoxia, which arises as a result of a disorganized or dysfunctional vascular network and poor O_2 supply [78][79][80]. Hypoxia is an important driver of malignant progression, metastatic spread, and resistance to therapies and an indicator of poor prognosis in almost all solid tumors [81][82][83]. As documented by an extensive literature, hypoxia in the TME exerts multifaceted effects on every tumor component, influencing the nature and function of the inflammatory cell infiltrate and contributing to the establishment of immune resistance and tumor escape mechanisms [78][79][80][84][85][86][87][88][89][90][91].

Hypoxia is one of the critical signals regulating MP migration into tumors and conditioning the balance between their anti-/pro-tumoral functions [92][93][94]. Under hypoxic conditions, MPs are functionally reprogrammed through the differential expression of genes implicated in inflammation, angiogenesis, tissue disruption, mitogenesis, and immunoregulation [95]. Recent results point to the hypoxic environment as a direct trigger of human macrophage polarization towards a pro-tumoral “M2-like” state, confirming and extending studies in rodent tumor models showing that the intra-tumor O_2 gradient is a critical regulator of the M1- to M2-skewed transition [96][97][98]. The correlation among the extent of M2-polarized TAM infiltration in hypoxic areas, tumor progression, and poor patient prognosis supports the hypothesis that reduced oxygenation contributes to MP acquisition of a pro-tumoral state [97]. Elucidation of the mechanisms underlying TAM/TADC dysregulated functions within the hypoxic TME may have important implications for their therapeutic reprogramming in tumors (see Chapter 2.3 for details).

2.3. Targeting MPs in Cancers

Considerable efforts from several research groups have been dedicated to the development of anti-tumor immunotherapeutic strategies targeting MP recruitment to, and/or survival and functional polarization in, tumors [99]. Many studies have been carried out in experimental animal models, and a few drugs are currently under clinical trial investigation both as monotherapies or in combination with standard therapies .

The use of bisphosphonates encapsulated in liposomes or PEGylated nanoparticles to selectively deplete TAMs, owing to their phagocytic activities, showed promising anti-tumor effects in preclinical studies, reducing tumor burden, angiogenesis, and metastases. These agents are currently undergoing clinical trials as neoadjuvants in combination with chemotherapy and hormonal therapy. Targeting the CSF1/CSF1R pathway, which is critical for Mn/macrophage survival and differentiation toward a M2 phenotype, with mAbs and small molecule inhibitors was used as an approach to neutralize immunosuppressive M2-like TAMs in tumors or induce their reprogramming toward a M1 phenotype and is being studied in phase I/II clinical trials. Several CSFR1 inhibitors demonstrated some anti-tumor response and reduction in tumor cell invasion, in particular, in combination regimens with conventional therapy or T cell-directed immunotherapy. TAM accumulation in the tumor can be mediated by Mn recruitment through the CCL2–CCR2 axis, and CCL2 inhibition by specific Abs correlated with reduced TAM infiltration, tumor growth, and metastasis in various experimental models, alone or in association with chemotherapies, suggesting the efficacy of this approach [100][101]. Various CCL2-neutralizing Abs and a CCR2 inhibitor are now being tested in clinical trials, showing promises results [102][103]. TAM re-education from a pro-tumoral toward a pro- inflammatory/tumoricidal state was also proposed as a therapeutic strategy, eliminating the drawbacks and long-term toxicity of macrophage ablation. Immune checkpoint and/or anti-immunosuppressive cytokine inhibitors are currently being tested at both preclinical and clinical levels to boost TAM phagocytosis and effector functions or inhibit their immunosuppressive activity. Clinical trials combining anti-TAMs agents (such anti-CSF1R Abs) and immune checkpoint inhibitors are ongoing in different solid tumor contexts[104][105] (see Chapter 3.3 for details).

Promising developments in cancer-therapeutic strategies have also been made by targeting TADCs [106]. DCs have been used in vaccine preclinical models, and several phase I, II, and III clinical trials have tested the use of autologous Mn-derived DCs pulsed with tumor antigens to trigger anti-tumor T cell responses, with some results obtained in melanoma and prostate cancer patients . Furthermore, TADC depletion in mice bearing ovarian cancer by targeting specific markers was also shown to significantly delay tumor growth and enhance the effect of standard chemotherapies . More recently, the manipulation of TADCs to subdue their immunosuppressive functions and enhance their immune-stimulatory capacity has been carried out in preclinical studies, showing great promise[106][107](see Chapter 3.3 for details).

Encouraging results obtained in preclinical studies and early clinical trials across various therapeutic modalities and tumor types highlight the possibility of translating MP-targeted immunotherapeutic strategies to the clinical practice to complement and improve the efficacy of current anti-cancer therapies .

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