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Review

A review on the role of M2 macrophages in bladder cancer; pathophysiology and targeting

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ABSTRACT

Tumor-associated macrophages (TAMs) which are often referred to as immunosuppressive cells (M2 macrophage), constitute a subset of tumor microenvironment cells and affect tumor progression in solid tumors. Recently, these cells have gained remarkable importance as therapeutic candidates for solid tumors. In bladder cancer, major studies have focused on evaluating TAMs in response to Bacillus Calmette-Guerin (BCG) therapy. M2 macrophages may directly impact the BCG-induced immune responses against tumor in bladder cancer. They are the main inhibitors of the tumor microenvironment that promotes growth and metastasis of the tumor. However, the clinical significance of M2 macrophages in bladder cancer is controversial. In this review, we will discuss the clinical significance of M2 macrophages in prognosis of bladder cancer as well as worth of their potential targeting in bladder cancer treatment. In the following, we will introduce important factors resulting in M2 macrophage promotion and also experimental therapeutic agents that may cause the inhibition of bladder cancer tumor growth.

1. Introduction

Bladder cancer (BC) is the 11th most common cancer worldwide [1]. Around 20% of patients diagnosed with BC die of this cancer. BC patients require life-long surveillance. Therefore, BC has s significant impact on mortality, quality of life as well as its high economic burden [2]. Men are at risk of BC 3-4 times more than women; moreover, the incidence of BC has been reported twofold in white men compared to their black peers. BC is the cancer of elderly as its prevalence and incidence peak in the seventh and eighth decades of life [3]. The global BC age- and death- standardized incidence rates per 100,000 have been reported 6.71 and 2.96 respectively [4].

The most frequent type of BC is transitional (urothelial) cell carcinoma (TCC) and comprises 90% of bladder cancers [5]. Two-third of TCC patients are classified as non-muscle invasive bladder cancer (NMIBC). These patients require transurethral resection of bladder tumor that is followed by intravesical chemotherapy and immunotherapy in patients with moderate or high-risk disease. Patients with NMIBC are at risk of cancer recurrence [6]. Treatment of MIBC is radical cystectomy and 25% of these patients will die because of cancer metastasis. Non-urothelial bladder cancer encompasses a variety of adenocarcinoma, squamous cell carcinoma, small cell carcinoma, and mixed histology of adenocarcinoma and squamous cell carcinoma [7].

Due to the relapse and progression of BC as well as noticeable side effects of its current therapeutic methods, BC therapy is recognized as a challenging issue in the pharmaceutical field. Social and economic burden of current treatments and follow up procedures are high and make BC one of the most expensive tumor to manage [8].

Antitumor immune responses encompass several pathways including several cells which are remarkably sensitive to environmental stimuli. The innate immune response is directed by macrophages, neutrophils, eosinophils, natural killer (NK) cells, and mast cells whereas the adaptive immune response is derived by B-lymphocytes (B-cells) and T-lymphocytes (T-cells). Communications between the innate and adaptive immune cells are made by direct cell contact or/and by cytokines [9]. Tumor microenvironments (TMEs) encompass both cellular and non-cellular milieus that work together in tumor development, progression and migration [10]. In addition to cancerous cells, effector cells of innate and adaptive immune system such as macrophages and also non-immune cells are present in TME (Fig. 1) [11].

In spite of extensive researches focusing on BC to unravel the molecular and cellular mechanisms of the disease, the underlying factors

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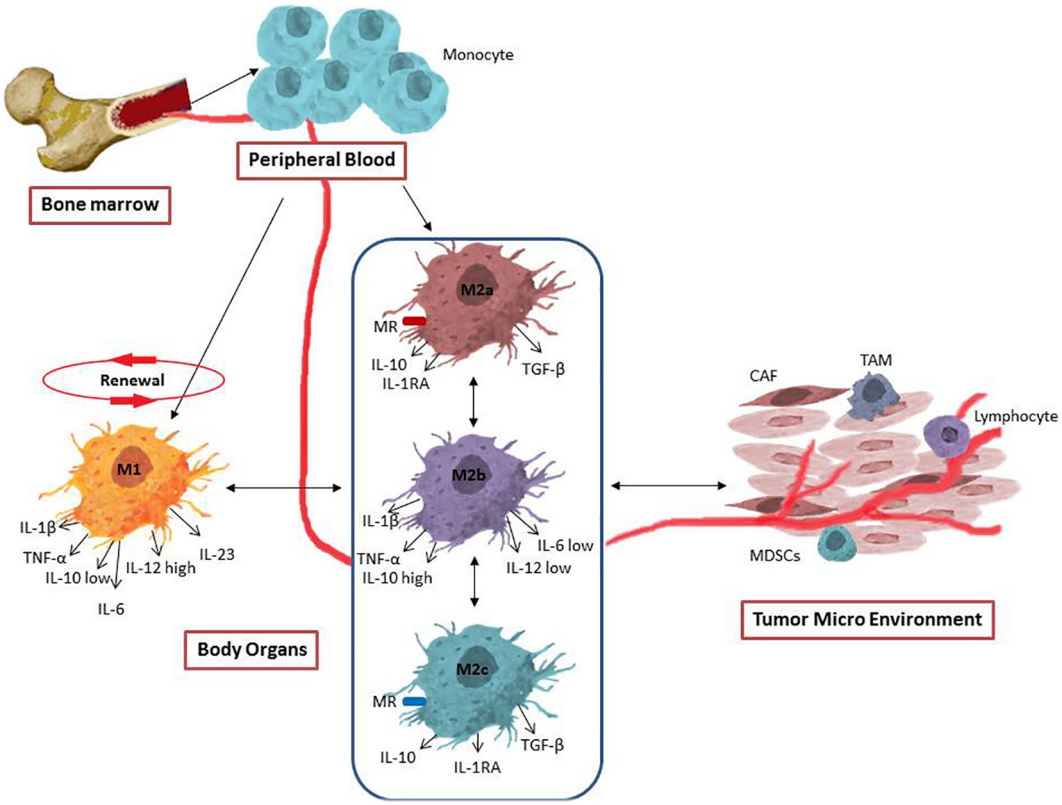

Fig. 1. Differentiation of macrophages from monocytes or renewing from tissue-resident macrophages and their polarization to M1 and M2 (including M2a, M2b and M2c) in response to different signals from tumor microenvironment. Polarized macrophages acquire different panel of special cytokines and chemokines that are able to recruit other immune cells and tumor prognosis.

promoting urothelium into bladder carcinoma remain unclear yet. Researches about the presence and function of TME of BC revealed an opposite role for immune cells such as macrophages. Although M1 subtype of the tumor-associated macrophages (TAMs) suppresses tumor growth by reactive oxygen species and cytokines to activate cytotoxic T-cells, M2 phenotype has been found to develop and progress BC by suppressing inflammation [12,13].

According to the high impact of BC on patients, families and health administration systems, it is necessary to develop methods to predict cancer risk, recurrence and metastasis of BC. TAMs have been shown to have the capacity of prognostication of clinical outcomes of BC [13-17]. Also, its potential role in developing novel immunotherapy approaches may direct new hopes for BC treatment [17-19].

There is a necessity to develop novel prognostic and therapeutic strategies to manage the current problems in the treatment of BC including the high level of recurrence and metastasis, Therefore this article reviews research studies on macrophage biology and M2 macrophages as important TAMs influencing BC poor prognosis.

2. Macrophages: function and classification

Macrophages are a conspicuous population of phagocytic immune cells present in almost all tissues. In the case of infection or tissue injury, bone marrow originated monocytes are recruited to the targeted sites and then differentiated into dendritic cells and macrophages. In human, macrophages are characterized by expression of CD16, CD68, CD163, CD115, and CD312 [20]. Macrophages play different roles in the innate and adaptive immune system such as killing and phagocytosis of pathogenic agents and apoptotic cells, presenting the antigens of phagocytized agents to T lymphocytes, inflammation, immunomodulation, wound healing and neovascularization [21-25]. In addition to the mentioned functions they take part in some diseases such as autoimmune disorders and tumors [26-28].

Macrophages have an incredible capacity for phenotype switching in response to divers physiological and pathophysiological conditions [29]. Macrophages are plastic cells which can be activated through receiving microenvironmental signals and obtain functionally divers phenotypes [30].

In the course of inflammation, macrophages secrete inflammatory mediators such as nitric oxide, interleukin-1 beta (IL-1β), tumor necrosis factor-alpha (TNFα) activating body defense. Even though these inflammatory macrophages are efficient in the initial phase, but they can cause extensive tissue injury and it is necessary to be controlled fast, therefore, macrophages go through apoptosis or polarization into an anti-inflammatory phenotype that reduces the pro-inflammatory response and facilitate wound healing [26].

In fact, Macrophages are assumed as an extremely diverse population of cells. They are able to repetitively shift their function reacting to signals receiving from their environment. In response to different cytokines and mediators, they are polarized and express new surface markers and gain varied responsibilities. Many researchers have found that simple classification of macrophages to only two M1 and M2 subsets are not sufficient enough and fail to encompass all macrophages. Therefore it has been proposed that binary grouping of these cells should advance to a “spectrum model” [31].

2.1. Classically activated or M1 macrophages

In the host body, classically activated or M1 macrophages are typically stimulated by infection or tissue damage. Furthermore, they can be activated in vitro by co-culture of bacterial ligands such as LPS (lipopolysaccharide) or cytokines like TNF-α and interferon-γ [32]. These Macrophages have pro-inflammatory characteristics and secrete cytokines such as Interleukin-1 (IL-1), IL-6, IL-12 and TNF-α [33]. Also,

these cells secret higher amounts of nitric oxide (NO) and reactive oxygen species (ROS) [34]. In addition to the role of M1 secreted cytokines in defense against invading pathogens, they are capable to stimulate other immune cells such as T helper 1 and 17 (Th1 and Th17) cells as well as natural killer cells (NK) [35,36]. The capacity of typically activated (M1) macrophages in producing reactive oxygen/nitrogen species and pro-inflammatory cytokines, which are central for defending pathogens and tumors, makes this set of macrophages as "good macrophages" [37]. Also, the role of M1 macrophages in other inflammatory conditions such as obesity [38-40] and autoimmune diseases [41,42] has been confirmed frequently [43].

2.2. Alternatively activated or M2 macrophages

Alternative activation of macrophages by a series of stimulators such as IL-4, IL-10, IL-13 as well as ligands for Toll-like receptors and IL-1 receptor leads to phenotype differentiation to anti-inflammatory M2 macrophages [36]. These cells exert their anti-inflammatory properties by the production of IL-10, CCL18, CCL22 and lower secretion of IL-12 [35]. Tissue remodeling capacity of M2 macrophages is due to their production of some growth factors including TGF-β [44], 1,25-dihydroxy-vitamin D3 [45], BMP-2 [46], osteopontin [46]. However M2 macrophages can mediate the immunity against helminthes parasites [47] but they are assumed as "bad macrophages" because of their role in asthma development [48,49], suppression of immunity against tumors as well as their role in tumor progression and invasion.

M2 macrophages can be detected by surface expression of CD163, CD206, dectin cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN) [50]. Based on various roles, activating stimuli, and surface markers M2 macrophages are categorized to 4 subclasses including M2a, M2b, M2c, and M2d [51]. M2a macrophages are polarized by IL-4 and IL-13 and chiefly involved in Th2 responses fighting parasites. M2s macrophages show pro-fibrotic and wound-healing properties [52]. Immune complexes, LPS, and IL-1R ligands trigger the polarization of M2 macrophages toward M2b macrophages which act as immune-regulating cells by expression of TNFα, IL-1, IL-6, and IL-10 [53]. M2c macrophages have been reported to involve in angiogenesis and tissue repair mechanisms and their population are increased in the presence of glucocorticoids, TGFβ, and IL-10. M2c macrophages secret TGFβ and IL-10 and express CD163, CD206 and RAGE receptors on their surfaces [37]. However there are little data about M2d macrophages functions, but so far adenosines and IL-6 are defined as necessary stimuli for the polarization of this subclass of M2 macrophages. M2d macrophages have been detected to secrete vascular endothelial growth factor-A (VEGF-A), TGF-β, IL-10, and IL-12 [54,55]. Recently, a new subtype of TAMs with an M2-like phenotype is defined as "macrophage receptor with collagenous structure (MARCO)" macrophages. Interestingly using monoclonal antibody against MARCO causes polarization of TAMs into a pro-inflammatory phenotype in breast and colon carcinoma and melanoma. Anti-MARCO treatment can enhance the efficacy of checkpoint inhibitor therapy by anti-CTLA4 [56].

2.3. Other non-M1/M2 subtypes of macrophages

Recently a few phenotypes of macrophages have been reported which does not belong to traditional M1 or M2 categories. These macrophages have important functions in host immune system including:

2.3.1. $CD169^+$ macrophages

Siglec-1 expressing or $CD169^+$ macrophages exist in bone marrow, liver, lymph node, and spleen and do not mediate phagocytosis. However the activation process of $CD169^+$ macrophages are not fully understood but it is established that they are essential for immune regulation and late erythroid maturation [43,57].

2.3.2. $TCR\alpha\beta^+$ and $TCR\gamma\delta^+$ macrophages

Another non-M1/M2 subtype of macrophages expresses the T-cell receptor (TCR) on its surface. The T-cell receptor is vital for antigen recognition, and it was accepted by researchers for many years that expression of this immunoreceptor is limited to T cells but in 2006 the expression of TCR on the other immune cells was confirmed by reporting experimental data. TCR^+ macrophages are able to phagocyte and release CCL2. Both murine and human TCRαβ and TCRγδ macrophages involve in infectious and inflammatory conditions [43].

2.4. Tumor associated macrophages (TAMs)

Experimental studies reveal the plasticity of macrophages during tumor establishment. In the sites of chronic inflammation where the condition is suitable for tumor development, macrophages display M1 phenotype, but after tumor progression macrophages exhibit M2 like phenotype. In other word, initial tumor infiltrated macrophages exhibit M1 phenotype but by tumor development and changing the composition of TME, M1 macrophages undergo polarization and change their characteristics to M2 like phenotype [58].

It is notable that macrophage presenting in TME, exhibit M2-like phenotype to help tumor growth and development by cancerous cell proliferation, angiogenesis, and metastasis [20].

Tumor associated macrophages (TAMs) are the most frequent innate immune cells of the TME, which play fundamental roles in tumor progression [59]. Macrophages are the most important antigen presenting cells (APCs) to T-cells. Macrophages are also regulators of tissues homeostasis in TME. Macrophages display remarkable plasticity; in spite of the classic role of macrophages in inflammation and host defense, there are growing data that show TAMs may affect tumor growth, progression, response to treatment, and metastasis.

In other hands in vivo studies demonstrate that higher frequency of TAMs infiltration in tumors is connected to poor prognosis of numerous cancers. These findings underscore the role of TAMs in tumor development [29,60-63]. Tumor developing activity of TAMs can be resulted from: 1-decreased inflammatory cytokines such as IL-6 and TNF-α, 2-increased secretion of TGF-β, IL-10 and prostaglandine-E2 (PGE2), 3-lower antigen-presenting capacity and subsequently poor priming tumor-specific T-cells, 4- production of angiogenic factors such as VEGF and platelet-derived growth factor (PDGF) involving in lymphangiogenesis and metastasis [64,65].

Different subclasses of macrophages play different roles in TME, which are under control of a number of immune mediators such as interleukin-4, interleukin-10, and immunoglobulins [66-68].

Controversially, higher TAMs penetration is associated with improved survival in some tumor types. These outcomes propose that TAMs include distinct pro- and anti-tumor subpopulations depending on diverse micro-environmental stimuli [64].

2.5. Origin of TAMs

After the recruitment of monocytes to the tumor site, the tumor environment rapidly promotes their differentiation into TAMs. In the most of cases TAMs are differentiated from blood circulating monocytes of bone marrow and recruited to TME in response to growth factors and chemokines including CSF1, CXCL12, VEGFA, CCL 2, CCL18, CCL20 from tumor cells and tumor stromal cells [69-71].

Even though, there is evidence that TAMs can be derived from renewing of tissue-resident macrophages such as epidermal Langerhans cells, lung alveolar, brain microglia and peritoneal macrophages originated from embryonic yolk sac precursors [72].

2.6. Signals for TAMs polarization

Recruitment and stimulation of TAMs are regulated by distinguished factors including cytokines, chemokines and growth factors.

TAMs are differentiated by receiving signals from different microenvironments, to a protumor phenotype by some factors that actively created by tumor cells, immune system constituents, TAMs, and factors producing from tissue stress. In the following, we mention the several endogenous factors that are associated with the TAM polarization to M2 macrophages. It is significant that the inhibition of these factors can prevent the polarization of the TAMs toward the M2 phenotype for example inhibition of CCR5 with Maravorc, an agent was primarily produced for HIV treatment [73], led to repolarization of M2 phenotype toward M1phenotype [74]. *Re*-education of macrophages toward anticancer phenotypes by manipulating cytokines or chemokines could be providing cancer-treating strategies in the future.

2.6.1. Signals from immune system

There is a set of recognized stimuli from immune cells which is involved in TAMs polarization toward pro-tumor type for instance IL-4 and probably IL-13 from Th2 $CD4^+$ cells [66], IL-10 from T regulatory cells [67,75], immunoglobulins from B-cells [68], and milk fat globule-epithelial growth factor 8 protein (MFG-E8) from mesenchymal stromal cells [76].

2.6.2. Signals from tumor cells

It has been shown that a vast signals originating from cancerous cells can affect the polarization of TAMS including: 1- microparticles (MPs) driven from tumor cells [77], 2- presence of lactate in TME as an oncometabolite [78], 3-circulating micro RNAs (miRNAs) [79], 4- long noncoding RNAs (lncRNAs), a class of non-protein-coding transcripts that are over 200 nucleotides in length [80-86], 5- Tumor-derived exosomes (TEXs), a kind of microvesicles containing cytosolic/transmembrane proteins, lipids, miRNAs, lncRNAs, and DNA [87-96], 6-chemokines including colony stimulating factor 1 (CSF1) [97,98], CCL2, CCL 3, and CCL 14//HCC-1 [99], 7- Cathelicidin-related antimicrobial peptide [100,101], 8- Yes-associated protein 1 (YAP1), [102,103], 9- Epidermal growth factor receptor (EGFR) [104], 10-Osteopontin (OPN) a secreted matrix glycoprotein [105-110], 11-Periostin a protein involves in adhesion and migration of epithelial cells [111], and 12- Soluble NKG2D ligands [112-119].

2.6.3. Signals from TAMs

Already, an elevated amount of macrophage migration inhibitory factor (MIF) was reported in tumor cell progression and angiogenesis in human melanoma cells [120]. So after MIF recognized as an important factor for TAM polarization in the melanoma mouse model [121].

Tumor-induced TAM polarization is reduced by MIF antagonist or deficiency that diminishes the expression of proangiogenic genes in TAMs. In addition, tumor-infiltrated macrophages through IL-10 production cause TAMs self-polarization [122]. Moreover, monocytes can be differentiated by autocrine CXCL12 to a discrete line of cells that are able to induce proangiogenic and immunosuppressive functions [123].

2.6.4. Signals from tissue stress

2.6.4.1. Hypoxia. Oxygen deficiency in TME is a crucial stressor leading to tumor development via tumor cell proliferation [124], angiogenesis [125] cell adhesion [126], and metastatic transformation [127]. It has been elucidated that hypoxia associated tumor cell proliferation and metastasis are facilitated chiefly through hypoxia-inducible factor (HIF)-1α and HIF-2α. These factors also regulate macrophage function. An in vitro study has been revealed that the expression of HIF in macrophages is an important factor for macrophage-mediated T-cell suppression and weakening the adaptive immune system in tumors [128].

2.6.4.2. Oncostatin M and eotaxin. In addition to the role of promoting inflammation, it is understood that oncostatin M (a member of interleukin 6 family) and eotaxin (a CC chemokine subfamily of eosinophil chemotactic protein) are associated to epithelial-mesenchymal transition (EMT) [129] and promote metastasis in breast cancer [130]. Surprisingly, oncostatin M and eotaxin which are released by cancer cells under hypoxic circumstance can progress macrophages infiltration to TME and their polarization into M2-like phenotype compared with same cytokines secreted by normoxic TME [131].

2.6.4.3. High mobility group box 1 (HMGB1). Recently, Li et al. introduced TAMs with PD1 expression that is phenotypically and functionally similar to M2 macrophages. Exosomal HMGB1 obtained from esophageal squamous cell carcinoma is efficient in triggering clonal expansion of macrophages into $PD1^+$ TAMs, which has the phenotype and the function of the M2. Therefore, combined treatments with targeting PD1 expressed in TAMs and tumor-derived exosomal HMGB1 can maintain protective immune system against tumor [132].

2.6.4.4. Ligands for Toll-like receptors (TLRs). The presence of high-mobility group box 1 protein (HMGB1), extracellular ATP, and Tumor-derived extracellular matrix (ECM) components are sensed by a family of receptors on the surface of macrophages called Toll-like receptors (TLRs) and initiate their signaling cascade. Stimulation of TLR2 and TLR6 induce the production of tumor necrosis factor-α (TNF-α) by macrophages which have been associated with the progression of lung cancer [133]. Protease cleavage of ECM components such as biglycan and hyaluronan has been found as important factors in directing TAM polarization through TLR2 and TLR4 [134].

3. M2 macrophages in tumorigenesis

As described above, TAMs may have both tumoricidal and tumorigenic properties, because they can be by a mechanism that is not yet known, differentiate into tumoricidal macrophages (M1) or tumorigenic macrophages (M2) [135]. However, TAMs are mainly polarized to M2 phenotype in many types of tumors with the low antitumor property through various mechanisms. In animal cancer models including primary lung tumors, metastatic lung tumor, prostate tumors and colon xenografts, M2 macrophages of TAMs early increase during tumorigenesis. The M2 macrophages able to stimulate the tumor growth in vitro and tumorigenesis in vivo in xenograft mice model [136]. To evaluate the potential role of M2 macrophages in tumorigenicity, Qi et al. found that glioma cell lines co-cultured with M2 macrophages increase cell growth and tumorigenesis in nude mice model. It was shown that IL-10 secreted by M2 macrophages enhances cell growth through stimulation of the JAK/STAT signaling pathway in glioma [137].

4. Detection of TAMs in bladder cancer tissues

This section deals the diagnostic studies of TAMs especially especially M2 macrophages in the tumor microenvironment of bladder cancer tissues, because the phenotypic detection of macrophages and its association with prognosis of the disease can be effective in inhibiting or targeting these cells in future studies. In addition, the tumor microenvironment cells may impact the treatment response to BCG, which can lead to the development of new treatments for bladder cancer.

4.1. M2 phenotype associated with poor prognosis in bladder cancer

Lima et al. evaluated the expression of TAMs using CD68 (monocyte and macrophage marker) and CD163 (M2 specific cell surface receptor) antigens in patients with bladder cancer treated BCG. Patients who were resistance to BCG immunotherapy had high stroma-predominant $CD163^+$ macrophage counts and low tumor $CD163^+$ macrophages compared to patients whose treatment was successful. It has been shown that decrease of oxygen leads to accumulation of M2 macrophages in tumor hypoxic areas [138], in this case, hypoxia-induced

factor (HIF)-1α increases the expression of vascular endothelial growth factor (VEGF) and decreases the production of cytokines derived from Th2 [139]. High expressions of $CD163^+$ macrophages in the stroma were associated with low expression of HIF-1α in tumor areas, whereas there was a high expression of HIF-1α in tumor nests. Furthermore, decreased recurrence-free survival was observed in patients presenting M2 phenotype with BCG failure. It has been suggested that high expression of immunosuppressive macrophages with $CD163^+$ phenotype in stroma may be a useful biomarker of BCG treatment outcome [140]. Endothelial Per-Arnt-Sim domain protein 1 (EPAS1) is also induced under hypoxia and involved in neoangiogenesis and energy metabolism. It has been shown that EPAS1 is expressed in a small subset of TAMs, which have multiple functions in tumor progression and mediating bladder cancer progression [141]. A similar study was performed by Takeuchi et al. who stained infiltrated TAMs with CD68 and CD163 markers using immunohistochemistry in 21 patients with bladder cancer. The higher expression of $CD163^+$ macrophages was detected in the stroma and tumor areas associated with a higher stage and grade of the tumor. The predominance of M2-polarized macrophages associated positively with microvessel counts (MVCs) in patients [142].

Bladder cancer cells can express macrophage receptors at high levels that indicate the poor outcome of diseases. Maniecki et al. showed that bladder cancer cell lines did not express CD163; however, when cocultured with macrophages the CD163 expression in bladder cancer cell was induced in an IL-6 or IL-10 independent pathway. The high level of CD163 gene expression was significantly correlated with a poor 13-year overall survival. In addition, CD163 gene expression was significantly elevated in muscle-invasive (T2-T4), and aggressive cancers. It is suggested that tumor cells expressing CD163 may be a subgroup of tumor cells with a phenotype polarized toward epithelial-to-mesenchymal transition and high invasive properties induced by TAMs [143].

Tan et al. conducted a meta-cohort analysis for identifying molecular subtypes in 2411 tumors including non-muscle invasive and muscle-invasive bladder cancer. The Squamous-cell carcinoma-like of muscle-invasive bladder cancer revealed a high expression of PD1, CTLA4 signaling, and macrophage M2 infiltration [144]. In addition, Miyake et al. conducted a cohort study with the long-term follow-up using immunohistochemical analysis on surgical specimens provided from 154 non-muscle invasive bladder cancer patients. They assayed T regulatory and TAM around the cancer lesion after intravesical BCG therapy using forkhead box P3 (FOXp3) and CD204 markers, respectively. TAM count was significantly associated with IL-6 positive cancer cells and T reg count. In 71 patients treated with BCG, high counts of TAM and Treg were correlated with shorter recurrence-free survival [17]. Pichler et al. reported a high expression of $CD68^+$ and $CD163^+$ TAMs as well as $CD25^+$ and $FOXP3^+$ regulatory T-cells in bladder cancer patients who were unresponsive to BCG. In addition, prolonged recurrence-free survival was observed in patients with an increased expression of $CD4^+$ and $GATA3^+$ T lymphocytes. While T-bet^+ T lymphocytes, TAMs and Tregs were negatively associated with prolonged recurrence-free survival [145]. Takayama et al. examined tissue TAMs of 41 bladder cancer patients who received intravesical BCG with CD-68 marker. Recurrence-free survival increased in patients with a decreased count of TAMs. In addition, patients with lower cancer cell-to-lamina propria TAM ratio had the increased recurrence-free survival [14].

In another study, $CD68^+$ cells were observed in 40 NMIBC patients treated with TURB and BCG instillation. M1 and M2 infiltrations were found in patients with disease recurrence, even before endovescical BCG instillation [146]. Ayari et al. also found that NMIBC patients with increased infiltration of $CD68^+$ TAMs did not respond to BCG adjuvant therapy [147]. These results indicate the importance of using TAMs diagnostic markers in predicting response or resistance to BCG treatment in patients with NMIBC.

4.2. M2 phenotype associated with good prognosis in bladder cancer

Despite the association of M2 macrophage with the progression of disease and metastasis, as well as its association with BCG therapy failure, few studies have shown that TAMs with M2 phenotype may have a protective effect on bladder cancer that is referred as follows:

In contrast to the studies listed above, a study showed that macrophage infiltration in the tumor microenvironment has a protective effect in bladder cancer patients with $CD163^+$ cancer cell. Aljabery et al. stained tumor cells and TAMs with a CD163 and Ki-67 (proliferation marker) in 103 patients with urinary bladder cancer with stages of pT1–T4 treated with cystectomy and pelvic lymph node dissection. Cancer cells with CD163 expression had a positive correlation with macrophage infiltration. Surprisingly, patients with $CD163^+$ tumor cells and strong macrophage infiltration were reported with longer cancer-specific survival (76 months), compared to patients with $CD163^+$ and weak macrophage infiltration (28 months). Additionally, M2 macrophages with $CD163^+$ phenotype were inversely associated with lymph node metastasis [148].

Immunohistochemical analysis was performed with CD68, MAC387 (M1 macrophages) and CLEVER-1/Stabilin-1 (M2 macrophage and lymphatic/blood vessels) markers in 184 patients with urothelial bladder cancer undergoing radical cystectomy. It has been found that $CD68^+$ and MAC387 were correlated with an increased risk of progression and poor differentiation. A reverse correlation was found between the Stabilin-1^+/CLEVER-1^+ vessel count and tumor stage and grade. In univariate analyses, the MAC387 alone and in combination with $CD68^+$ macrophages, was associated with poorer survival [149].

5. Factors that affect M2 macrophages of tumor microenvironment in bladder cancer

One of the major problems in cancer therapy is the immunosuppressive property of the tumor microenvironment. The polarization of macrophages into tumoricidal M1 or tumorigenic M2 macrophage is an important event in establishing the tumor microenvironment. Most previous studies listed above reported that M2 macrophage infiltration is associated with a poor prognosis of bladder cancer. In addition, immunosuppressive immune cell tumor microenvironment as well as tumor cells themselves produce factors modulating macrophage activation and polarization into M2-type TAMs, which promote the growth of the tumor, progression, and metastasis through angiogenesis and lymphangiogenesis. Therefore, to develop more effective cancer drugs, it is necessary to determine either tumor- or non-tumor inducing factors that promote or inhibit M2-macrophage polarization. However, few studies have focused on the modulation of TAMs (M2 type) in bladder cancer, which highlights the need for future studies. In the following, previous studies are discussed to reveal the critical factors needed for M2-macrophage polarization in bladder cancer (Tables 1 and 2).

5.1. The factors that promote M2 macrophages in bladder cancer

5.1.1. Monocarboxylic acid transporter

Zhao et al. used a microfluidic coculture chip to study the macrophage-cancer cell interactions in the microenvironment of bladder cancer. It has been shown that transitional cell carcinoma of the bladder cells (TCCB) polarize macrophages toward M2 phenotype in a manner that depended on cancer cell-TAM lactate flux. They claimed that the main reason of immunosuppressive microenvironment within the TCCB is lactate shuttle, and MCTs (monocarboxylic acid transporter) may be a new treatment target for TCCB [150].

5.1.2. Bone morphogenetic protein

Bone morphogenetic protein (BMP) is a secreted growth factor belonging to the TGFb superfamily that involve in the regulation of cell

Table 1
Factors promote tumorigenesis of bladder cancer through M2 polarization.

Factors	Study (year published)	Type of study	Function	Its role in tumorigenesis
MCT	Zhao et al. (2015) [150]	In vitro	Translocation of monocarboxylate compounds such as lactic acid	Polarization of macrophages toward M2 phenotype in a manner that depended on cancer cell-TAM lactate flux
BMP	Martínez et al. (2017) [151]	In vitro	Regulation of cell differentiation during oncogenesis and embryogenesis	BMP4 secretion by bladder cancer cells provide macrophage polarization toward M2 phenotype
CXCL1	Miyake et al. (2016) [18]	In vivo	It recruits and activates immune cells at the tumor microenvironment	CXCL1-expressing TAMs/CAFs in nude mice, enhance growth of subcutaneous UCB tumors
PI 3-K/Akt signaling	Dufresne et al. (2011) [154]	In vitro	An intracellular signaling pathway important in regulating the cell cycle	M1 promoted cellular invasiveness in T24 cells in a way depending on PI 3-K/Akt signaling pathway activation in tumor cells

MCT: monocarboxylic acid transporter, BMP: bone morphogenetic protein, CXCL1: C-X-C motif ligand 1, TAM: tumor associated macrophage, CAF: cancer-associated fibroblast, UCB: urothelial cancer of the bladder.

Table 2
Factors that inhibit tumorigenesis of bladder cancer through effect on M2 macrophages.

Factor or factors	Study (year published)	Type of study	Function	Its function in inhibition of bladder cancer
PA-MSHA	Liu (2017) [157]	In vivo	Enhancement of innate immunity	Inhibition of tumor growth and increase of ratio of M1/M2 macrophage
Adriamycin, docetaxel, mitomycin C and gemcitabine	Hori (2017) [158]	In vivo	Chemotherapy agents are toxic for tumor cells	Decrease regulatory T cells and M2 macrophages of around tumors
Mitomycin C/BCG	Svatek (2015) [159]	In vivo	BCG: enhancement of innate immunity Mitomycin C: chemotherapeutic agent with anti- tumor property	Increase of M1 phenotype in tumor-bearing mice treated with sequential mitomycin C and BCG

PA-MSHA: Pseudomonas Aeruginosa-mannose-sensitive hemagglutinin.

differentiation during oncogenesis and embryogenesis. In bladder tissue, BMP–dependent signaling arising from stromal tissue mediates urothelial homeostasis through urothelial cell differentiation. It has been shown that BMP4 secretion by bladder cancer cells provides macrophage polarization toward M2 phenotype. In contrast, MiR-21 inhibited the BMP receptors type II (BMPR2) and was led to the resistance of tumor cells to the pro-differentiating mediated by BMP ligands, enhancing tumor growth [151].

5.1.3. Chemokine

It has been shown that expression of chemokine (C-X-C motif) ligand 1 (CXCL1) is associated with tumor neoangiogenesis and aggressiveness in human urothelial cancer of the bladder and prostate cancer [152,153]. The immunohistochemical analysis revealed that high level of CXCL1 in urothelial cancer of the bladder cells can be correlated with potential recruitment of TAMs/CAFs, poor prognosis and a high potential of metastasis. In addition, CXCL1 signaling in the tumor microenvironment is associated with metastasis, intravesical recurrence, and drug resistance through promoted invasion ability. CXCL1-expressing TAMs/CAFs in nude mice, enhanced growth of subcutaneous urothelial cancer of the bladder tumors when injected together. In the orthotopic bladder cancer model was also revealed that CXCL1 production in TAMs/CAFs enhances the growth of tumor cells and implantation into the murine bladder wall. Therefore, targeting CXCL1 signaling to disrupt this chemokine can be an attractive therapeutic approach for human urothelial cancer of the bladder [18].

5.1.4. PI 3-K/Akt signaling

Dufresne et al. co-cultured the M1 or M2 macrophages to investigate both inflammatory and anti-inflammatory conditions in regulation of human urothelial bladder cancer (UBC) T24 cell behavior. It has been shown that T24 cell/M2 co-cultures had more number of viable cells in comparison with T24 cell/M − 1 co-cultures. M-2-derived factors have the ability to suppress the inhibitory effect of M − 1-derived factors on T24 cell growth. In contrast to M2, it has been found that M1 promoted cellular invasiveness in T24 cells in a way depending on PI 3-K/Akt signaling pathway activation in tumor cells [154]. Such that PI 3-K inhibition decreased the invasiveness of EGFR-expressing bladder cancer cell lines.

5.1.5. Stromal hyaluronan

The disruption of stromal hyaluronan reduces lymphangiogenesis and angiogenesis tumor associated with impaired macrophage recruitment. Kobayashi et al. showed that TAMs recruited to tumor microenvironment were dependent on a hyaluronan (HA)-rich tumor stroma. They defected the HA synthase 2 (Has2) gene in stromal fibroblasts and observed severe reduction in calling macrophages when inoculated with tumor cells into nude mice. A decrease in the M2 population was also observed due to the deficiency in stromal HA, which confirm the essential role of Has2-derived stromal HA in the recruitment of TAMs to the tumor microenvironment [155].

5.1.6. MiR-21/PDL-1

MicroRNA-21 (miR-21) is one of the most abundant miRNAs in normal mammalian tissues and account for approximately 10% of total miRNAs in several types of tumor cells. MiR-21 inhibits M1 macrophage polarization through downregulating JAK2 and STAT1. It has been shown that deficiency of miR-21 stimulates the of macrophage polarization toward an M1 phenotype in the presence of tumor cells. In addition, promoted STAT1 signaling mediated by the deficiency of miR-21 upregulates PD-L1 expression in macrophages, which can lead to inhibition of M1 anti-tumor activity. This study revealed the value of a combination of miR-21 inhibition and immune checkpoint blockade (PD1/PDL-1 inhibitor) to target the tumor microenvironment cells [156].

5.2. Factors inhibited M2 macrophages in bladder cancer

5.2.1. Pseudomonas aeruginosa-mannose-sensitive hemagglutinin

Liu et al. developed an animal model of bladder tumor through inducing intravesical *N*-methyl-N nitrosourea to evaluate effects of Pseudomonas Aeruginosa-mannose-sensitive hemagglutinin (PA-MSHA) on the inhibition of bladder cancer cell proliferation. It has been shown that PA-MSHA inhibited tumor growth and increased the ratio of M1/M2 macrophage. They suggested that PA-MSHA may inhibit proliferation, invasion and migration bladder cancer cells, also stimulates apoptosis through inducing M1 polarization [157].

5.2.2. Chemotherapy agents

Hori et al. induced orthotopic bladder cancer in mice by N-butyl-N-(4-hydroxybutyl) nitrosamine (BBN) and investigated the immunological effects of chemotherapeutic agents including adriamycin, docetaxel, mitomycin C and gemcitabine. This study showed that the antitumor properties of chemotherapeutic agents are similar to those of BCG. They found that there were changes in tumor microenvironment immune cells that resulted in fewer regulatory T cells and M2 macrophages of around tumors [158].

5.2.3. Mitomycin C/BCG

Svatek et al. showed that there was M1 phenotype (low arg1 and il10 gene expression, high il6 expression) in tumor-bearing mice treated with sequential mitomycin C and BCG. However tumor-bearing mice treated PBS,TAMs represent an M2 phenotype identified by low il6 and MHC II expression and high il10 and arg1 [159]. These results indicate that BCG immunotherapy associated with mitomycin C can affect macrophage polarization toward M1 type. However, what mechanisms will increase the M1 macrophage polarization will require future studies.

6. Conclusion

Macrophages are known to recruit into the tumor microenvironment through polarization from an antitumorigenic type (M1 type) toward a tumorigenic M2 phenotype. Many clinical studies have supported a significant correlation between the high macrophage content of tumors and poor prognosis in bladder cancer patients. Although much evidence indicates that most of TAMs are polarized into M2 type, however, the mechanisms responsible for the regulation and imbalance of M1 to M2 polarization ratio remain unclear.

To treat the early-stages of bladder cancer, BCG is the most common intravesical immunotherapy and gold standard treatment. The BCG controls the growth of cancer and protects the patient from returning the disease. Protective effect of BCG is mediated through an increased number of macrophages in the tumor microenvironment of bladder cancer, the peri-tumoral bladder wall and urine [160]. BCG-activated macrophages could directly interact with bladder cancer cells and also affect them through releasing pro-inflammatory cytokines including IL-12, IL-1β, TNF-α, GM-CSF and apoptotic signaling molecules. In addition, IL-12 releasing activated macrophages stimulates TH1 to produce IFN-γ cytokine [161]. This cytokine stimulates macrophage cytotoxicity. Therefore, for the therapeutic efficacy of BCG, preservation of tumor killer macrophages (M1 type) is very important. On the other hand, TAMs in tumor microenvironment mainly polarize into M2 type that can neutralize the protective effect of BCG in patients. Therefore, a supplementary therapeutic approach to specifically target or inhibit the tumorigenic macrophages is necessary for NMIBC patients receiving intravesical BCG. Unfortunately, previous studies have been less focused on M2 macrophages in bladder cancer and only a limited number of in vitro and in vivo studies have investigated the suppression of M2 macrophages.

It is important to note that all types of TAMs are not associated with poor prognosis in patient with bladder cancer, since tumor killer

macrophages with similar function of M1 type are needed for the efficacy of BCG, therefore it is imperative that tumorigenic macrophages (M2 type) are specifically identified and targeted. With this definition, for targeting or inhibiting tumorigenic macrophages, finding the specific antigens of TAMs (M2 type) is crucial. Several molecules including CD163, CD204 and CLEVER-1/Stabilin-1 have been applied for assessing M2 macrophages in patients with bladder cancer. Most of the studies showed that decreased recurrence-free survival was observed in patients presenting M2 phenotype with BCG failure. However, a study showed that M2 macrophages with CD163 phenotype were inversely associated with lymph node metastasis [148]. A reverse correlation was found between the Stabilin-1^+/CLEVER-1^+ (M2 macrophage marker) vessel count and tumor stage and grade. In contrast, the MAC387 (M1 macrophage marker) alone and in combination with CD68 macrophages, was associated with poorer survival [149]. It may be appropriate to look for other more specific antigens to accurately measure M2 macrophages in a patient with bladder cancer. It is doubtful whether M2 macrophages are targeted or inhibited in a patient with bladder cancer, since what is known is just inhibition of M2 macrophage in vitro and in vivo in a limited series of studies. However, considering the importance of tumor killer macrophage (M1 type) in a patients receiving BCG, it is crucial specifically inhibit the M2 macrophages of TAMs to enhance the efficacy of the intravesical BCG in patient with BCG therapy failure. Researchers have been focused on therapeutic manipulation, the M2 macrophages can be switched toward M1 macrophages that suppress the growth, proliferation and angiogenesis of tumor. In glioblastoma was found that phagocytosis of macrophages is activated by interfering the SIRPa-CD47 signaling pathway, such that anti-CD47-elicited phagocytosis resulted in functional switching of murine macrophages into M1 direction [162].

In general, the clinical significance of TAMs in bladder cancer is controversial. From pre-clinical studies mentioned above, it is understood that none of the studies have specifically inhibited or targeted M2 macrophages in the tumor microenvironment, and therefore the precise function and role of M2 macrophage in bladder cancer are ambiguous. Because of the strong efficacy of the BCG and prolonged survival of patients, we suggest additional fundamental and preclinical experiments to demonstrate the efficacy and practicality of this novel and promising approaches for treating patients with bladder cancer.

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