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Review

The Peritoneal Macrophages in Inflammatory Diseases and Abdominal Cancers

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Peritoneal macrophages (PMs) are the major cell type of peritoneal cells that participate in multiple aspects of innate and acquired immunity in the peritoneal cavity. PMs have an ability to release a large amount of pro-inflammatory and anti-inflammatory cytokines and therefore play a critical role in regulating the differentiation of innate immune cells and inflammatory T cells. Accumulating studies demonstrate that the immunological reactions and inflammatory responses of PMs are strongly related to the pathogenic processes of various inflammatory diseases and abdominal cancers. Consequently, the regulation of PM activation has gradually emerged as a promising target for immunotherapy, and better understanding of the distinctly biological function of PMs in individual diseases is crucial for designing specific and effective therapeutic agents. This review covers the characterization and immunological function of PMs in hosts with inflammatory diseases and abdominal cancers.

Key words: Peritoneal macrophages (PMs); Inflammatory diseases; Abdominal cancers

INTRODUCTION

The macrophages represent a group of immune cells that participate in both innate and acquired immunity[1]. Recent studies demonstrate that macrophages are critical in many inflammatory diseases and cancers, and they have gradually emerged as attractive targets for immunotherapy[2]. To date, the most common macrophage sources are bone marrow, spleen, and peritoneal cavity. Compared to bone marrow-derived macrophages (BMDMs) and splenic macrophages (SPMs), peritoneal macrophages (PMs) appear to be more mature with higher expression of inducible cytokines and are more stable in their functionality and phenotype[2,3]. Therefore, PMs isolated from the peritoneal cavity are the common source of macrophages for various in vitro assays, including stimulation with Toll-like receptor (TLR) ligands, cell signaling assay, phagocytosis, cytokine production, chemokine production, and toxicology study[4].

PMs are the major cell type of peritoneal cells (more than 30%)[5]. Like BMDMs and SPMs, PMs can be classified into classically activated macrophages (M1) and alternatively activated macrophages (M2) following stimulation (Fig. 1)[6]. This classification method is mainly based on cell phenotype and function. Notably, M1-polarized PMs have long been identified to play an important role in host defense, which express Th1 cytokines and inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-2 (IL-2), and interferon-γ (IFN-γ). M2-polarized PMs predominantly express a large amount of Th2 cytokines and anti-inflammatory cytokines, including IL-4, IL-13, IL-10, and transforming growth factor-β (TGF-β), thereby down-regulating inflammatory processes[6]. Accumulating studies have demonstrated that PMs in the peritoneal cavity strongly express CD206 mRNA, which is the characteristic phenotype of M2-polarized macrophages[5,7]. Therefore, M2-polarized PMs are the major composition of PMs. Additionally, PMs can be classified into another two subsets based on morphology: large PMs and small PMs[8]. These two macrophage subsets exhibit distinct

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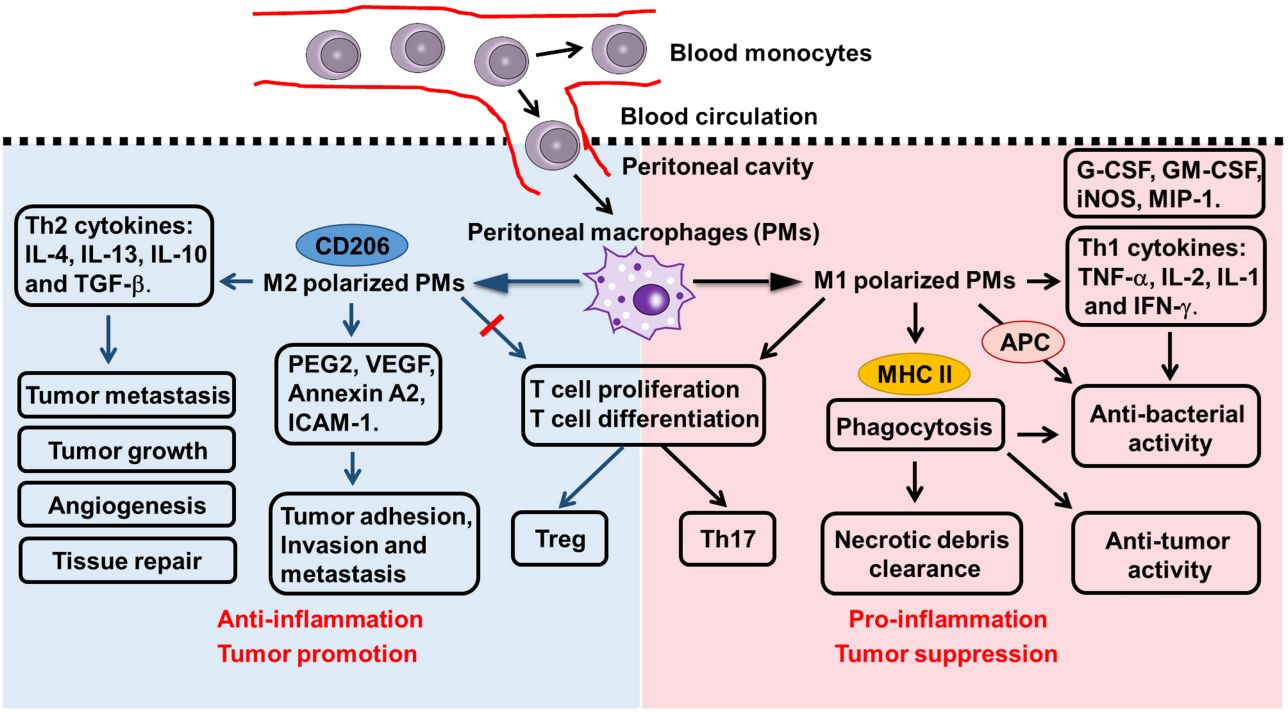

Figure 1. The characterization and function of peritoneal macrophages (PMs). PMs are the blood monocytes that migrate into the peritoneal cavity. The same as with bone marrow-derived macrophages and spleen macrophages, PMs can be classified into classically activated macrophages (M1) and alternatively activated macrophages (M2) based on cell phenotype and function. On the one hand, M1-polarized PMs play an important role in inflammation and tumor suppression. These cells are characterized with a high level of major histocompatibility complex II (MHC-II) and predominantly express Th1 cytokines, granulocyte colony-stimulating factor (G-CSF), granulocyte macrophage colony-stimulating factor (GM-CSF), inducible nitric oxide synthase (iNOS), and macrophage inflammatory protein-1 (MIP-1). MHC-II empower the M1-polarized PMs with the ability of phagocytosis and thereby participate in necrotic debris and tumor cell clearance. Notably, PMs can also function as antigen-presenting cells (APCs) in innate immune response, thereby enhancing the activity of host defense. Furthermore, the interaction of M1-polarized PMs and T lymphocytes can promote the proliferation of T cells and increase the proportion of Th17 in T-cell differentiation. On the other hand, M2-polarized PMs play an important role in anti-inflammation and tumor promotion. Under steady condition, M2-polarized PMs are the major composition of PMs, which are characterized with a high level of CD206. These cells predominantly express Th2 cytokines, prostaglandin E2 (PEG2), vascular endothelial growth factor (VEGF), annexin A2, and intercellular adhesion molecule 1 (ICAM-1), and therefore promote tissue repair, angiogenesis, tumor growth, and tumor metastasis. In addition, the interaction of M2-polarized PMs and T lymphocytes can suppress the proliferation of T cells and increase the proportion of regulatory T cells (Tregs) in T-cell differentiation. Consequently, the physiology of PMs can be varied depending on the environment or stimuli to which they are exposed, and these cells are important for immunological homeostasis in peritoneal cavity.

origin and morphology. On the one hand, large PMs have been characterized as fetal-originated tissue resident macrophages with a high level of F4/80 and a low level of major histocompatibility complex II (MHC-II). Under steady condition, large PMs compose the major population of PMs and are characterized with high expression of transcription factor GATA6[9–11]. It has been proven that the GATA6 expressed in large PMs selectively regulates the level of aspartoacylase and therefore control the survival, differentiation, and metabolism of resident PMs[10]. On the other hand, small PMs appear to be generated from embryogenic precursors with a low level of F4/80 and a high level of MHC-II[3,8]. It has been reported that the PMs have a cross-talk between T lymphocytes, which are enriched in IL-17 receptor A and express a proangiogenic gene profile, and therefore directly promote ovarian cancer cell proliferation[12].

Functionally, PMs are involved in various types of immunological reactions and inflammatory responses in the peritoneal cavity. A well-recognized function of PMs is phagocytosis and antibacterial activity. Upon infection, PMs were largely thought to contribute in defense processes like inflammatory reactions. However, the physiology of PMs can be varied depending on the environment or stimuli to which they are exposed[13–15]. Extensive studies have revealed a significant immunosuppressive role of PMs in the tumor abdominal metastasis. In addition, it is also proved that PMs can suppress the proliferation of T cells and inhibit the inflammation in inflammatory disease[5,7]. Not surprisingly, the regulation of PM activities

in the peritoneal cavity is a hallmark of inflammatory diseases and abdominal cancers. Therefore, a better understanding of the characteristics and the function of PMs is of great significance for therapeutic strategies in the treatment of inflammatory diseases and abdominal tumors. In this review, we mainly discuss the possible role of PMs in inflammatory diseases and abdominal cancers by correlating the current knowledge and future perspectives.

FUNCTION OF PMs IN INFLAMMATORY DISEASES

Macrophages belong to a mononuclear phagocyte system that is widely spread throughout the body, including blood monocytes and tissue macrophages[16]. Notably, blood monocytes that migrate into the peritoneal cavity can transform into tissue macrophages and acquire new characteristics, which we call PMs. PMs are one of the best studied macrophage populations. Previous studies have shown that PMs are implicated in the regulation of peritoneal cavity homeostasis and mainly function as immune defense[17]. Through the expression of MHC-II molecules, macrophages are engaged in phagocytosis and are therefore effective at microbial killing and the clearance of necrotic debris[3,18]. In addition, macrophages secrete a large amount of proinflammatory and anti-inflammatory cytokines, which leads to the differentiation of $CD4^+$ T cells into Th1, Th2, Th17, and regulatory T cells (Tregs), thus contributing to the host immune response[19,20]. By contrast, a number of studies have shown that PMs were able to produce "quieting" effects in the inflammatory process as well[21–23]. It is reported that PMs in the peritoneal cavity are identified to produce a high level of suppressive cytokines, such as IL-10 and TGF-β, which play an inhibitory function in inflammation[5,23,24]. Consequently, PMs play a double-edged role during inflammatory diseases and are important for the immunological homeostasis in the peritoneal cavity.

Infections

Infection is a kind of disease caused by the invasion of infectious agents, such as bacteria, virus, fungi, and parasites[25]. At the beginning of the disease, the infection may be limited to a small area; however, without effective treatment, the infection can become a very serious system infection and consequently develop to sepsis. The interaction between host and infectious agents can lead to the generation of innate and adaptive immune responses. With infections such as microbes and superantigens, PMs normally exert a defense effect to the peritoneum[17]. Many cytokines, such as granulocyte colony-stimulating factor (G-CSF), granulocyte macrophage colony-stimulating factor (GM-CSF), TNF-α, IFN-γ, and IL-6, are critical for the defense effect of PMs[26,27]. In addition to secreting cytokines, PMs also play an important role as antigen-presenting cells (APCs) in the innate immune response during infection[28]. Early research found that peritoneal cells have the potential to further differentiate into dendritic cells (DCs) and are deemed as a reservoir of dendritic progenitor cells[29,30]. Interestingly, some other studies have shown that PMs may also possess immunosuppressive capacities under stimuli or infections[31–33]. When virus infection occurs, such as hepatitis C virus-induced hepatic cirrhosis, PMs display a decreasing inflammatory profile in ascites with basal level of ERK1/2 phosphorylation compared with alcohol-induced hepatic cirrhosis[34]. Emerging research demonstrates that in acute inflammation, PMs display anti-inflammation ability through the IL-10 inhibitory loop[24]. In addition, PMs induced by various agents significantly suppress the immune response initiated by concanavalin A[33]. These studies clearly support the concept that PMs facilitate the initiation and advancement of the immune response to exotic bacterial and abnormal antigens.

Food Allergy

Food allergy is a type of allergic disease with hyperimmune response and sensitization to food protein[35,36]. Clinically, in food allergy patients, the allergic reaction triggers immunoglobulin E (IgE) expression and is characterized with gastrointestinal symptoms. Anatomically, the gastrointestinal tract is present in the abdominal environment surrounded with a large amount of PMs. Therefore, PMs may play a role in the regulation of food allergy. A recent study has shown the possible role of PMs in the pathogenesis of food allergy, indicating that there is an accumulation of PMs in the place of cecal appendix during the disease process[37]. It is reported that the histopathological modifications in the different regions of digestive tract mucosa are significantly related to the infiltration of PMs in OVA-immunized rabbits[38]. In addition, this process of infiltration revealed the participation of PMs in local intestinal immune response during the allergy[38]. Additionally, in the areas of the gastrointestinal tract, PMs are normally located close to specialized lymphoid tissue and wrapped by a basal membrane to separate them from the intestinal epithelium[37]. However, the rich plexus of capillaries, nerve endings, and lymphatic vessels intimately associated to intestinal lymphoid tissue may contribute to the function of PMs. Although PMs could not directly react to the allergens, they still release products like prostaglandins, cytokines, and chemokines that in turn influence the activities of adjoining cells[38]. Further studies reported that the macrophage inflammatory protein-1a (MIP-1a) in murine peritoneal cavity elevated histamine levels, which is important for the immune regulation of food allergy[37,39]. Therefore, PMs negatively mediate the pathogenesis of food allergy by

secreting bioactive molecules, such as prostaglandins, cytokines, chemokines, and MIP-1a.

Peritonitis

Peritonitis is an inflammatory disease of the peritoneum that lines the inner wall of the abdomen and is usually caused by bacteria or fungi infection[40]. Clinically, the classical symptom of peritonitis is severe abdominal pain, especially when the pain gets worse with body movement. Additionally, bacterial peritonitis can spread rapidly into the blood, leading to sepsis, and could result in multiple organ failure and death. It is reported that the engulfment function of macrophages is required to prevent the release of noxious materials and therefore prevent the pathologic progression of bacterial peritonitis[41]. Functionally, Tim4 and MerTK in mouse resident PMs are found to contribute to the process of engulfment[42]. It is reported that the mutation of either Tim4 or MerTK affects the development of autoimmunity in mice[43,44]. Furthermore, GATA6 plays a critical role in the differentiation programming of PMs. Specifically, the inhibition of mTORC2 increases the expression of GATA6 in the resolution phase in the zymosan-induced peritonitis model[45]. Thus, mTORC2 has a critical role in regulating differentiation and metabolic reprogramming of PMs. In the peritonitis animal model, the mice have a low expression level of mTORC2 in PMs; therefore, the proliferation and differentiation from M2 macrophages were inhibited[45]. Interestingly, PMs isolated from peritonitis patients were active against human tumor cell lines without further stimulation, which indicated that the activated PMs may represent a useful cell type for cancer immunotherapy[46]. The PMs were primed in an inflammatory environment during peritonitis, and the quantity was dramatically increased. To our knowledge, the characterization and physiological function of PMs can shift under the peritonitis condition, and PMs seem to be useful in human cancer for adoptive cellular immunotherapy.

Inflammatory Bowel Disease

Inflammatory bowel diseases (IBDs) are chronic immune diseases of the gastrointestinal tract with unknown etiology[47]. Patients with IBDs are characterized with weight loss, diarrhea, and rectal bleeding. In a dextran disodium sulfate (DSS)-induced colitis model, the pathology slide of a colon indicated extensively distributed inflammation with loss of the entire crypts and the surface of epithelium. In addition, there was an accumulation of macrophages at the site of the inflammation, which indicated that macrophages play an important role in the pathological processes of IBDs[5,48]. Recent research revealed that PMs are also crucial in maintaining gastrointestinal homeostasis[49,50]. It is reported that in IBDs, there are at least two different routes for endogenous PMs to migrate to the gut (Fig. 2). First is via the lymphatics to the blood circulation before migrating to the lesion sites, and second is via the lymphatics to the murine intestinal lamina propria and are restricted almost exclusively to follicular structures present in the gut wall, such as Peyer patches and solitary intestinal lymphoid tissue, prior to migrating to the lesion sites[51]. Indeed, few PMs enter into the circulation system and finally migrate to the specific inflammatory sites, partially due to the receptors in the peritoneal cavity recognizing the peritoneal cells, restricting the migration of peritoneal cells[52]. However, the same as with food allergy, PMs can release prostaglandins, anti-inflammatory cytokines, and chemokines to influence the activities of adjoining cells though a plexus of capillaries and lymphatic vessels. Thus, it is conceivable that PMs bear anti-inflammation efficacy and are able to treat inflammatory diseases. Interestingly, a recent study found that the adoptive transfer of PMs can effectively remit DSS-induced experimental colitis by secreting anti-inflammatory cytokines, such as IL-10 and TGF-β^5. This is mainly due to the isolated and intravenously infused PMs with immunosuppression ability that can migrate to the lesion sites directly through blood circulation. Therefore, PMs can be used as a new candidate of immunologic suppression cells for IBD cell adoptive therapy.

Diabetes Mellitus

Diabetes mellitus (DM) is a type of metabolic disease characterized by hyperglycemia. The chronic hyperglycemia of DM exhibits an inflammatory phenotype, which is associated with dysfunction and failure of various organs, such as the cardiovascular system[18,53]. Previous studies reveal that the macrophages have multiple roles in glucose regulation and also function in lipid metabolism as well as in the inflammation of adipose tissue, especially in the peritoneal cavity[54]. Of note, the inhibition of macrophage migration inhibitory factor (MIF) in diabetic mice was effective in reducing inflammation in the pancreas; thus, the transmigration of PMs might be involved in the initiation and development of DM[55,56]. Moreover, $CD4^+$ T cells, especially Th17 cells, were proven to be associated with the onset and progression of autoimmune diseases, such as type 1 diabetes[57]. It was reported that the progression of diabetes elevates the expression level of IL-17 in periapical, hepatic, and renal tissues[58], and the cytokine secretion capacity of PMs was identified to contribute to this process[59,60]. Consistently, the thioglycollate-elicited PMs produced high levels of IL-17 after stimulation with lipopolysaccharide (LPS) in vitro[60]. In addition, the high level of IL-17 produced by PMs promotes the polarization of $CD4^+$ T cells into Th17 cells, which in turn promotes the development of diabetes[58]. By contrast, functionally in type 2 diabetes, the rat PMs expressed lower levels of nitric oxide (NO) and a higher concentration of citrulline,

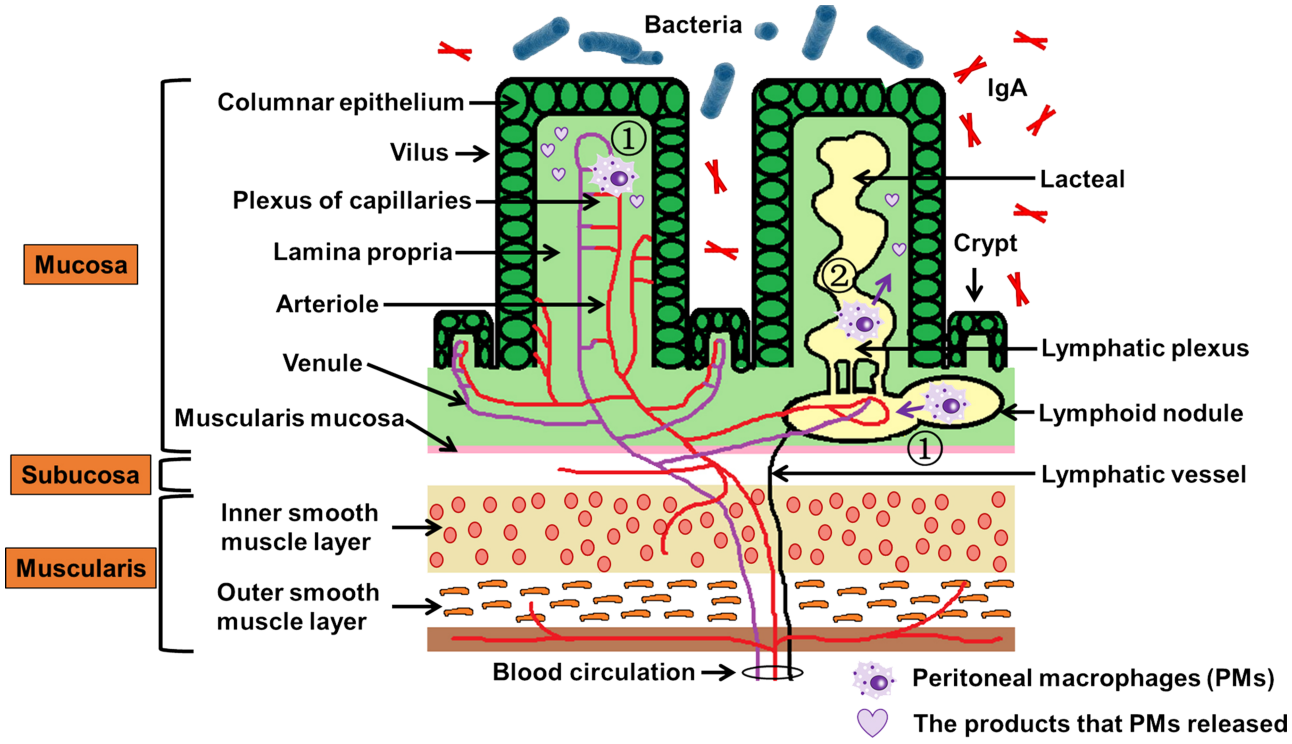

Figure 2. The routes for PMs to migrate to the inflammatory site of the colon. In inflammatory bowel diseases (IBDs), the injury of the colon is starting from the mucosa to the muscularis. However, most PMs cannot directly migrate to the mucosa through blood circulation. Prior to migrating to the lesion sites, most PMs are restricted in specialized lymphoid tissue. There are at least two different routes for endogenous PMs to migrate to the mucosa and participate in gut immunoregulation. First is via the lymphatics to the blood circulation and then to the mucosa. Second is via the lymphatics to the lamina propria and then to the mucosa. PMs are able to release a large amount of products, such as prostaglandins, cytokines, and chemokines, and therefore influence the activities of adjoining cells though the rich plexus of capillaries, nerve endings, and lymphatic vessels.

showing anti-inflammatory effects[61]. PMs have a major role in the inflammatory response in diabetes, and, in general, PMs from diabetic mice have a reduced capacity of cytokine release and immune response[62].

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory disorder of the joints. The abundance and the activation of macrophages in the inflamed synovial cavity significantly correlate with the severity of RA[63]. In addition, the downregulation of macrophage activation prevents the irreversible joint damage; therefore, it is conceivable that macrophages critically contribute to the pathologic progress of RA[63]. Further study revealed that flavonoids are able to ameliorate adjuvant-induced arthritis in rats by downregulating TNF-α secretion through the unfolded protein response (UPR) pathway in M1-polarized PMs, which indicate that M1-polarized PMs are involved in both the initial step and the pathogenesis of RA by promoting the IRE1/mTORC1/TNF-α-regulated inflammatory response[64]. In addition, in complete Freund's adjuvant-induced arthritis mice model, a high population of PMs before adjuvant immunization can effectively protect the mice against arthritis[65]. By contrast, in the late phase of arthritis, the quantity of PMs is increased in response to the inflammation, and the number of PMs is related to the severity[65,66]. Of note, the depletion of the PM population during inflammation resulted in a significant decrease in neutrophil infiltration and proinflammatory cytokine production[67]. It was also reported that the specific knockdown of TNF-α in PMs by intraperitoneal administration of chitosan and siRNA nanoparticles dramatically reduced the systemic and local inflammation in a murine arthritis model[68]. The upregulation of Tregs and the downregulation of Th17 can successfully ameliorate experimental inflammatory arthritis[69]. Interestingly, PMs function in the regulation of $CD4^+$ T-cell differentiation by secreting different kinds of cytokines, such as IL-10, TGF-β, TNF-α, IL-6, and IL-17, and are therefore important for initiating and driving both early and late phases of arthritis.

FUNCTION OF PMs IN ABDOMINAL CANCERS

Abdominal cancer refers to a variety of cancers that grow or metastasize in the abdominal cavity[70]. The most common forms of abdominal cancer are ovarian cancer,

uterine cancer, gastrointestinal cancer, stomach cancer, renal cancer, liver cancer, and pancreatic cancer. Clinically, the growth and the spread of cancer cells in the peritoneal cavity are very fast, due to the suppressed environment provided by the PMs[5,71,72]. It was reported that PMs affect the growth and metastasis of cancer cells by cell–cancer cell interaction and paracrine activity of soluble factors released to the environment[72]. Annexin A2 is one of the important proteins that mediate the interaction between ovarian cancer and PMs. It encourages cell adhesion, motility, and invasion of ovarian cancer cells[71,72]. Generally, in a tumor-bearing mouse, it was found that the cytotoxicity of PMs is significantly decreased, whereas the cytotoxicity of SPMs was markedly increased[3]. In addition, it was reported that the coculture of granulosa cells with PMs resulted in cell proliferation and contributed to follicular growth in ovarian cancer[73]. Thus, the dissemination of cancer cells in the peritoneal cavity is a major problem in postoperation management[74,75]. Notably, in a tumor-bearing mouse study, the interaction between PMs and cancer cells could in turn lead to a phenotype shift of PMs[76]. Additionally, it was reported that PMs from abdominal cancer have been identified to have significant antitumor efficacy through growth inhibition by cytokines or immunity[77–79]. In human ovarian cancer, the number of PMs collected from patients treated with sizofiran and recombinant IFN-γ was found to increase more than 30 times[74,75]. In vitro, stimulation of these activated PMs with LPS could induce a large amount of cytokines, such as IL-1, IFN-γ, TNF, and prostaglandin E2 (PGE2), and therefore could exert an antitumor effect on ovarian cancer[74,75]. In an SL2 lymphoma mice model, PMs were immunized with SL2 lymphoma cells in the peritoneal cavity for 9 days. Afterward, the immunized PMs were isolated and intraperitoneally injected to treat the SL2 lymphoma mice model. Surprisingly, these immunized PMs slightly inhibit the growth of lymphoma cells in vivo[80]. In the azoxymethane (AOM)- and DSS-induced colitis-associated cancer mouse model, PMs exerted a different role in different disease stages. In the early stage, when mice were experiencing the inflammation of colitis, the PMs increased the proportion of both granulocytic myeloid-derived suppressor cells and Th17 cells by secreting IL-17 and therefore promoted the development of colitis-associated colon cancer[59]. In the late stage, in mice with colon cancer, the M2-polarized PMs played a key role in colitis-associated colon cancer, including the expression of enhancement of migration- and invasion-associated factors, such as G-CSF, GM-CSF, CXCR4, vascular endothelial growth factor (VEGF), TGF-β, and intercellular adhesion molecule 1 (ICAM-1)[81]. Consistently, the M2-polarized PMs also significantly increased the expression of inflammation-associated cytokines, such as IL-1β, IL-10, IL-12, IL-6, and TNF-α[81]. Therefore, M2-polarized PMs promote the change from inflammatory hyperplasia to colon cancer and metastasis. In addition, the M1-polarized PMs also exerted a functional change in the colitis-associated colon cancer model. This functional change is similar to the M2-polarized PMs; however, there was no polarization change during peritoneal metastasis[81]. Of note, multiple studies have shown that the function of PMs is strongly associated with the initiation and development of abdominal cancers, and targeting PMs might become a promising therapeutic method for the immunotherapy of abdominal cancer.

THE INFLUENCE FACTORS FOR THE FUNCTION OF PMs

PMs are one of the best-studied macrophage populations. In previous years, considerable efforts have been made to broaden our understanding of the function of PMs. Actually, the physiologic function of PMs can be affected by many influencing factors. Here we summarized some important influencing factors that directly affect the number, phenotype, and function of PMs. First, age is one of the important factors that affect the quantity and quality of PMs. It is reported that the function of rat PMs, such as the secretion of cytokines and phagocytosis in response to M1/M2 activators, is gradually diminished by aging[82]. Additionally, aging increases the frequency of $CD163^{+}CD68^{+}$ mature macrophages and exerts deficient control of infectious and inflammatory diseases. Second, several groups have determined the varied immune responses elicited by PMs, especially under pathological conditions. For example, the total number of PMs and their functions decreased under blood loss[83]. Third, CO_2 pneumoperitoneum by laparotomy will inhibit the phagocytosis function of PMs and their secretion of cytokines[84]. However, this effect lasts only 12 h after surgery, which then returns to normal within 24 h[84]. Fourth, many chemicals increase the phagocytosis activity and M1 polarization of PMs, such as cisplatin, liposome, and herbal extracts[85]. The intraperitoneal administration of chemical drugs is a very common route in animal disease models, and in this process, the PMs may serve as a key mediator. It was reported that with the treatment of ganoderma lucidum polysaccharide liposomes, the expression of MHC-II on the PM surface was significantly increased and the secretion of NO and the activity of inducible nitric oxide synthase (iNOS) were enhanced in PMs[86]. In addition, with the treatment of gypenosides liposome, the phagocytosis activity and cytokine secretion of PMs were also enhanced[87]. These studies strongly suggested the potential use of PMs as a delivery system for chemical drugs[86,87]. Fifth, TLRs are the major receptors expressed on the surface of PMs, which empower the PMs with the ability to recognize molecular patterns conserved through

evolution in a wide range of microorganisms[2]. Similar to BMDMs, it was reported that the TLR2-blocked PMs showed impaired release of TNF-α, IFN-γ, and IL-6 in response to both live and heat-killed *Staphylococcus aureus* infection[27]. Thus, TLRs play a critical role in the activation of PMs, which is usually associated with gene expression alteration. Sixth, some cytosolic proteins may also affect the physiology of PMs. For example, heat shock protein 70 (HSP70) is a kind of cytosolic protein that has an important role in growth, development, and apoptosis. PMs treated with HSP70 experienced not only enhanced functional state but also initiated immense morphological changes leading to increased endothelium adherence, increased migration to the inflammatory site, and increased antigen uptake[88]. Finally, in order to isolate as many murine PMs as possible from the peritoneal cavity, Brewer's thioglycollate medium was used to boost monocyte migration into the peritoneum. Accordingly, this procedure will raise macrophage yield by 10-fold, but this type of PMs were shown to be more mature and stable[2]. The phenotype of PMs can be varied based on the environment to which they are exposed, and the distinct phenotype of PMs can be induced by the stimulation of a distinct influencing factor.

CONCLUDING REMARKS

It is now well accepted that PMs serve as central inflammatory mediators that respond to microbes and superantigens. However, in abdominal cancers, the function of PMs could be more sophisticated. Generally, in the early stage of abdominal cancer, PMs exert an anti-inflammatory effect and promote cancer growth and metastasis. By contrast, in the later stage of abdominal cancer, PMs exert a proinflammatory effect and show a significant antitumor efficacy through growth inhibition by cytokines or immunity. Accumulating studies suggest that the regulation of PM activation is involved in various inflammatory diseases and abdominal cancers, and targeting PMs present a promising approach for immunotherapy. Therefore, a better understanding of the distinct biological function of PMs in individual diseases is crucial for designing more specific and effective therapeutic agents for the treatment of inflammatory diseases and abdominal cancers.

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