Chapter

Functional Biomaterials Modulate Macrophage in the Tumour Micro-environment

Tsung-Meng Wu, Kuang-Teng Wang, Hisang-Lin Tsai, Fan-Hua Nan and Yu-Sheng Wu

Abstract

The inflammation response requires the cooperation of macrophages with immune cell function and active factors, such as cytokines and chemokines. Through this response, these factors are involved in the immune response to affect physiological activities. Macrophages can be categorized into two types: 'M1' and 'M2'. M1 macrophages destroy the pathogen through phagocytosis activation, ROS production, and antigen-presenting, among other functions. M2 macrophages release cellular factors for tissue recovery, growth, and angiogenesis. Studies have determined that tumour tissue presents with numerous macrophages, termed tumour-associated macrophages. Tumour cells and peripheral stromal cells stimulate the tumour associated with macrophages (M2) to produce factors that regulate angiogenesis. Modulating the balance of the M1 and M2 function has already gained interest as a potentially valuable immune disease therapy. However, applications of the immunotherapy in clinical treatments are still not clear with regard to the cellular working mechanism. Therefore, we summarized the functions of common biomaterials involved in the modulation of the macrophage.

Keywords: macrophage, polarization, tumour micro-environment, biomaterials, cytokines

1. Introduction

Inflammation has been demonstrated to be a critical factor in the induction of immune disease. Immunotherapy is a novel therapeutic approach for anti-inflammation, which could help avoid drug resistance. However, findings have indicated that the balance of inflammation and anti-inflammation is crucial. Cellular ROS are produced by stress to clear pathogen infections [1]. The inflammatory response involves macrophages, dendritic cells, and M cells, which are crucial protectors. These cells present partial antigens to enhance the T-cell activation and cytokine production, which modulate the host micro-environment. Cytokines are produced and released as signals to regulate the immune cell function.

Immunotherapy was developed as an approach to rectify the imbalanced inflammation. Immunotherapy was hypothesized as a possible alternative therapy applied in the early phase of clinical therapy and immunomodulation in the early stages of immune disease. The common immunotherapy employs natural functional

materials including triterpenoids and polysaccharides. Studies have demonstrated that functional polysaccharides can promote macrophage differentiation into M1 or M2, and the ratio modulates the host micro-environment through cytokine secretion.

Polysaccharides such as beta-glucan are considered to be biological response modifiers (BRMs) that activate macrophages and modulate the inflammation response. Findings have indicated that beta-glucan combines with receptors expressed on the macrophage cell surface, such as Toll-like receptor. Once combined, alveolar macrophages, Kupffer cells, Langerhans cells, mesangial cells, and microglial are activated through toll-like receptor 4–mediated signalling pathways to modulate the immune response.

2. Macrophage activation

Macrophages are present in almost all tissues and coordinate developmental, metabolic, and immunological functions, thereby contributing to the maintenance of homeostasis. Macrophages have a complex role in tissues and act on lipopolysaccharide (LPS), interferon-γ (IFN-γ), and interleukin (IL)-4 to polarize the M0 into M1. Macrophages are activated by exposure to various stimuli. The stimuli that act on macrophages are categorized into danger, homeostatic, metabolic, and modulatory signals. Danger signals include pathogen-associated molecular patterns, such as LPS. Tissue macrophage exposure to danger signals results in an inflammatory response. Findings have indicated that tumour environments contain numerous transmitters, such as M-CSF, IL-6, IL-10, TGF-β, and COX-2, which induce tumour megakaryocytes to differentiate into M2 macrophages, which, in addition to having poorer antigen-presenting and cytotoxic abilities, also secrete factors that inhibit immune cells, resulting in an enhanced immune inhibitory effect of the tumour environment as shown in **Figure 1**. We investigated the modulation of M1 and M2 in the tumour environment by using immunomodulators to delay or inhibit the tumour to identify alternative approaches to reduce the side effect of tumour chemotherapy. Inflammation is a crucial adaptive response for animals, and the mechanism involves a complex interaction of molecular mediators. The functions of immune cells in a micro-environment are mediated by responses that occur at all levels of biological organization [2]. This process involves cooperation among cells and mediators, and the classical immune response varies based on a wide range of factors, including the stage of the inflammation process, the tissue or organ involved, and whether the inflammation is acute and resolving or chronic and nonresolving [3]. The inflammation process involves vascular permeabilization, active migration of blood cells, and passage of plasma constituents into injurious tissue [4]. Studies have demonstrated that the infiltration of immune cells during the inflammation process plays a crucial role in atherosclerosis [5]. Blood leukocytes are mediators of host defences and inflammation localized in the earliest lesions of atherosclerosis in experimental animals. The study of inflammation in atherosclerosis provided new insights into the mechanisms underlying the recruitment of leukocytes [6]. Recently, studies have indicated that inflammation plays a role in Alzheimer disease (AD) [7]. Inflammatory components involved in AD neuroinflammation include brain cells (such as microglia and astrocytes), the complement system, and cytokines and chemokines [8]. Regarding cancer development [9], proinflammatory cytokines, including chemokines; matrix metallopeptidase (MMP)-9; vascular endothelial growth factor (VEGF); and IL-1α, IL-1β, IL-6, IL-8, and IL-18, are primarily regulated by the transcription factor nuclear factor (NF)-kB, which is active in most tumours and is induced by carcinogens [10]. Cutaneous wound repair

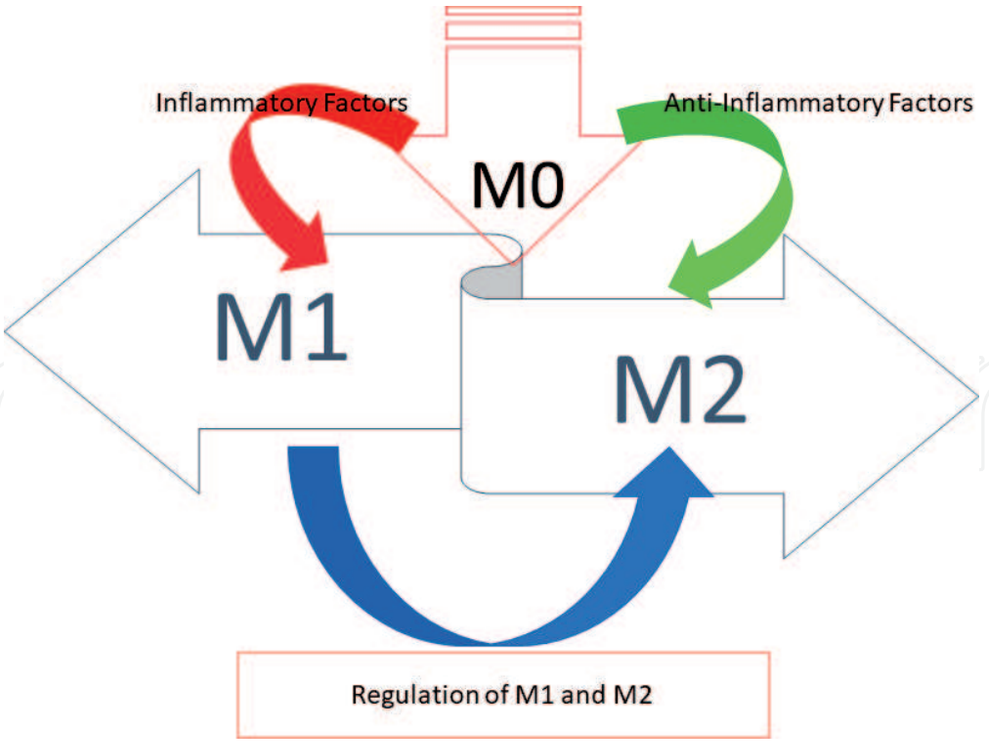

Figure 1.
Macrophages can be categorized into two types: 'M1' and 'M2'. M1 macrophages destroy the pathogen through phagocytosis activation, ROS production, and antigen-presenting, among other functions. M2 macrophages release cellular factors for tissue recovery, growth, and angiogenesis. We thought that the regulation of macrophage is beneficial to reduce the auto-immune disease.

is a tightly regulated and dynamic process involving blood clotting, inflammation, new tissue formation, and tissue remodeling [11]. Thrombin is the protease involved in blood coagulation. Thrombin deregulation can lead to haemostatic abnormalities, which range from subtle subclinical to life-threatening coagulopathies (i.e., during septicaemia) [12]. Inflammation and blood coagulation is part of the innate host protection mechanism against vascular injury, infection, or other wounds. Cells of the innate immune system, endothelial cells, and platelets are actively involved in acute and chronic inflammation; they release proinflammatory mediators and recruit leukocytes [13]. The protease-activated receptor (PAR) family serves as sensor of serine proteinases in the blood clotting system in the target cells involved in inflammation. Activation of PAR-1 by thrombin and of PAR-2 by factor leads to a rapid expression and exposure of both adhesive proteins that mediate an acute inflammatory reaction and of the tissue factor that initiates the blood coagulation cascade on the membrane of endothelial cells [14]. In this process, cooperation among cells and mediators occurs, and a wide range of factors are involved in the classical immune response: (1) the stage of the inflammation process; (2) the tissue or organ involved; and (3) whether the inflammation is acute and resolving or chronic and nonresolving [15]. The inflammation process involves vascular permeability, active migration of blood cells, and the passage of plasma constituents into injurious tissue [4]. Studies on the infiltration of immune cells have demonstrated that the inflammation process plays a crucial role in atherosclerosiss [5]. Blood leukocytes, mediators of host defences and inflammation, localize in the earliest lesions of atherosclerosis in experimental animals. The study of inflammation in atherosclerosis has provided numerous new insights into the mechanisms underlying the recruitment of leukocytes [6]. Studies have reported that inflammation is involved in Alzheimer's disease (AD) [7]. Inflammatory components involved in AD neuroinflammation include brain cells (such as microglia and astrocytes), the complement system, and

cytokines and chemokines [8]. Regarding cancer development, proinflammatory cytokines, including chemokines, MMP-9, VEGF, and IL-1α, IL-1β, IL-6, IL-8, and IL-18, are primarily regulated by the transcription factor NF-kB, which is active in most tumours and is induced by carcinogens [9, 10]. Macrophages play a crucial role in inflammation process, tumour growth, and tumour progression by induced angiogenesis. Studies have reported that promotion of angiogenesis with the production of proangiogenic factors, such as TGFβ, VEGF, PDGF, members of the fibroblast growth factors family, and angiogenic chemokines [16], and the development of breast cancer and several other human tumours was correlated with macrophage infiltration [17]. VEGF-C production by tumour-associated macrophages (TAMs) was reportedly involved in peritumoral lymphangiogenesis and the subsequent dissemination of cancer cells with formation of lymphatic metastasis [18]; moreover, macrophage colony-stimulating factor (M-CSF) and VEGF actively recruit circulating blood monocytes at the tumour site [19].

3. Polysaccharide function on the immunomodulation

Evidence has indicated that acetyl-xylogalactan extracted from *Sarcodia suieae* induced macrophage polarization through the IL-1β, TNF, and Malt-1 expression [20]. Nakanishi et al determined that celecoxib can alter the immune inhibitory effects of the tumour micro-environment by promoting the transformation of TAMs into M1 macrophages, leading to inhibited tumour growth [21]. In 1968, Ikekawa et al. reported that the fruiting body extracts from *Lentinus edodes*, *Trametes versicolor*, *Ganoderma tsugae*, *Flammulina velutiper,* and *Tricholoma matsutake* demonstrated significant antitumour activities in transplanted Sarcoma 180 tumour cells [22, 23]. Studies have reported that *Antrodia camphorata*-derived beta-glucan demonstrated inhibitory effects on tumour growth in Sarcoma 37, Sarcoma 180, Erlich ascites sarcoma, Yoshida sarcoma, and LLC1 transplanted tumour [24]. Daily intake of *A. comphorata*-derived beta-glucan for 18 consecutive days was demonstrated to slow tumour growth and reduce the rate of metastasis [25]. Cytotoxic T-cell activity and tumour occurrence rate were investigated and the results revealed that daily oral intake of *Grifola frondosa*-derived beta-glucan or Lentinan can enhance cytotoxic T-cell activity and reduce tumour occurrence rate [26]. Furthermore, the addition of conditioned medium with tumour cells into the progenitors of dendritic cells was determined to further inhibit the maturation of dendritic cells and lower the antigen-presenting capability of the dendritic cells [27]. Studies have reported that tumour cells secrete M-CSF, thereby inhibiting dendritic and T-cell differentiation and antitumour ability [27–30]. In the tumour environment, the amounts of M1 and M2 macrophages are not equal [31]. Tumour environments are known to contain a large number of transmitters such as M-CSF, IL-6, IL-10, TGF-β, and COX-2, which induce tumour megakaryocytes to differentiate into M2 macrophages, which have poorer antigen-presenting and cytotoxic abilities and secrete factors that inhibit immune cells, resulting in an enhanced immune inhibitory effect of the tumour environment [16, 32–41]. M2 macrophages in tumour-bearing mice enhance tumour growth and immune inhibitory effects. M2 macrophages also secrete cytokines, such as IL-10 and TGF-β, in high quantities, which attract noncytotoxic Treg-cells and Type 2 helper T cells to congregate in tumour tissues, which in turn inhibit the differentiation and normal functions of T cells, including their cytotoxic ability, which further leads to T-cell apoptosis [38, 40, 42–44]. The Th1 and Th2 polarization is built on cytokine patterns, which begin when the antigen-presenting cells interact with the naive T cells and polarize into type 1 and type 2 cells in response to the type of antigen encountered [45]. Th1 and Th2 cells secrete different cytokines.

Th1 cells are dependent on IL-2, IFN-γ, and TNF, which are involved in cell-mediated immunity against pathogens. Th2 cells are mostly dependent on IL-4 and IL-5, which stimulate the production of IgE antibodies and eosinophil responses, resulting in allergic diseases [46, 47]. An imbalanced Th1/Th2 immune response is linked to certain hypersensitivity disorders such as allergy, asthma, and hay fever [48]; therefore, studies have suggested that using BRM to restore the balance between Th1 and Th2 immune response could be a treatment option for the IgE-dependent hypersensitivity [49]. *Ganoderma lucidum* is a medicinal mushroom, which has been widely used for hundreds of years as a folk medicine in oriental countries such as China and Japan for its immunomodulating and antitumour effects. Numerous biological available substances with immunity enhancement effects, in particular polysaccharides, have been isolated from the extract of *G. lucidum* [50].

Antimicrobial peptides are effective components of innate immunity that are widely present in the biological system. Hepcidin is a 25-amino acid antibiotic peptide synthesized in the liver, which is reportedly responsible for regulating iron balance and recycling in humans and mice. Studies on 0–100 μg/mL concentrations of hepcidin incubated with HT1080, Hep-G2, and HeLa for 24 h revealed higher growth inhibition ratios after treatment with 70 μg/mL hepcidin in HT1080 cells. Hepcidin was very effective at inhibiting the growth of fibrosarcoma cells [51, 52]. Studies on tachyplesin, an antimicrobial peptide present in leukocytes of the horseshoe crab (*Tachypleus tridentatus*), demonstrated that tachyplesin was able to inhibit the growth of TSU tumour cells on the chorioallantoic membrane of chicken embryos and B16 tumour cells in syngeneic mice. Tachyplesin also blocked the proliferation of both tumour and endothelial cells in culture in a dose-dependent manner, whereas proliferation was relatively unaffected in nontumorigenic cell lines Cos-7 and NIH-3T3 [53]. D-K4R2L9 is a peptide with 15 amino acid residues, comprising of Leu, Lys, and Arg residues, which binds to and lyses B16-F10 mouse melanoma cells in culture at concentrations that do not harm normal 3T3 fibroblasts or erythrocytes, thereby preventing intravenous-injected D122 lung carcinoma cells from forming lung tumours in mice [54, 55]. Another antimicrobial peptide, bovine lactoferricin (LfcinB), is a 25-amino acid, highly basic peptide with a disulphide bridge between two cysteines; thus, LfcinB is a cyclic twisted antiparallel β-sheet solution structure. The effects of LfcinB on neuroblastoma growth were investigated in vivo, which revealed that SH-SY-5Y xenografts in nude rats were significantly inhibited after injections of 1.0 or 2.0 mg of LfcinB compared with untreated controls [56]. Related research has demonstrated that antimicrobial peptides can activate specific innate immune responses and lead to immunomodulatory effects in the host when there is a risk of damage. Furthermore, the antimicrobial peptides are proposed to modulate the host's immune system through inflammatory responses and stimulate the beneficial aspects of inflammation, including inhibition of tumour growth.

4. Conclusion

Immunotherapy is being developed and presents certain advantages of alternative medicine because immunomodulation factors, such as mushroom beta-glucan, antimicrobial peptides, and triterpenoid, represent a novel therapeutic approach for cancer therapy and may provide an alternative to deal with the problem of drug resistance. However, exploring current insights into tumour biology and tumour micro-environment is complex and involves chemistry, biology, instrumentation, and formulation science. Therefore discovering a novel, more effective tumour-targeting treatment is difficult. Immunotherapy is hypothesized to be an alternative therapy that could be applied in the early phase of clinical tumour therapy.

Competing interests

The authors declare no competing interests.

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