Chapter

Mucosal Macrophage Polarization Role in the Immune Modulation

Tsung-Meng Wu, Shiu-Nan Chen and Yu-Sheng Wu

Abstract

Immunotherapy has advantages including few side effects and low probability of abuse by patients. Recently, functional materials with immunomodulatory functions, which act through reduction of free radicals, have been developed for cancer and anti-inflammatory therapy. However, the therapeutic application of natural functional materials involves a complex mechanism along with various organic factors. These substances, including polysaccharides and triterpenoids, have immunomodulatory effects. However, to our knowledge, the mechanism underlying the action of such substances in the physiological immunity of animals remains unclear. Immune cells, particularly macrophages, are crucial in the modulation of immune response. Macrophages polarise into two types, namely, M1 and M2, from the M0 form, based on the physiological microenvironment factors. M1 macrophages have functions in pathogen elimination through phagocytosis, oxidative damage, and complement system activation. M2 macrophages are involved in tissue recovery and tumour tissues containing ample M2 macrophages that release growth factors, which promote angiogenesis. In this study, we focus on the immunomodulation of the macrophage to further understand the effects of the physiological microenvironment factors on macrophage polarisation.

Keywords: macrophage, polarisation, immune modulation

1. Introduction: immune cells in the mucosal system

The mucosal system is ubiquitous throughout the body; the mucosal tissue is typically present in association with various organ systems, including the gastrointestinal tract, respiratory tract, and genitourinary tract, as well as the exocrine glands associated with these systems, such as the pancreas, lacrimal glands, salivary glands, and breasts. According to their location and function, mucosal tissues can be divided into nasopharynx-associated lymphoid tissue (NALT) [1], bronchus-associated lymphoid tissue (BALT) [2], and gut-associated lymphoid tissue (GALT) [3]. The surface area of the mucosal system is very broad; its physiological functions include gas exchange, food absorption, and sensory function. The mucus on the mucosal surface acts as a protective barrier inside the body to protect the body from foreign pathogenic infections [4]. Because of the distribution of mucus over a large surface area, the probability of mucosal tissues coming in contact with pathogens is higher than that of other tissues in the body. Nevertheless, these tissues are responsible for the evasion of the pathogens. Adhesion molecules, expressed by tissues and organs, enable the binding of lymphocyte receptors that attract lymphocytes towards the mucosal surface.

GALT, the largest lymphoid organ in the human body, contains 70–80% of the lymphoid tissues of the human body. The main GALT components include lamina propria (LP), Peyer's patches (PP), and mesenteric lymph node (MLN).

A mucosal immune response involves various cells, particularly macrophages. Macrophages are present in almost all tissues and have distinct location-specific phenotypes; their gene expression profiles demonstrate considerable functional diversity in innate immune response, tissue development, and tissue homoeostasis [5, 6]. Resident macrophages in different organ tissues are named differently. For instance, microglia cells have pathogenetic significance regarding perivascular inflammatory phenomena in the brain [7, 8], Kupffer cells have a major role in the homoeostatic function of the liver and are associated with the tissue damage [9], and alveolar macrophages (AMs) are a key determinant of pulmonary immune responses and thus have a role in lung inflammation (e.g. asthma) [10]. Previously, tissue-resident macrophages were considered to be recruited from circulating blood monocytes. However, recent studies have demonstrated that tissue-resident macrophages, such as microglial, Kupffer, and Langerhans cells, are established prenatally; they arise independently from the haematopoietic transcription factor [11, 12], which is required for the development of haematopoietic stem cells (HSCs) and all $CD11b^{high}$ monocytes and macrophages, but is not required for yolk sac (YS) macrophages and for YS-derived $F4/80^{bright}$ macrophages in several tissues, which can all persist in adult mice independently of HSCs [12]. Kupffer cells and other resident macrophages (e.g. microglia) originate from the YS in a colony-stimulating factor-1 receptor (CSF-1R)-dependent and Myb-independent manner and may be maintained through local proliferation, resulting in extensive mitosis after stress or an exchanged tissue microenvironment [13, 14].

2. Phenomenon of macrophage and its importance in the immune response

Macrophages are primarily divided into two types based on function and differentiation: classically activated (M1) and alternatively activated (M2) macrophages (**Figure 1**). Both have roles in innate resistance and constitute a link between inflammation and autoimmune disease. In mouse models, macrophages contain CD11b, F4/80, and CSF-1R, where F4/80 is the surface protein for M1 and M2 macrophages [15, 16]; these are circulating monocytes (present in the peripheral blood), which are secreted in response to chemokines produced in response to exposure to an antigen (e.g. pathogens entering the organism from the portal vein of the intestines). When interacting with pattern recognition receptors, antigens may lead to M1- or M2-polarising activities, depending on the secreted Th1 cytokine [interferon (IFN)-γ], Th2 cytokines [interleukin (IL)-4 and IL-13], and other immune factors [17–19]. Macrophage is also role in the antigen presenting, to induce the B cell active and response to the antibody production. The antibody production is from the plasma cell (active B cell), where there is a molecule material expression on its surface. A part of these receptors is named B-cell receptors (BCRs).

B-cell receptor is a B-cell membrane-bound surface protein that acts as a cellular receptor. During B-cell differentiation, differentiated B cells, transferred as plasma cells, secrete immunoglobulins (Igs). Structurally, Igs are similar to the BCRs and are called antibodies [20].

The main functions of antibodies include neutralising the antigen, activating complement reaction, and participating in the adaptive immunity. An antibody comprises two heavy and two light chains, is Y shaped, and is divided into variable and constant regions. The variable region contains the antigen-binding sites [21],

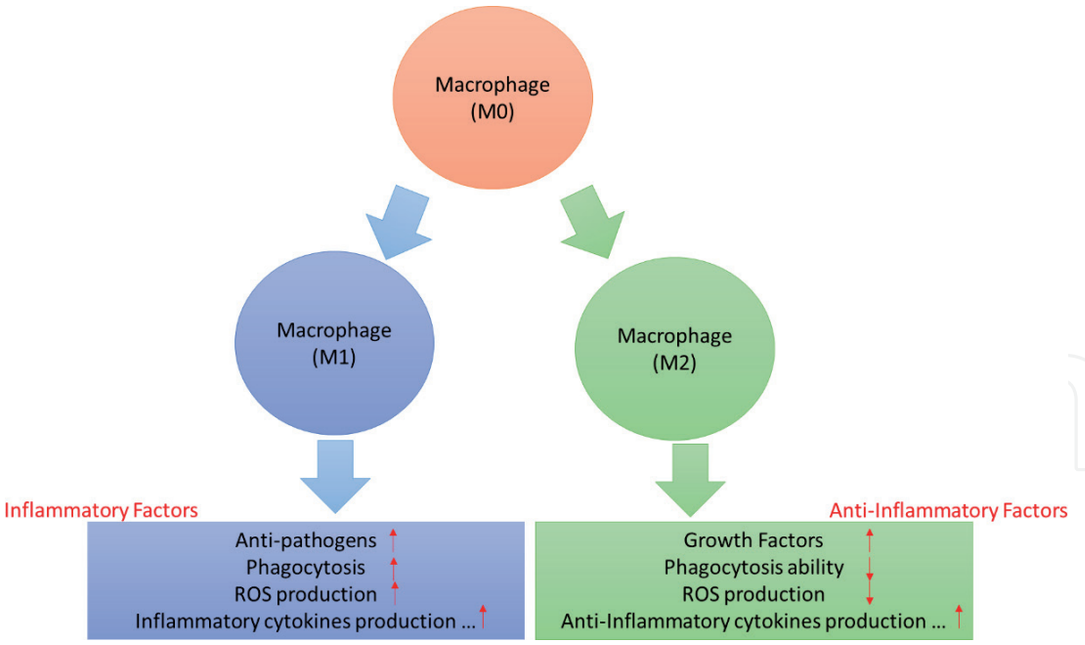

Figure 1.
The inactive macrophage is differentiated into M1 or M2 macrophage by various stress and stimulants in the host microenvironment. M1 macrophage is participating in the inflammatory response, a major function in the pathogen clearance. M2 macrophage is in contrast to the M1 macrophage.

and each antigen-binding site has three structures complementary to the antigen and a highly recognisable region that determines the antigen-antibody specificity, called the complementarity-determining region (CDR) [22]. By using different combinations of CDRs with heavy and light chains, B cells can be induced to produce various specific antibodies. The antibody immobilisation region has several major functions. First, these regions in different antibody types can bind to Fc receptors (FcRs) on different cells, such as FcRγ on phagocytic cells (e.g. neutrophils and macrophages) [23]. Similarly, the IgG-immobilised region binds to the antigen bound to the antibody; the FcRε on mast cells, neutrophils, and basophils can bind to the IgE-immobilised region [24], inducing the cell to perform a specific antigenic reaction with an inflammatory response modifier. Second, the FcR of the antigen-antibody complex binds to complement, triggering a complement chain reaction. IgG secreted by pregnant women is also transported to the abdomen through their blood flow [25]. Some lymphocytes are called innate-like lymphocytes (ILLs), and the mechanism by which B-1 cells secrete antibodies is different from that used by B cells [26].

2.1 B-1 cells

B-1 cells are called natural antibodies and include the IgG, IgA, and IgM isotypes [27, 28]. Natural antibodies are secreted when B-1 cells are not stimulated by foreign pathogens, which can bind to different pathogens but have low affinity.

2.2 Ig isotype switching (class switching)

B cells can express different C-region genes during cell maturation and proliferate during the reaction [29]. It simultaneously expresses IgM and IgD through RNA modification [30]. As the immune function continues to respond, antibodies in the same variant region can be expressed as IgG, IgA, and IgE. This process is called homotypic conversion or class switching, which protects all parts of the body at the appropriate time by using specific antibodies produced by the same antigen.

2.3 Ig isotype

According to the structural differences of the heavy chain, Igs are divided into five isotypes [25]:

i. IgG, a major Ig in the blood, exists in a monomeric form and thus easily spreads throughout the body through peripheral blood. For instance, in humans, IgG enters the foetus through the placenta, providing passive immunity to the foetus. IgG has a modulating function, which efficiently promotes the phagocytosis of pathogens [31].

ii. IgA, present in serum as a monomer, can diffuse outside blood vessels. In most of the body, IgA is present as a dimer, mainly in mucus and particularly the intestinal and respiratory mucosa. The main function of IgA is antigen neutralisation [32]. Transforming growth factor (TGF)-β and IL-4 can effectively promote IgA isotype switching [33].

iii. IgM is mainly distributed in the blood and less in the lymph. IgM is effective in activating the complement system and is important for controlling infection [34].

iv. IgE is the immunoglobulin that the body mainly produces when the allergens invade. IgE is relatively low in blood and body fluids and strongly binds to the Fc receptors of the mast cells under the blood vessels, submucosa, and connective tissue [35].

v. IgD is the least among other types of immunoglobulins in the body, and there is no clear biological function discovery [36].

Class switching is mainly caused through the influence of cytokines or antigen secretion, which stimulates B cells to express different Igs. For instance, IL-4, IL-5, IL-10, and TGF, present in GALT, enable B cells to secrete IgA after isotype switching [37, 38]. When B cells isolated from mice were exposed to TGF-β in an in vitro culture, the proportion of IgA secreted by the TGF-β-treated B cells was significantly higher than that secreted by the untreated cells [33]. Through homologous switching, B cells secrete antibodies specific for an antigen and supply it to the appropriate body part in a timely manner. The vertebrate intestinal mucosal immune system secretes a large amount of secretory IgA (sIgA) [39]. In mucus, the proportion of sIgA is higher than that of other antibody isotypes. sIgA mainly neutralises pathogens and limits the entry of pathogens into the body. Mcghee et al. found that coculture of B cells of PP with either IL-5 or IL-6 can promote the differentiation of B cells into IgA-secreting plasma cells [40]. Plasma cells release intact J chain-linked IgA dimers, which bind to the endothelial Ig receptors expressed by intestinal epithelial cells and undergo transcytosis [41]. Piskurich et al. cocultured human colonic cell line (HT-29) with IFN-γ and found that IFN-γ stimulated the expression of the poly-Ig receptor gene in a concentration-dependent manner, as detected through immunofluorescence [42]. In other words, IFN-γ can stimulate the expression of poly-Ig receptors. In mice with poly-Ig receptor gene deficiency, IgA expression in serum is significantly higher than that in normal mice, whereas sIgA expression in the mucosal sites is significantly lower than that in normal mice; taken together, poly-Ig receptor gene defects cause IgA to accumulate in the serum of mice. Thus, poly-Ig receptors are crucial for sIgA expression in the mucosal sites [43–45].

3. Immunomodulation in the mucosal system

In the mucosal system, the immune response is an important reaction regulating the physiological homoeostasis, including immunomodulation, in the whole body. The major mucosal systems controlling the immune response are as follows:

3.1 LP of the intestinal mucosa

The LP of the intestinal mucosa is located below the intestinal epithelial cells and includes various cell types, including Ig-derived plasma cells, T cells, dendritic cells, macrophages, and various cytokines [46]. Under normal conditions, the LP of the intestinal mucosa exhibits high levels of TGF-β [47] and IL-10 [48], which promotes antigen-activated B-cell isoforms. The pathogen enters the LP of the intestinal mucosa from the intestines. The pathogen is recognised by the immune system, and it stimulates B cells to undergo isotype switching to secrete IgA, IgG, and IgM. In a study, rats were administered inactivated *Entamoeba histolytica* through feeding, and IgA, IgG, and IgM were detected in serum and faeces on postfeeding days 2, 4, 6, 8, and 10. IgG and IgM expression in rat serum increased, and IgG and IgA expression in faeces also increased [49].

3.2 PP

PP, located below intestinal epithelial cells, is also the induction sites of the intestinal mucosal immune response [50] and has a high number of B and T cells compared with other lymph nodes [51]. PP contains numerous cytokines, including TGF-β, IL-4, IL-6, and IL-10, which stimulate B cells to secrete Igs [52, 53]. The upper part of PP includes specialised epithelial cells called microfold (M) cells [54]. The antigen in the intestine can enter the lymphoid tissue of the subsequent layer through M cells and initiate an immune reaction. However, the proportion of M cells in the intestine is not high; thus, the ability of M cells to deliver antigens is limited [55]. PP is an indispensable immunotolerance-related tissue, particularly in mice [56].

3.3 MLN

Lymph nodes are tissues located at the junction of the lymphatic system and higher organs [57]. The vast lymphatic vasculature collects lymph from tissues and returns it to the blood. MLNs are the lymph nodes in the intestinal mucosal immune system [58]. When an antigen enters the body through the intestinal mucosal system, it encounters the lymphatic system and is recognised; the antigen-presenting cells are then activated. These cells carry the antigen to the MLN, perform the antigen presentation reaction, and finally activate appropriate T and B cells [59–61].

3.4 Relationship between intestinal immune response and Igs

GALT macrophages have different characteristics from macrophages in other parts of the body; that is, they have good phagocytic and bactericidal abilities [62]. $CD4^+FOXP3^+$ regulatory T (T_{Reg}) cells are located in the regulatory layer of the intestinal mucosa. T cells differentiate into T_{Reg} cells in the presence of TGF-β. The balance between functional T and T_{Reg} cells highly affects the homoeostasis of intestinal mucosal immune response [63].

4. Immunomodulation of macrophages in the immune system

Polysaccharides extracted from mushrooms or algae have immunomodulatory functions, such as increasing macrophage activity, regardless of whether innate or adaptive immunity is activated [64]. For instance, the phagocytic activity of cells, the killing ability of natural killer cells, and the promotion of immune cells to secrete cytokines activate the immune system. In our previous laboratory studies, mushroom polysaccharide administration could enhance the tumour-suppressive and antiallergic ability in mice, along with significant enhancement in the wound-healing ability in rats. Immune cells of the innate immune response, such as macrophages and dendritic cells, or other nonimmune cells, such as epithelial cells, have many nonspecific recognition receptors associated with antigens that evade pathogens. Based on molecular identification and binding, complement receptor type 3 (CR3) on these cells can identify polysaccharides [65]. When polysaccharides bind to CR3, it triggers a series of signalling to activate transcription factors. Cells secrete a cytokine that triggers an inflammatory response, and the antigen exhibits the major histocompatibility complex of the cell, thereby activating other immune cells to achieve immunomodulatory functions [66, 67]. Dectin-1 belongs to the c-type lectin receptor family and is expressed on the cell membranes of macrophages, dendritic cells, neutrophils, and T and B cells [68]. Dectin-1 binds to polysaccharides to promote macrophage phagocytosis and respiratory burst; it also promotes the degranulation of neutrophils and secretion of cytokines and chemokines from immune cells [69–72]. Polysaccharides from *Antrodia camphorata* were cocultured with immature dendritic and T cells isolated from healthy human blood, and the polysaccharides could promote dendritic cell maturation and stimulate T-cell proliferation and IFN-γ performance [73, 74]. Coculture of polysaccharides with macrophages can promote the secretion of immune-related factors and cytokine gene expression, such as nitric oxide (NO), tumour necrosis factor (TNF)-α, IL-1β, and IL-6, to promote macrophage activity [75–78].

Based on our teams' experimental results, the functional polysaccharide can stimulate macrophages and further activate cytokines TNF-α, IL-12, IFN-γ, IL-2, IL-4, IL-10, and IL-17, which are associated with apoptosis and cell cycle. Growth hormone, a multipeptide hormone regulator, promotes growth and cell proliferation [75, 78, 79]. Polysaccharides can reduce CCl_4-induced liver damage by regulating related antioxidant enzymes and effectively reducing oxidative damage in liver tissue [80, 81]. In mice, intraperitoneal polysaccharide injection could effectively prevent lipid peroxidation and inhibit the production of reactive oxygen species in the liver [82, 83]. Taken together, the immunomodulation function of polysaccharides may effectively regulate cellular immune response [84].

5. Immunomodulation of macrophage differentiation

Immune cells are crucial in immune response modulation. As mentioned, macrophages polarise into M1 and M2 macrophages, which have distinct functions and are affected by the physiological microenvironment factors. M1 macrophages perform pathogen elimination through phagocytosis, inflict oxidative damage, and complement system activation. M2 macrophages have tissue recovery functions. Tumour tissues contain considerable amounts of M2 macrophages that release angiogenesis-promoting growth factors.

Inflammatory reactions can induce chronic diseases; thus, reducing inflammation is important for inhibiting chronic disease. To achieve anti-inflammatory effects, immunotherapy is a novel therapeutic approach without known side effects

and drug resistance problems. However, anti-inflammatory processes involve complex reactions; for instance, cellular ROS production for eliminating pathogens can also induce cellular apoptosis [85, 86]. Thus, the balance between inflammatory and anti-inflammatory processes is essential. In case of any imbalance, natural functional materials, such as triterpenoids and polysaccharides, can be applied for immunomodulation.

In summary, polysaccharides can regulate macrophage differentiation to modulate host physiological response through cytokine secretion. Polysaccharides, such as beta-glucan, are known biological response modifiers that can activate leukocytes, monocytes, and macrophages [87, 88]. The activation mechanism involves the polysaccharides binding to the receptors, such as Toll-like receptor, expressed on AMs or Kupffer, Langerhans, mesangial, or microglial cells. After the binding, the immune cells are activated via Toll-like receptor four-mediated signalling pathways to modulate the immune capacity. The activated immune cells then produce IFN-γ, TNF-α, ILs, and other cytokines to modulate the anti-inflammatory process.

In conclusion, the use of the functional materials as alternative medicines in clinical therapy is feasible; however, before implementation, the substance's immunomodulatory mechanism should be clearly realised, particularly in the immune cell signal transduction.

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Conflict of interest

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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