



Review

Macrophages in food allergy: An enigma



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ABSTRACT

Macrophages, the characteristic cell type in inflammatory reactions, participate in a variety of immunological events in humans and other mammals. They act as regulatory switches for both innate and acquired arms of immune system and play a vital role in tissue repair. Recent studies have shown the possible role of macrophages in food allergic reactions. Since, there is involvement of alveolar as well as peritoneal macrophages in the pathogenesis of several food allergies, the present review covers the relevance of macrophage related immunological response in food allergic reactions.

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1. Introduction

The prevalence of food induced allergic manifestations has been found to be increasing since last couple of decades in the developed as well as developing parts of the world. Although food allergy cases were common in the earlier years too; but they were not well characterized. In 99–55 BC, the Roman philosopher and poet Lucretius wrote “What is food to one man may be fierce poison to another” with reference to the adverse effects induced after food consumption. Hippocrates, an ancient Greek physician, had also described some symptoms of seasonal allergic reactions (source: <http://www.doctorsreview.com/history/mar06-history/>). Majority of food allergic reactions are caused by eight foods termed as “Big Eight” including peanut, soybean, tree nut, egg, milk, fish, crustaceans, and wheat (Kumar et al., 2012a). In the recent past significant progress has been made in food allergy research and several foods including lupines, green gram, red kidney beans, chickpea and cherry have been shown to induce allergenic reactions (Verma et al., 2012). Food-induced anaphylaxis is a severe allergic reaction that may encompass multiple organ dysfunction including lungs, spleen, intestine and heart leading to occasional fatal outcomes (Kumar et al., 2012a). Food allergy may induce several clinical symptoms including nasobronchial asthma, allergic rhinitis, atopic dermatitis, swelling of tongue and lips, migraine

and angioedema in the susceptible individuals (Misra et al., 2011; Kumar et al., 2012a). Most of the allergic reactions occur within minutes to hours after the ingestion of allergic food and due to relatively quick onset, it is also known as immediate type I hypersensitivity reaction (Parisi et al., 2013). All the proteins in a food do not elicit immune provocation but, there are some proteins which cause allergic reactions owing to the presence of IgE inducing antigenic sites (epitope) upon them. Following consumption and cellular uptake allergenic food proteins are processed by proteosomal complex and presented on the surface of antigen presenting cells (APCs) like macrophages, B-cells and dendritic cells (DCs). Subsequently, the APCs bearing processed peptides on their major histocompatibility complex (MHC) grooves interact with the naïve T-cells and mold the immune response toward Th1, Th2 or Th17 type (Lafaille, 1998). The allergic reaction is an amalgamated result of interaction between several cytokines, surface receptors and antibodies including, IL-4, IL-13, CD40, MHC-II, and IgE. Several cells or cellular components like T-helper cells, B-cells, natural killer (NK) cells, DCs, neutrophils, eosinophils, neutrophils, Toll-like receptors (TLRs) have been related to food allergic reactions (Kumar et al., 2013; Zaslona et al., 2009). Though acquired immune system plays a major role in the food allergic manifestations mainly via IgE production, nonetheless, innate immunity has also been found to play an important role as well. There are several reports advocating the involvement of non IgE mediated and late phase allergic reactions in food allergy (Kalach et al., 2012). However, the role of macrophages in food allergy has not been explored thoroughly, till date. In this review attempts have been made to reveal the possible role of macrophages in food allergy by correlating the current knowledge and future perspectives.

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2. Macrophages and food allergy

Macrophages, one of the most important constituents in host defense, play a conspicuous role in innate and acquired immunity. They are the major component of the mononuclear phagocyte system that comprises closely related cells of bone marrow origin, including blood monocytes, and tissue macrophages (Oh et al., 2012). Monocytes from blood migrate into various tissues and transform into macrophages (Murray and Wynn, 2011). Earlier, macrophages were largely thought to contribute in destructive processes like tissue injury and inflammation under stress conditions, but lately, extensive studies have revealed a significant role of macrophages in the suppression of inflammation and wound repair (Jones, 2000). Thus, the ultimate homeostasis of immune response is governed by the balance of aforesaid opposite functions of macrophages. It can therefore be presumed that macrophages act as a principal site of immune regulation, assisted by several membrane receptors on their surface (Mahida, 2000). During an inflammatory response, macrophages demonstrate three major functions – (i) phagocytosis; (ii) antigen presentation; and (iii) immuno-modulation through production of various cytokines and growth factors (Fujiwara and Kobayashi, 2005). During the inflammatory processes macrophages get activated by several factors including interferon-gamma (IFN- γ), granulocyte-macrophage colony-stimulating factor (GM-CSF), tumor necrosis factor-alpha (TNF- α), bacterial lipopolysaccharide (LPS), and extracellular matrix proteins (Duffield, 2003). Moreover, activated macrophages may get deactivated by anti-inflammatory cytokines like interleukin-10 (IL-10) and transforming growth factor-beta (TGF- β) which are produced by macrophages, Th1 cells, regulatory T-cells and certain subsets of activated T-cells and B-cells (Kitamura, 1998; Sabat et al., 2010). Since, macrophages produce a wide range of biologically active molecules participating in both beneficial and hazardous responses, therapeutic intervention strategies for targeting macrophages and their products may open new avenues for controlling several immunological disorders (Duffield, 2003). The macrophages stimulate the proliferation and activation of T-cells which is facilitated by physical interaction between T-cells and macrophages presenting antigenic peptides on MHC grooves (Reimann and Kaufmann, 1997). T-helper (Th) cells, then activate B-cells through the formation of an immunological synapse, finally culminating into secretion of antibodies by B-cells. Macrophages may be involved in the immune response to dietary antigens by participating either in induction of oral intolerance or allergic sensitization. In food allergy, mast cells and basophils release allergic mediators like histamine, cysteinyl leukotrienes, mast cell proteases and prostaglandins. Mast cells and basophils have specific receptors like Fc ϵ RI, which on ligation with IgE triggers cell signaling events which ultimately leads to allergic manifestations. The macrophages express Fc ϵ RII surface receptor, which has low affinity to IgE in comparison to Fc ϵ RI receptor (Acharya et al., 2010; Kumar et al., 2012b). However, the involvement of macrophages in allergy via Fc ϵ RII receptor stills turns out to be an unresolved puzzle and they could be involved in alleviation or downregulation of allergic phenomenon. Further, macrophages may have an important role in the oral tolerance induction against the food allergens. The T-cell immunoglobulin and mucin domain (Tim) gene family expressed on many types of immune cells including T cells, B cells, dendritic cells, macrophages, and mast cells; have been shown to be involved in asthma, allergic rhinitis, food allergy, and autoimmunity (Li et al., 2013). The presence of Tim in macrophages has also revealed the possibility of their involvement in food induced allergic reactions. In a murine model with peanut allergy, it has been reported that the single deletion of either mast cells, basophils, or macrophages prevents the severity of allergic reactions including death (Arias

et al., 2011). The combined deficiency of macrophages and mast cells averted nearly all the clinical and physiological signs of anaphylaxis. The blockade of both IgE and IgG1 signaling has been shown to be necessary to abolish anaphylactic responses of peanut. The mast cell responses were found to occur through the IgE and IgG1 mediated reactions only, whereas the phagocytic responses were observed to be IgG1 mediated (Arias et al., 2011). Moreover, it has been reported that HLA-DR (a MHC class II cell surface receptor encoded by the human leukocyte antigen complex) expression in breast milk macrophages was significantly lower in the mothers whose infants were allergic to cow milk, than in the mothers of a healthy infant (Järvinen et al., 1999). Further, a significant difference was observed in the total number of leukocytes present in the breast milk of mothers with an allergic child as compared to those with a healthy child (Järvinen et al., 1999).

2.1. Alveolar macrophages in food allergy

Alveolar macrophages, the predominant cells of the airway space, are involved in various types of inflammation and other immunological reactions. Microarray analysis of the alveolar macrophages isolated from bronchioalveolar lavage (BAL) explored 50 differentially expressed genes. Out of these genes, 19 were linked to the stress or immune responses and 9 were related to heat shock proteins (HSPs). The involvement of HSP gene family, particularly HSP60, has been shown to play a pivotal role in allergic asthma (Madore et al., 2010). A significant difference in the HSP60 protein level expressed in alveolar macrophages of allergic and control subjects has also been reported (Madore et al., 2010). However, elaboration of the precise role of HSP60 in the allergic responses needs further investigation. The pulmonary alveolar macrophages have also been reported to play an important role in the maintenance of immunological homeostasis of lungs via down modulation of local T cell responses in the steady state, although, this pathway for T cell suppression is reversible via granulocyte/macrophage colony stimulating factor (GM-CSF) (Bilyk and Holt, 1995). These results suggest that secretion of GM-CSF by macrophages under stimulation of agents like LPS provides a potential mechanism for up regulation of local T cell responses during acute inflammation. In addition, cytokines like IL-4, TGF- β and TNF- α , which are also known to play a key role in allergy exhibit a weak but significant modulatory effects, inducing nitric oxide (NO) production and lymphocytostatic activity in pulmonary alveolar macrophages (Bilyk and Holt, 1995). It has been reported that following alveolar macrophages depletion, pre-sensitized animals respond to aerosol challenge via secondary serum IgE responses, and the accumulation of large numbers of allergen-specific and non-specific antibody forming cells in respiratory tract regional lymph nodes, lungs and airway tissues (Tenor et al., 1992). Moreover, an increased number of activated alveolar macrophages have been reported in the airways inflammation in cases of asthma (Tenor et al., 1992). In response to an inflammatory stimuli, there is upregulation of adhesion molecules on macrophages which facilitate cell-cell contacts between leukocytes and endothelial cells or with other leukocytes. The expressions of two adhesion molecules namely intercellular adhesion molecule-1 (ICAM-1) and endothelial leukocyte adhesion molecule-1 (ELAM-1) in alveolar macrophages recovered in BAL from normal subjects and asthmatic patients have been studied by Chanez et al. (1993). This study showed an increase in percentage of cells expressing ICAM-1 or LFA-1 in asthmatic patients as compared to normal subjects. The study highlights the importance of alveolar macrophages in the inflammation during asthma and suggests that macrophage

interactions with other cells play a crucial role in inflammatory reactions (Chanez et al., 1993).

2.2. Peritoneal macrophages in food allergy

The gut immune system, also known as Gut Associated Lymphoid Tissue (GALT) has evolved mechanisms to discriminate between harmless antigens, commensal microorganisms and dangerous pathogens (Palová-Jelínková et al., 2005). It is associated with mucosal surfaces covering the largest area of the body (200–300 m²). There is a single layer of columnar epithelium that separates lumen filled with dietary, bacterial and viral antigens from lymphocyte rich environment of loose connective tissue stroma (lamina propria), which possesses abundance of plasma cells, T-cells, B-cells and DCs. Many chronic diseases, including allergy, may occur as a result of genetically or environmentally induced changes in mucosal immunity and tolerance which leads to impaired mucosal barrier function, disturbed exclusion and increased penetration of microbial, food or airborne antigens into the circulation and consequently leading to exaggerated immune responses to antigens, allergens, super antigens and mitogens (Tlaskalová-Hogenová et al., 2002). In humans and mice, mutations in the genes that control innate immune recognition, acquired immunity, and epithelial permeability have been found to be associated with gut inflammation. This suggests that perturbing homeostasis between gut antigens and host immunity represents a critical determinant in the development of gut inflammation and allergy (MacDonald and Monteleone, 2005). When an allergen is recognized as a foreign substance, it is engulfed by WBCs including macrophages. These macrophages act as APCs and present the antigen to T-helper (Th) cells, thereby getting activated and releasing an array of cytokines depending upon the nature of foreign antigen. The Th cells then stimulate humoral arm of the acquired immunity comprising of B cells. The B cells secrete antibodies in response to foreign substances and ultimately these antibodies help in neutralization and disposal off the allergen.

Till date, information on the role of peritoneal macrophages in IgE-dependent allergic reactions and oral tolerance is not very clear and needs thorough elucidation. It has been reported that OVA sensitized New Zealand rabbits had histopathological modifications of the digestive tract mucosa in different regions along with a high infiltration of peritoneal macrophages (Fontanella et al., 2005). The localization of peritoneal macrophages was found to be significantly enhanced in caecal appendix. The observed increase in cells is probably related to enhanced recruitment of monocytes from peripheral blood toward the appendix. This process could be induced by chemical mediators, and demonstrates the participation of macrophages in local intestinal immune response during sensitization phenomena (Fontanella et al., 2005). Peritoneal macrophages are normally present within the GI tract in areas close to specialized lymphoid tissue, separated from the epithelium by a basal membrane and intimately associated to a rich network of capillaries, nerve endings and lymphatic vessels. These cells express membrane receptors for intestinal mediators and release products like prostaglandins, cytokines and chemokines that in turn influence the activities of adjoining cells (Fontanella et al., 2005). The peritoneal macrophages also constitute a critical element in the effectors phase of immune reactions, by secretion of several proinflammatory or anti-inflammatory mediators (Kang et al., 2005). Majority of the peritoneal macrophages in intestinal mucosa exhibit a mature phenotype, but the information regarding their precise role is obscure. The subpopulations of peritoneal macrophages may function to exacerbate the allergic reaction or alternatively may act for containment of inflammation as a counter regulatory measure. Platelet-activating factor

(PAF), a phospholipid mediator of anaphylaxis, is released from basophils of several mammalian species, that aggregates platelets and releases their vasoactive amines. Besides blood basophils, peritoneal macrophages are a likely source for PAF, which adds a new dimension to macrophage function in allergy (Mencia-Huerta and Benveniste, 1979).

3. Macrophages in oral tolerance

Tolerance to food antigens locally in the gut without compromising with pathogen-specific immune responses is a phenomenon known as oral tolerance. Oral tolerance could be an outcome of clonal anergy of responsive antigen specific T or B-cell populations, which may be accompanied by coherent activation of regulatory populations like Treg cells (Kumar et al., 2012b). The APCs like macrophages and DCs have been found to be the critical switches, which mold the mucosal immune response against dietary antigens and commensal microflora toward tolerance rather than antigenicity. The phenomenon is thought to originate in the gut-draining lymph nodes, which support the generation of FoxP3 (+) regulatory T (Treg) cells (Hadis et al., 2011). It has been reported that proliferation of Treg cells in the intestine and production of IL-10 by gut-resident macrophages was blunted in mice deficient in chemokine (C-X3-C motif) receptor 1 (CX3CR1) (Hadis et al., 2011). Oral tolerance induction comprises the generation of Treg cells in the gut-draining lymph nodes, followed by migration into the gut and subsequent expansion of Treg cells driven by intestinal macrophages (Hadis et al., 2011). In mice suffering from colitis, it has been reported that IL-10 produced by CD11b⁺ myeloid cells may act on Treg cells to maintain Foxp3 expression (Murai et al., 2009). Denning et al. (2007) observed that a population of CD11b⁺F4/80⁺CD11c[−] macrophages was found to be present in the lamina propria that expressed several anti-inflammatory molecules, including IL-10. These macrophages induced the differentiation of Foxp3⁺ regulatory T cells by a mechanism dependent on IL-10, retinoic acid and exogenous TGF- β . In contrast to CD11b⁺F4/80⁺CD11c[−] macrophages, lamina propria CD11b⁺DCs produce IL-17 but it could be suppressed by lamina propria macrophages, indicating a dynamic interaction between these subsets which may influence the balance between immune activation and tolerance (Denning et al., 2007). The CD11b, a CD18 subfamily of integrin receptors is found on APCs in a significant proportion and participate in the regulation of oral tolerance phenomenon. It has been demonstrated that oral tolerance was defective in CD11b knockout (CD11b^{−/−}) mice and was subsequently restored by adoptive transfer of wild-type APCs (Ehrichtiou et al., 2007). It was observed that CD11b deficiency in APCs leads to enhanced IL-6 production which ultimately promotes preferential differentiation of naive T cells to Th17 cells (Ehrichtiou et al., 2007). Subsequent antigen feeding and immunization of CD11b^{−/−} mice showed significantly enhanced production of IL-17 within the draining lymph nodes. The enhanced number of Th17 cells interfere with the establishment of oral tolerance. Considering the outcome of the study, CD11b was found to facilitate the induction of oral tolerance by suppressing Th17 immune differentiation. At the same time the impaired CD11b may induce the allergic sensitization. Sublingual allergen-specific immunotherapy (SLIT) is a safe and efficacious treatment for type 1 allergies induced by several allergens including OVA. In a study using fluorochrome-labeled OVA it was observed that OVA was predominantly captured by oral CD11b⁺CD11c[−] cells (Mascarelli et al., 2011). CD11b⁺CD11c[−] cells found in the lamina propria of the small intestine resemble tolerogenic macrophages since they express the mannose receptor CD206, as well as class-2 retinaldehyde dehydrogenase (RALDH2); and further support the

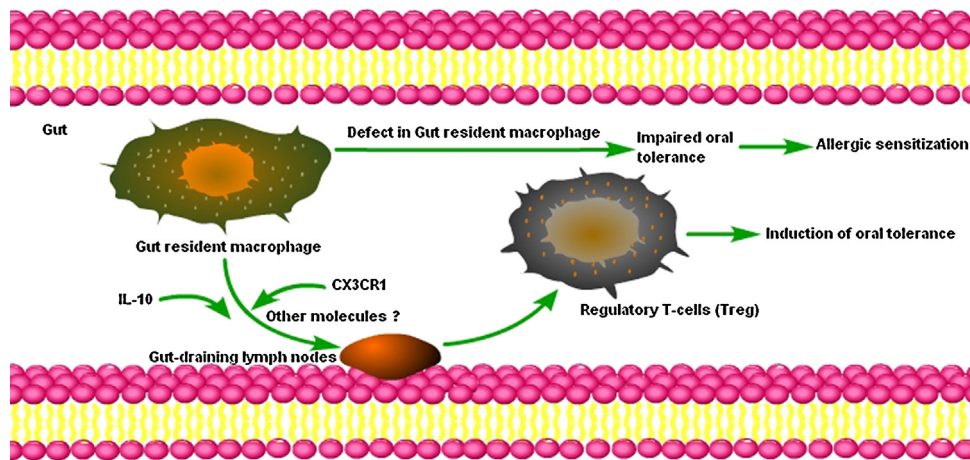


Fig. 1. Diagrammatic representation showing the possible involvement of the gut resident macrophages in the oral tolerance as well as allergic sensitization. Where, IL-10 = interleukin-10 and CX3CR1 = chemokine (C-X3-C motif) receptor 1.

differentiation of IFN γ /IL-10-producing Foxp3⁺CD4⁺ regulatory T cells (Tregs). Thus, among the various APC subsets present in gastro intestinal tract tissues of mice, macrophage-like cells play a key role in tolerance induction following SLIT (Mascarell et al., 2011). The lung interstitial macrophages, a cell population with no previously described in vivo function, prevent induction of a Th2 response in mice challenged with LPS and an experimental harmless airborne antigen. Bedoret et al. (2009) have shown that interstitial macrophages, but not alveolar macrophages, were found to produce high levels of IL-10 which inhibited LPS-induced maturation and migration of DCs loaded with the antigen in an IL-10-dependent manner. Specific in vivo elimination of interstitial macrophages led to overt asthmatic reactions to innocuous airborne antigens inhaled with low doses of LPS (Bedoret et al., 2009). Figs. 1 and 2 demonstrate the probable role of different macrophages in the induction of oral tolerance and allergic sensitization.

4. Immune molecules associated with macrophage during food allergy

Several immune mediators have been reported to be secreted by macrophages in the different immune reactions (Table 1). Macrophage migration inhibitory factor (MIF) regulates action within the immune system and also possess a direct proinflammatory role in several diseases including allergy (Luea et al., 2002). Mizue et al. (2005) studied the role of MIF's in asthma using genetic approaches in a mouse model and extended the investigation in a cohort of asthma patients. This study revealed that mice genetically deficient in MIF when challenged with OVA showed reduced pulmonary inflammation and airway hyperresponsiveness than genetically matched, wild-type controls. MIF deficiency also resulted in low titers of specific IgE, IgG1, IgG2a, and decreased pulmonary Th2 cytokine levels (Mizue et al., 2005). In a study carried out on 151 white patients having mild, moderate or severe asthma, a significant association was found between mild asthma and low-expression of MIF allele (Mizue et al., 2005). Polymorphisms in the MIF promoter region have been reported as one of the risk factors in the pathogenesis of atopy in a Japanese population (Hizawa et al., 2004). Shimizua et al. (1997) have reported that MIF plays an important role in the pathogenesis of atopic dermatitis (AD) and delayed-type hypersensitivity (DTH). It was observed in this study that the mean serum MIF concentration in the AD patients were 36.4 ± 3.7 ng/ml, however in healthy individuals it was found to be 13.1 ± 1.8 ng/ml. Further, immunohistochemical study of the

inflammatory skin lesion in AD patients demonstrated that MIF protein was diffusely expressed throughout the whole epidermal layer (Shimizua et al., 1997).

Macrophage inflammatory protein (MIP) is a chemokine produced by several cell types including macrophages and DCs. The MIP-1 α (CCL3) and MIP-1 β (CCL4) are the two major subtypes of MIP produced by macrophages in humans (Sherry et al., 1988). The genes for MIP in humans have been shown to be located on chromosome 17 (Irving et al., 1990). MIP has been reported to activate granulocytes which in turn enhances the synthesis and release of other pro-inflammatory cytokines including IL-1,

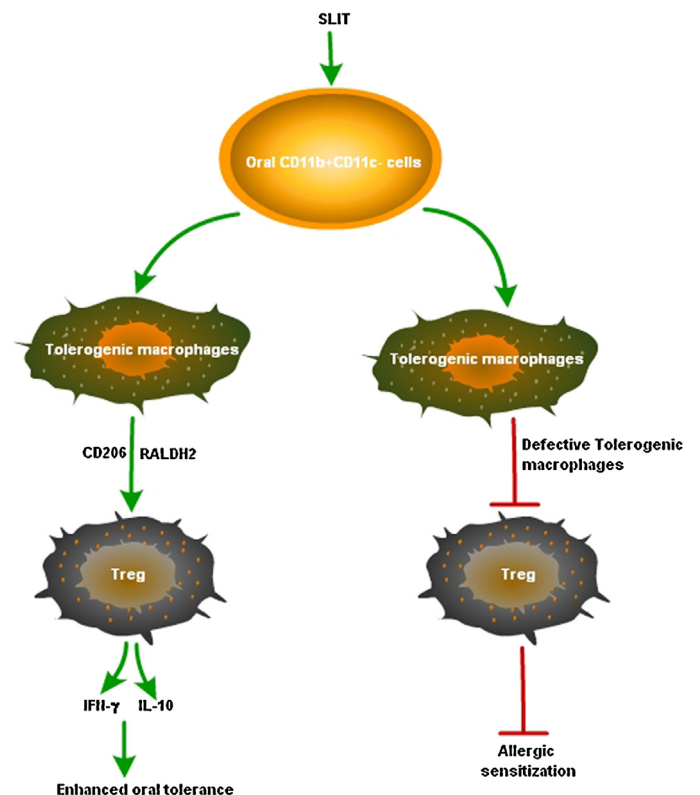


Fig. 2. Pictorial illustrations of pivotal role of tolerogenic macrophages in the sublingual immunotherapy (SLIT). Where, RALDH2 = class-2 retinaldehyde dehydrogenase, Treg = regulatory T-cells, IFN- γ = interferon- γ , IL-10 = interleukin-10.

Table 1
Immune mediators secreted by macrophages and its functions.

S.N.	Mediator	Function
1.	MIP-1 α or CCL3	MIP-1 α is highly related members of the CC chemokine subfamily a novel activator of basophils and mast cells (Alam et al., 1992; Menten et al., 2002).
2.	MIP-1 β or CCL4	Like MIP-1 α , MIP-1 β is highly related members of the CC chemokine subfamily (Menten et al., 2002). The recruitment of regulatory T cells (Tregs) to B cells (Bregs) and antigen presenting cells (APCs) by MIP-1 β plays a central role in the normal initiation of T cell and humoral responses (Bystry et al., 2001).
3.	MIF	The MIF plays a role in the initiation and maintenance of allergic rhinitis. Its level is correlated with the severity of the clinical symptoms of AR (Nakamaru et al., 2004).
4.	ICAM-1	The expression of ICAM-1 in the lamina propria of patients with food allergy has been found substantially increased (Veres et al., 2001). The high proportion of ICAM-1-expressing cells was associated with gastrointestinal and multiorgan symptoms in the cow milk allergy infants (Österlund et al., 2003).
5.	ELAM-1	The ELAM-1 has been reported to be increased in the allergic inflammation. Its up-regulation on vascular endothelium found to be associated with late cutaneous responses to allergen. Its role in the certain primate models of asthma has been reported as well (Arm and Lee, 1992).
6.	CX3CR1	CX3CR1 regulates proliferation of Treg cells in the intestine and production of IL-10 by gut-resident macrophages (Hadis et al., 2011).
7.	ILs	Macrophages are reported to secrete cytokines like TNF-alpha, IL-1beta, IFN-alpha/beta, IL-6, IL-10, IL-12 and IL-18 (Hadis et al., 2011).

Where: MIP=macrophage inflammatory proteins; MIP-1 α or CCL3=macrophage inflammatory proteins; MIP-1 β or CCL4=macrophage inflammatory proteins; MIF=macrophage migration inhibitory factor; IL-6=interleukin-6; TNF- α =tumor necrosis factor; ICAM-1=intercellular adhesion molecule-1; ELAM-1=endothelial leukocyte adhesion molecule-1; CX3CR1=the chemokine (C-X3-C motif) receptor 1; ILs=interleukins.

IL-6 and TNF- α from fibroblasts and macrophages (Irving et al., 1990). To explore the effect of MIP-1 α on histamine secretion from basophils and mast cells, a study was carried out by Alam et al. (1992) on leukocytes from allergic and normal subjects (Alam et al., 1992). It was observed that MIP-1 α caused dose-dependent release of histamine from basophils in 70% allergic donors. Furthermore, histamine release by MIP-1 α in these patients was relatively fast, which occurs within the first 3 min. Murine MIP-1 α has also been found to enhance histamine release from mouse peritoneal mast cells (PMMCs) in a dose-dependent manner. In vitro studies showed that MIP-1 α is required for optimal mast cell degranulation, along with cross-linking of the high-affinity IgE receptor Fc ϵ RI, indicating the possibility of MIP-1 α as a co-stimulatory signal for mast cell-mediated immediate hypersensitivity reactions (Miyazaki et al., 2005). The role of MIP-1 β has not explored so far in food allergic reactions, although its role in the allergic lung inflammation has been well documented (Katoh et al., 2000).

Cytokines are important cell-signaling protein molecules, secreted by numerous cells and participate extensively in inter-cellular communications. Several cytokines mainly Th2 type have been found to be involved in food allergic reactions (Kumar et al., 2012b). There may be a significant role of macrophages in the modulation of food allergy response via secretion of key cytokines. For example, in patients exhibiting a late phase allergic reaction, alveolar macrophages collected after 18 h of bronchial allergen challenge, showed high levels of IL-6 and TNF- α (Broide et al., 2000). These cytokines are known to up-regulate the endothelial cell expression of adhesion molecules participating in the development of inflammatory reaction in bronchial asthma (Broide et al., 2000). Lassalle et al. (1993) studied the effect of alveolar macrophage supernatants from asthmatic patients on the expression of adhesion molecules, ICAM-1 and ELAM-1 by human endothelial cells. In this study, alveolar macrophages-derived TNF was found to play a key role in endothelial cell stimulation. The TNF concentration in alveolar macrophages was directly correlated to ICAM-1 and ELAM-1 expression by endothelial cells and a neutralizing anti-TNF antibody was found to decrease the endothelial cell stimulation. It was concluded that beside mast cells and lymphocytes, macrophages may also participate in the induction of the bronchial asthma (Lassalle et al., 1993). In another study, Lactobacilli isolated from Kimchi (Korean traditional dish), was tested for its

capacity to modulate Th1/Th2 balance and it was elucidated that Lactobacilli from Kimchi may modulate the Th1/Th2 balance via macrophages activation in the hypersensitivity reaction (Won et al., 2011).

5. Conclusion

In conclusion, recent studies revealed the possible role of macrophages in food allergic manifestations, but to date comprehensive investigations deciphering their precise role in food allergy are lacking. Considering the enormous plasticity exhibited by macrophages in their functional phenotypes, the current state of art suggests a dichotomous role of macrophages in food allergy which could either be related to regulatory or proinflammatory processes. Taken together, further in depth elaboration is required to understand the explicit role of macrophages in food allergy which may lead to significant diagnostic as well as therapeutic intervention strategies.

Conflict of interest

The authors have declared that there is no conflict of interest.

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