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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.

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 angiodema 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, nutrophils, eosinophils, nuocytes, Toll-like receptors (TLRs) have been related to food allergic reactions (Kumar et al., 2013; Zasłona 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 FcεRI, which on ligation with IgE triggers cell signaling events which ultimately leads to allergic manifestations. The macrophages express FcεRII surface receptor, which has low affinity to IgE in comparison to FcεRI receptor (Acharya et al., 2010; Kumar et al., 2012b). However, the involvement of macrophages in allergy via FcεRII receptor stills turns out to be a 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