An Overview of Cluster of Differentiation 14 (CD14) and its Possible Roles in Allergic Diseases

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Abstract
Allergic rhinitis (AR) is a common condition. Estimates of its prevalence vary widely but good epidemiologic studies suggest that 20 to 30% of adults and up to 40% of children are affected[1]. Symptoms can have significant negative impact on the patients quality of life, often interfere with sleep, and contribute to poor performance at work and school. In approaching the patient with rhinitis symptoms, clinicians must distinguish AR from non-AR (NAR) and nasal symptoms due to mechanical factors but not miss the presence of local nasal allergy. Treatment for more severe disease should employ anti-inflammatory as well as symptomatic medication, and allergy immunotherapy (AIT) should be strongly considered for not only its effectiveness but also its disease-modifying effects. The main challenges in AR relate to its treatment. Symptomatic and topical anti-inflammatory medication is often not fully effective, and AIT can be inconvenient and expensive, and there is much room for improvement in both forms of treatment. The cluster of differentiation (CD14) is a human gene. The protein encoded by this gene is a glycosylphosphatidylinositol (GPI)- anchored molecule expressed mainly on cell surface of macrophages and monocytes. The x-ray crystal structure of human CD14 protein shows a monomeric, bent solenoid molecule with a hydrophobic amino-terminal pocket that can bind to many acylated ligands. CD14 acts as a pattern recognition receptor that promotes innate immune responses to infection by sensitizing host cells to bacterial LPS (endotoxin), lipoproteins, lipoteichoic acid, and other acylated microbial products. It allows delivery of these microbial products to many TLR signaling complexes which then induce intracellular proinflammatory signaling cascades after ligand binding. Many research works have studied the role of CD14 in different allergic phenotypes. Results of these studies were controversial, as some studies have found that the sCD14 level in certain allergic diseases was significantly higher in periods of illness than its level at recovery period. While other studies reported inversely relationship between serum sCD14 level and certain allergic phenotypes. Also, up till now, few studies have focused on the association between serum sCD14 level and the severity of allergic diseases
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Introduction:

Allergic rhinitis (AR) is a common condition. Estimates of its prevalence vary widely but good epidemiologic studies suggest that 20 to 30% of adults and up to 40% of children are affected. Symptoms can have significant negative impact on the patients' quality of life, often interfere with sleep, and contribute to poor performance at work and school. In approaching the patient with rhinitis symptoms, clinicians must distinguish AR from non-AR (NAR) and nasal symptoms due to mechanical factors but not miss the presence of local nasal allergy. Treatment for more severe disease should employ anti-inflammatory as well as symptomatic medication, and allergy immunotherapy (AIT) should be strongly considered for not only its effectiveness but also its disease-modifying effects. The main challenges in AR relate to its treatment. Symptomatic and topical anti-inflammatory medication is often not fully effective, and AIT can be inconvenient and expensive, and there is much room for improvement in both forms of treatment. **(1).**

A Medline search retrieved original studies from 2005 to 2015 on the impact of AR on work productivity. Pooled analysis of studies in which the validated Work Productivity and Activity Impairment (WPAI) questionnaire had been used to collect data found an estimated 3.6% of missed work time (absenteeism) and 35.9% of work performance impairment (presenteeism) due to AR. The cost of absenteeism and presenteeism was estimated to be 3.2- to 13.5-fold higher than direct medical costs and to represent 76 to 93% of the total costs of AR. School performance is also affected by AR. In a case control study in the UK, students who were 15 to 17 years of age and currently symptomatic with AR were significantly more apt to have lower examination scores in the summer compared with the winter. The cost of AR was assessed in a representative sample of the Swedish population (18 to 65 years of age) in a report published in 2016. The mean annual direct and indirect costs because of AR were 210 Euros and 750.8 Euros, respectively. Of the total cost, 8.1% was due to absenteeism and 70.0% was due to presenteeism. The remainder was equally divided between pharmaceutical and health-care costs. The cost for the European Union countries for absenteeism and presenteeism caused by AR in untreated or inadequately treated individuals has been estimated at 55 to 151 million Euros per year **(1).**

Immunopathogenesis of Allergic Rhinitis:

1- Sensitization to allergens

AR is an IgE-mediated disease, triggered by exposure to environmental allergens. Those allergens are usually proteins and glycoproteins that come from airborne particles including pollens,

dust mites, insect feces, animal dander and molds. Sensitization rates vary between populations according to the host genetic factors and the type of allergens to which the patient is exposed **(2)**.

Clinical expression of the disease is a result of a cascade of immunological and biochemical events. Allergens are inhaled, superimposed to nasal mucosa, and diffuse into nasal tissues. Then, antigen-presenting cells (APCs) break antigens into antigenic peptides and migrate to lymph nodes to present the peptides to naïve CD4+ T lymphocytes (T cells) **(3)**.

The process of activation of CD4+ T lymphocytes includes the interaction of specific surface T-cell receptors with allergen MHC class II complexes on the APCs. Dendritic Cells (DCs) and signals from antigen presentation assist in the differentiation of naïve T helper cells into Th2 **(4)**.

Th2 lymphocytes activate the production of specific cytokines such as IL-4 that sustains Th2 cells. Th2 cells also produce IL-13 and prompt CD40 ligand (CD40L), which with IL-4 promotes heavy-chain class switching in B lymphocytes allowing the synthesis of IgE antibodies from B-cells **(3).**

IgE antibodies have the ability to bind to high-affinity receptors on the surface of dendritic cells, low-affinity receptors on monocytes-macrophages and B-lymphocytes and on high-affinity tetrameric receptors FcεRl on mast cells and on basophils. The latter interaction induces the cellular allergic reaction and the activation of several signaling cascades. One of these leads to granule exocytosis and release of preformed or newly created inflammatory mediators (such as histamine, leukotrienes, prostaglandins, platelet-activating factor, etc.) **(3).**

Recent studies reported that nasal allergen challenge also leads to an increase in T cells that express the prototypic Th2 chemokine receptor CCR4 and increased numbers of the Th2 transcriptional factors STAT6 and GATA3 in T cells and an increase in the ratio of GATA3:T-bet-T cells in the nasal mucosa of AR patients compared to healthy people **(5)**.

This agrees with the studies which reported that exaggerated Th2 responses observed in pathogenesis of AR may be due to dysregulation of Th1 transcription factors **(6)**.

The previous theory of Th1/Th2 imbalance promoted AR is supported by identification of new T-helper families, such as regulatory T cell (Treg), Th17 and Th9 **(7)**.

Treg cells play major role in preventing T helper 2 (Th2) differentiation, controlling airway inflammatory response, and inhibiting inappropriate Th2 responses to different aeroallergens. This is done by their contact with immune cells or by producing anti-inflammatory cytokines such as interleukin (IL)10 and transforming growth factor (TGF)-beta **(8)**.

2- Phases of nasal allergic reaction

The nasal allergic reaction is distinguished in early and late phases. The symptoms of early phase begin almost immediately after exposure to the responsible allergen, arrive at a peak in a few minutes, and subside within one to several hours **(4)**.

Within minutes from the exposure, the interaction between IgE and allergen leads to degranulation of mast cells and release of inflammatory mediators such as leukotrienes, prostaglandins, cytokines, and histamine. These molecules are responsible for symptoms such as sneezing, itching, nasal discharge, and nasal congestion. Histamine binds with H1 receptors and provokes all symptoms of the early phase **(4)**.

During the late phase, the most dominant symptom is nasal congestion. The mediators that have been released in the early phase stimulate the infiltration of nasal mucosa by basophils, eosinophils, neutrophils, mast cells and mononuclear cells. The mast cells have been found to play a major role not only in the allergic response but also in maintaining the allergic response chronically **(9)**.

This is mainly related to the fact that mediators released by mast cells degranulation play an important role in the recruitment of Th2 lymphocytes to target organs **(9)**.

The cysteinyl leukotrienes are mainly responsible for the activation of eosinophils. Eosinophils are predominant in the late phase response and are associated with the progression of allergic symptoms. Proinflammatory mediators, cationic proteins, eosinophil peroxidase, and cysteinyl leukotrienes are released from eosinophils **(10 ;9)**.

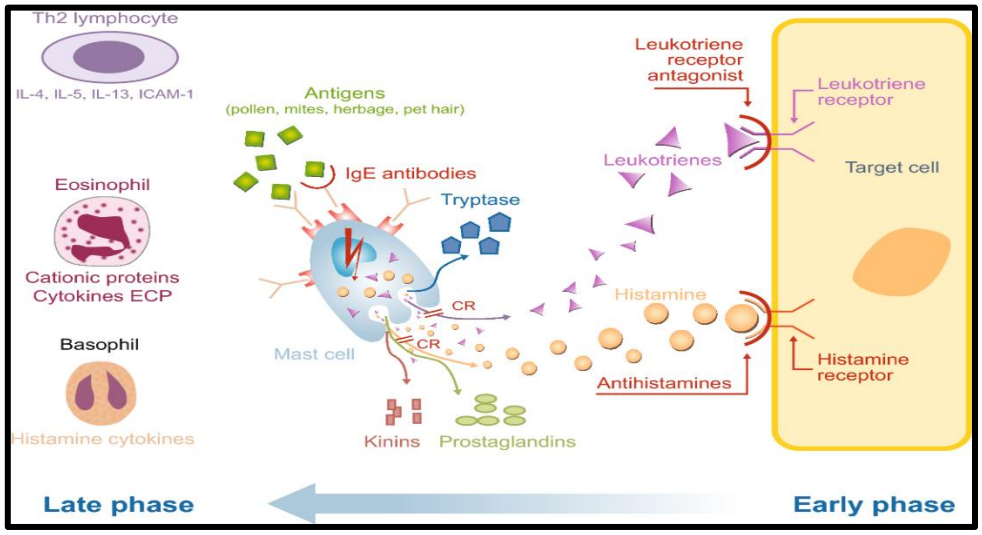

Figure 1: Early and late phases showing the pathophysiological processes and drivers of allergic rhinitis **(11)**.

Cluster of Differentiation 14 (CD14)

Structure:

The cluster of differentiation (CD14) is a human gene. The protein encoded by this gene is a glycosylphosphatidylinositol (GPI)- anchored molecule expressed mainly on cell surface of macrophages and monocytes. The x-ray crystal structure of human CD14 shows a monomeric, bent solenoid molecule with a hydrophobic amino-terminal pocket that can bind to many acylated ligands **(12).**

Tissue distribution:

CD14 is expressed as a membrane form (mCD14) on cell surfaces of macrophages, neutrophils and dendritic cells. It can be secreted into the medium in a soluble form (sCD14) which is secreted mainly by the liver and monocytes. The soluble form is also identified in the human breast milk with subsequent effects in the breastfed baby **(13).**

Functions and signaling pathways of CD14:

CD14 acts as a pattern recognition receptor that promotes innate immune responses to infection by sensitizing host cells to bacterial LPS (endotoxin), lipoproteins, lipoteichoic acid, and other acylated microbial products. It allows delivery of these microbial products to many TLR signaling complexes which then induce intracellular proinflammatory signaling cascades after ligand binding (**14).**

CD14 was identified as a co-receptor for TLR in detection of pathogen-associated molecular patterns (PAMPs). However, in the last decade, CD14 was considered to activate NFAT, regulating the life cycle of myeloid cells in a TLR4-independent manner. It also transports inflammatory lipids to induce phagocyte hyperactivation **(15).**

CD14, together with TLR4 and MD-2, constitute a multi-receptor complex that can recognize LPS on the cell membrane. The primary role identified for CD14 in LPS recognition was promoting the sensitivity of the innate immune cells to this inflammatory stimulus. CD14 is capable of binding LPS at very low concentrations allowing its delivery to the TLR4-MD2 complex for the initiation of the transduction pathway **(16).**

TLR4 is a specialized receptor that can engage all four adaptors (TIRAP, MyD88, TRAM and TRIF). Therefore, it is the only TLR that can activate both the TIRAP-MyD88-dependent pathway and the TRAM-TRIF-dependent pathway leading to the secretion of type-I interferons (IFNs) **(17).**

In the presence of LPS, CD14 and TLR4-MD2 are engaged together inside lipid rafts. After translocation into those lipid rafts, TLR4 activates the TIRAP-MyD88-dependent pathway, which leads to activation of NF-kB. Subsequently, the entire receptor complex, including CD14, is internalized and redirected into the endosome from which the activation of the TRAM-TRIF pathway begins **(18).**

In addition to the previously mentioned signaling pathways, CD14 has TLR4-independent signal transduction pathway in myeloid cells, such as DCs. After LPS stimulation, CD14 activates src

family kinase (SFK) and PLCγ 2 which in turn, hydrolyzes membrane phosphatidylinositol bisphosphate (PIP2) generating inositol-triphosphate (IP3) and dyacylglycerol (DAG) leading to an increase in intracellular Ca^{2+} concentration and activation of the phosphatase Calcineurin. Cytoplasmic NFAT transcription factors are subsequently dephosphorylated and migrate to the nucleus as shown in **(12).**

The importance of CD14-NFAT pathway in LPS-activated DCs include regulation of IL-2, production of prostaglandin E_2 (PGE_2) and induction of a proapoptotic pathway in terminally differentiated DCs **(12).**

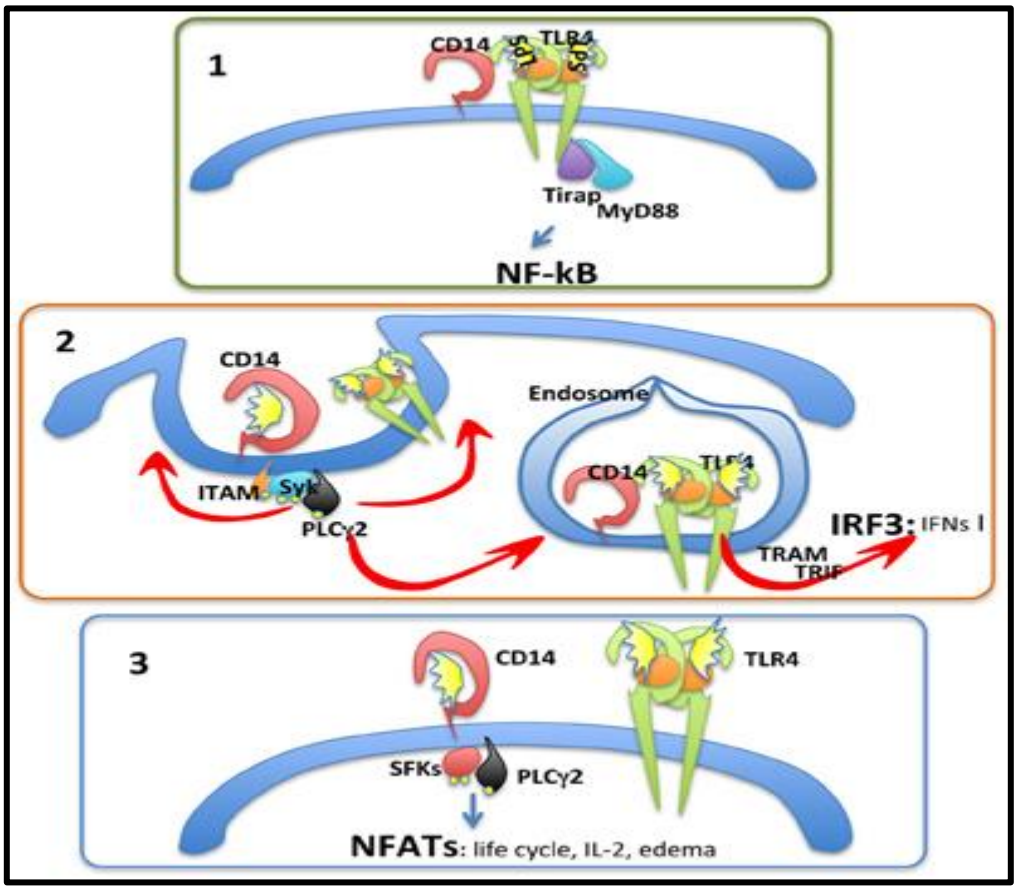

Figure (2): CD14 has 3 main functions. In panel 1, CD14 stimulates NF-kB-dependent cytokine production by recognizing low LPS doses. In panel 2, CD14 allows TLR4 endocytosis and type-I IFN expression. In panel 3, CD14 has autonomous signaling functions leading to the activation of NFATc transcription factor family members **(12).**

Role of CD14 in Allergic diseases:

Many research works have studied the role of CD14 in different allergic phenotypes. Results of these studies were controversial, as some studies have found that the sCD14 level in certain allergic

diseases was significantly higher in periods of illness than its level at recovery period. While other studies reported inversely relationship between serum sCD14 level and certain allergic phenotypes. Also, up till now, few studies have focused on the association between serum sCD14 level and the severity of allergic diseases **(19).**

The CD14 affects the immune response in different allergic phenotypes by several mechanisms. It is considered to be a marker of monocyte/macrophages activation which has a significant effect on the balance between Th1 and Th2 cytokines. Also, the sCD14 has been reported to have an essential role in the regulation of T and B cells proliferation and activation **(20).**

Acting as a receptor for lipopolysaccharide (LPS), the CD14 can provoke antigen presenting cells (APCs) to produce cytokines, such as TNF-alpha, IL-6, IL-8, and IL-12. Also, it induces endocytosis pathway of toll-like receptor-4 (TLR-4), and also provides significant molecular signals for the receptor subunits of IL5, IL3, and GM-CSF in human eosinophils **(12; 21).**

A specific region in chromosome 5(5q31-32) which contains a group of cytokine genes that regulate the allergic immune response, such as interleukin 4(IL-4), interleukin 13(IL-13), interleukin 9(IL-9), and granulocyte-monocyte-colony-stimulating factor (GM-CSF) was also identified to include the CD14 gene explaining the role of CD14 in different allergic conditions **(21).**

Regarding its role in allergic diseases, recent studies have suggested the measurement of serum levels of sCD14 in allergic patients as it might be helpful in the future to divide patients into atopic and non-atopic and could be used as a strong biological marker for diagnosis of certain allergic diseases and evaluation of the disease severity **(22).**

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