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Link between mast cells and bacteria: Antimicrobial defense, function and regulation by cytokines

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ABSTRACT

Bacteria and their products, such as LPS, act on mast cells (MCs) to induce the secretion of multiple cytokines, including IL-1, TNF, IL-18 and IL-33, which can be dosed in the site of infected tissues. Antigen-binding IgE cross-links FcεRI on mast cells involves the generation and activation of PKCδ, ERK, tyrosine kinases (*Syk* and *Lyn*) and mitogen-activated protein kinases (MAPKs), inducing the release of chemical mediators which provoke inflammation and hypersensitive reaction. Other stimuli, including, cytokines, neuropeptides, chemical and physical activators, can also act on MCs to release a plethora of inflammatory compounds. Activated MCs produce a broad spectrum of inflammatory cytokines, chemokines, lipid compounds and vasoactive amines, all involved in immune response. By producing TNF, MCs have an antibacterial defense and a protective function; while pathogenic bacteria and their products, such as LPS, have an inflammatory response through MC activation. LPS binding TLR4 produce MC generation IL-1 family members, and chemokines, which may recruit inflammatory cells at the infection site; whereas in $Kit^{W/W\text{-}v}$ mice, where MCs are genetically absent, the inflammatory effect is not present.

We report for the first time a link between MCs and bacteria emphasizing the mediation of inflammatory cytokines/chemokines. We can conclude that mast cells fight bacteria, and their immune response is perfectly integrated in the immune network. We hope that the understanding of microbial and mast cell interaction leads to more efficient therapeutic development in relation to microbial resistance.

Introduction

According to the recently published international consensus, study on the involvement of mast cells (MCs) in human biology and human diseases is increasing and involves more and more researchers.

The body of a healthy human possesses microorganisms ten times higher than the number of human somatic cells. There are about three hundred trillion bacteria in the intestine and one hundred trillion on our skin [1].

Some bacteria are beneficial to humans and some can provoke disease, whereas others are opportunistic guests that wait for the immune system to decrease before becoming pathogenic [2].

In this paper we report for the first time a link between MCs and bacteria, including some of their products.

The response to infection is crucial for the survival of an organism. Bacteria can cause disease by invasiveness, attacking and damaging the host cells, or by generating toxic compounds that poison the host cells. Certainly, many host defenses, including cellular immunity provided by macrophages, neutrophils, lymphocytes, eosinophils and MCs, are involved in fighting bacteria, a complex cascade of immunological events [3,4]. However, professional phagocytes, such as polymorphonuclear granulocytes and mononuclear phagocytes, are the major effectors of anti-bacterial defense.

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Some bacteria may release compounds, such as kinases, hyaluronidase, hemolysins, coagulases, which are not considered bacterial toxins but exert important effects and affect the host [5]. Endotoxins and exotoxins are bacteria toxins, generated by certain Gram-negative and Gram-positive bacteria, which are considered very potent poisons. Endotoxins are found in Gram-negative bacteria and are lipopolysaccharides (LPS) present in the cell envelope with less specific actions compared with exotoxins. LPS is released by the bacterial cell wall and is of great significance, not only for immunological reaction but also for therapeutic intervention [6]. When antigen-presenting cells (APC) encounter microbial products such as LPS they respond by expressing high levels of B7-1 and B7-2 which stimulate the response of T lymphocytes [7]. The binding of LPS to antigen-presenting cells and MCs produces cytokines and chemokines which promote the growth and differentiation of T cells [8]. MCs respond to many bacteria, including intracellular microorganisms and bacterial products (i.e. LPS), by generating inflammatory mediators [9,10].

Bacteria, and LPS, as well as other microbial compounds and signals, also activate macrophages which release IL-1-cytokine family members, including IL-1, IL-18 and IL-33, which trigger innate immunity [11]. LPS directly stimulates and activates MCs which release a plethora of inflammatory compounds including cytokines, which participate in innate immunity [12]. These cytokines exert an acute inflammatory action involving endothelial cells and leukocytes [13]. Inhibition of MCs producing cytokines reduces the pathologic complications of sepsis and diminishes the mortality associated with septic shock [14]. In addition, infections involve macrophages and T cells to produce IFNs which function to inhibit viral replication, and also exert important effects on MCs [15]. Microbial stimulus, including LPS in activating the innate immune reactions, provokes the release of IL-12 and IFN-γ generated by NK cells and T lymphocytes [16]. LPS binding to TLR4 activates MCs to induce and release mRNA expression of IL-4, IL-5 and IL-13, which in turn can provoke specific chemokine generation that causes the recruitment of inflammatory cells by increasing inflammation [17].

Presentation and testing of the hypothesis

IL-1 cytokine family members, such as IL-1, IL-18, IL-33, and IL-36, play a fundamental role in the initiation and amplification of immune responses. However, at the present time we do not know how many new IL-1 family members exist, and how differently they act on mast cells. The hypothesis is that there are many IL-1 inflammatory cytokines that act in different ways.

During bacterial infection, IL-1 released by macrophages and MCs increases (Fig. 1), leading to resistance of infections, and treatment with anti-IL-1 receptor antibody exacerbates the infection; while infected mice treated with recombinant IL-4 have reduced bacterial growth and inflammation.

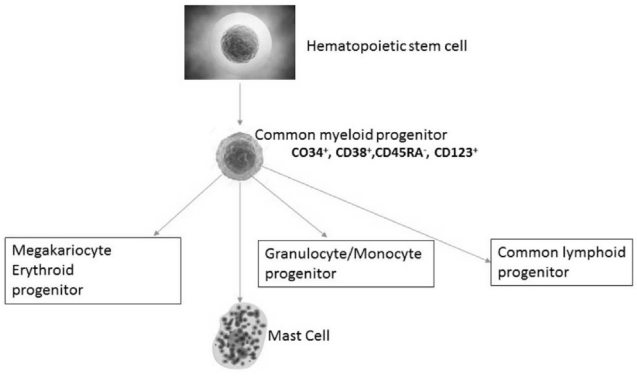

Fig. 1. Mast cell generation from hematopoietic stem cell.

IL-8, a CXC chemokine, which is important for mast cell functions and has the capacity to attract neutrophils to the site of inflammation, is generated by macrophages and is activated in the infected human body.

TLRs are proteins that enhance certain cytokine gene expressions in response to various pathogenic ligands and are involved in innate and adaptive immune responses [18,19]. TLR4 is a receptor for LPS which plays an important role in inflammation and is a risk factor for asthma mediated by MCs [20,21]. Activation of TLR4 by LPS on MCs leads to Th2 cytokine generation which enhances allergic inflammation, an effect also mediated by chemokines [22]. In fact, $CD4^+$ T cells, which are in a consistently elevated number in allergic tissue, are the primary orchestrators of the specific immune response implicated in the pathogenesis of allergic disorders [23]. T-cell activation increases the expression of IL-2 receptor (IL-2R), class II histocompatibility antigen (HLA-DR) and very late activation antigen (VLA 1–6) in allergic tissues, effects that can be inhibited by IL-35 [24]. It is believed that these effects are due to the presence of MCs, since LPS-mediated enhancement inflammation is not observed in genetically W/Wv mice, where MCs are absent [25].

Therefore, MCs control allergic inflammation through the activation of TLR4 that mediates the induction of GATA1 proteins, resulting in increased Th2 cytokine generation [12]. GATA1 was identified in nuclear protein from MCs as GATA motif-binding protein which controls human ST2 gene transcription, a receptor for IL-33 which modulates the Th2 response [26].

Mast cells were first described in the frog mesentery in the middle of the 19th century. They are multifunctional immune cells ubiquitous in the body, located preferentially around blood vessels, in connective tissue and in intraepithelial locations, and are the first line of defense [27,28].

Data and discussion

MCs are activated through cross-linking of their surface high affinity receptors for IgE (FcεRI), leading in seconds to degranulate and release stored mediators such as histamine, heparin, tryptase, chymase, kinogenases, carboxypeptidase A3 and TNF, and/or *de novo* later synthesized inflammatory compounds, such as growth factors, leukotrienes, prostaglandins, NO, and cytokines/chemokines [29]. Activated MCs release vasoactive mediators as well as chemotactic factors that promote leukocyte infiltration and exacerbate the inflammatory response [30]. A number of stimuli, especially engagement of receptors for the Fc portion of Ig (FcR), can activate MCs, and cross-linking of the FcεRI on its surface induces the release of biologically active preformed mediators [31,32].

MCs are mostly implicated in the pathogenesis of allergic diseases but they also perform important beneficial roles in host defense and in natural immunity to bacterial infection [33]. In addition, they participate in acquired immunity, inflammation, autoimmunity, metabolic disorders and infectious diseases [34].

In recent years, MCs have been seen to participate in pathological processes associated with classical inflammation without degranulation [35]. MCs FcεRI high affinity receptor for immunoglobulin E [(IgE) ($K_d = 10^{-10}$ M)] activation leads to the involvement of several cytoplasmic protein tyrosine kinases such as *Syk* and *Lyn,* and recruitment of adaptor molecules including PI3K/Akt, PLCgamma/Ca2+/PKC and Grb2/SOS/Raf-1/mitogen-acti vated protein kinase (MAPK) pathways [36]. Secretory molecules of the bacterial secretion system amplify the TLR signaling response by activating NFκB and/or MAPKs [37]. MAPKs, in turn, result in the induction of transcription factors AP-1 and c-*fos* and activate cytokine gene expression with the production of mRNA