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Mast cell activators as novel immune regulators

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Mast cells are an important cell type of the innate immune system that when activated, play a crucial role in generating protective innate host responses after bacterial and viral infection. Additionally, activated mast cells influence lymph node composition to regulate the induction of adaptive immune responses. The recognition that mast cells play a beneficial role in host responses to microbial infection and induction of adaptive immunity has provided the rationale to evaluate mast cell activators for use as antimicrobials or vaccine adjuvants. This review summarizes the role of mast cell activators in antimicrobial responses while also discussing the use of different classes of mast cell activators as potent vaccine adjuvants that enhance the induction of protective immune responses.

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Introduction

A long overlooked component of the body's immune arsenal are mast cells (MC), which are granulated hematopoietic cells that differentiate in the blood but mature in the tissues where they remain long lived, and sometimes capable of replicating when the tissue becomes overly inflamed. There are two major subsets of MC described in rodents, mucosal and connective tissue, that are distinguishable based on their granular contents. In recent years, several observations highlighting the ability of MCs to activate multiple arms of the immune system during infection have come to light. Through the release of immune suppressing mediators, MCs are also capable of contracting inflammation when it perceives that the infection is subsiding. In view of their powerful capacity to regulate the nature and intensity of inflammation at infection sites, there is a growing interest in the possibility of employing MC targeting immunomodulatory agents for medicinal use. Here we will review immunomodulatory roles of MCs during infection and some of the unique properties of MCs that support this role. We will also cover several studies demonstrating the efficacy of MC activators (MCAs) when used as adjuvants for vaccines. In view of the prior history of MCs as effectors of anaphylaxis, safety is an important consideration. We will discuss this topic as it pertains to the use of MCA as vaccine adjuvants.

Immunodulatory role of MCs

Since their discovery in 1863, MCs have mostly remained an enigma as their physiological role was difficult to pinpoint. For many years, interest in MCs was mostly linked to their prominent role in promoting various chronic inflammatory disorders such as asthma, allergic rhinitis, urticaria, inflammatory demyelinating disease and rheumatic disease [1–3]. The MC's role in these pathological conditions was primarily fostering excessive recruitment of various inflammatory cells into the inflamed site [4,5]. The first clues that MCs exhibit a beneficial and powerful role in combating various infectious diseases emerged only about two decades ago. These initial studies revealed that MCs at sites of infection have the innate capacity to directly recognize invading microbes or their products and promptly extrude their large collection of pre-stored granules [6,7]. MC granules contain various chemokines and cytokines as well as proteolytic agents and other agents which upon release, trigger the extravasation of various immune cells from the vasculature and the leakage of soluble vascular factors which together engage pathogens in infected tissue. The result of this MC mediated inflammatory response is accelerated clearance of the invading pathogen. For example, a mouse model of cytomegalovirus (CMV) infection demonstrated that CMV directly infects MCs and induces degranulation and secretion of CCL5 [8], which recruits T cells to infection sites. MCs contribution to CMV clearance was shown using mice deficient in MC. In the absence of MCs, viral replication was significantly increased compared to animals with sufficient MCs. CMV also persisted in the lungs of MC deficient mice longer than wild-type mice. The role of MCs in CMV clearance

was confirmed when MC deficient mice were reconsititued with MC and viral replication and clearance was similar to wild-type mice [8]. Concomitant with this vigorous innate immune response, MCs initiate the influx of different immune cells into lymph node that drain the infected site, which is the hallmark of the adaptive immune response [9,10]. Activation of draining lymph nodes (DLNs) occurs when MC granules released at the infection site reach this organ via the lymphatic system and release their cargo of pharmacologically active mediators. One of the most active MC granule compounds was TNF, since release of TNF from the MC granule triggers local production of key lymph node chemokines, such as CCL21, which induces massive migration of both antigen bearing dendritic cells from the site of infection and T cells from the circulation, causing significant lymph node hypertrophy [10]. The resulting interaction between incoming antigen presenting cells and recently sequestered T cells in the DLN resulted in a highly elevated pathogen-specific adaptive immune response. Thus, MCs have the capacity to initiate multiple arms of the immune system upon pathogen recognition at mucosal surfaces or the skin. However, not all MC responses to pathogens are beneficial. This is often the case after pathogens have overcome peripheral immune defenses and gained access into the blood where they now exhibit the capacity to simultaneously activate MCs all over the body. Under these circumstances, the wide-spread activation of MC leads to vascular leakage and shock.

The potent capacity of MCs to evoke protective and sometimes detrimental immune responses to pathogens is attributable to several unique traits. These include their preponderance in the skin and mucosal sites, which is where most pathogens initiate infection of the host. MCs are readily activated at infection sites because they have receptors that directly bind a wide range of pathogens or for various host molecules that opsonize pathogens. MCs may also be activated at infection sites without direct contact with pathogens as they respond vigorously to danger signals (DAMPS) released by neighboring infected host cells [11]. In addition to releasing pre-stored inflammatory mediators, activated MC can de novo synthesize and secrete of a wide range of inflammatory mediator for several hours [12]. MCs not only initiate the inflammatory response but also sustain these reactions. Their capacity to regranulate and undergo multiple bouts of degranulation is also another but largely overlooked trait to prolong inflammation [13]. The MCs degranulation and mediator response to pathogens can be different depending on the pathogen. For example, MCs secrete proinflammatory cytokines but not type 1 interferon beta (IFN-β) when challenged by Gram positive and negative bacteria but MCs secrete anti-viral type 1 IFN when challenged by viruses [14]. This differential response of MCs may be attributable to the nature of the receptors on the MC surface engaged by each pathogen as the different surface receptors trigger distinct degranulation and mediator responses in MCs.

Mast cell activators as antimicrobials

MCs possess antimicrobial properties and aide in killing bacteria and viruses [15]. Mouse models of infectious pathogens have demonstrated increased pathogen clearance in animals with sufficient MCs compared to mice that were deficient in MCs [16,17,18•]. Activation of MC with toll-like receptor 2 (TLR2) ligands induces MC expression of cathelicidin, a class of host-defense peptides able to limit viral replication [17]. For example, maximal protective responses against vaccinia virus required TLR2 responsive MCs that produced antimicrobial peptides [16,17]. LL-37 is a cathelicidin peptide released from activated MCs that can directly kill microbes, such as *Streptococcus pneumoniae* [19]. In addition to being produced by MCs, LL-37 is also a MC activator [20•,21]. LL37 induces MC migration [21], which may complement the antimicrobial properties of MCs since LL-37 may attract MCs towards infection sites to allow inflammatory mediators produced by MCs, such as Interleukin (IL)-1 and -8 and TNF and host defense peptides, contribute to host defense against bacteria and viruses [22]. Similarly, other peptides that activate MCs to degranulate, including retrocyclins (RC101) and protegrin-1, have antimicrobial properties and can kill *E. coli* in a dose-dependent manner [23].

In addition to activation by TLR ligands, MCs are activated by danger signals produced within the host after infection. Danger molecules, such as IL-33, which is released from viral-infected host cells, also activate MC to secrete the pro-inflammatory cytokine, TNFα and protect against a herpes simplex type 2 viral (HSV) infection [18•]. In the absence of MCs or IL-33-responsive MCs, HSV-infected mice have significantly increased mortality compared to HSV-infected mice with WT MCs or MC deficient mice reconstituted with IL-33 responsive MC [18•]. This suggests that MCs are important for maximal protection against HSV infections. Taken together, the inflammatory responses resulting from MC activation appear to be beneficial in resolving microbial infections induced by bacteria and viruses; thus, it is reasonable to suspect that MC activators may be utilized therapeutically to enhance the antimicrobial activity of MCs and improve microbial clearance after infection.

Vaccine adjuvant activity of mast cell activators (MCA)

In view of the powerful immunomodulatory capacity of MCs, particularly in boosting pathogen-specific adaptive immune responses during infection, the use of small molecule MC activators as adjuvants for vaccine is now being considered. For many decades, alum was the only adjuvant approved for use in FDA-approved vaccines.