

Corecognition of Pathogens: An Important Trigger for Mast Cell Response?

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In addition to having a well-established function in allergy, mast cells are recognized as effective sentinel cells and an essential part of innate immunity. It is well accepted that mast cells play a relevant role in the early immune response to invading pathogenic bacteria by attracting granulocytes and lymphocytes and therefore provide an important link between innate and adaptive immunity [1, 2]. The direct interactions between pathogens and mast cells, essential for the generation of early innate immune responses, as well as the generation of appropriate acquired immunity, are mainly mediated through a wide range of pattern recognition receptors such as Toll-like receptors (TLR) [3]. For example, bacterial components such as lipopolysaccharides (LPS) trigger mast cells for the release of histamine, eicosanoids, and cytokines such as TNF and IL-6. Both mast cell TNF and mast cell IL-6 have been shown to be critical for neutrophil activation, which is necessary for protection against bacterial infections [4, 5]. Pathogens that have invaded the cytosol are detected by various cytoplasmic pattern recognition receptors such as nucleotide-binding oligomerization domain (NOD)-like receptors (NLR). NOD1 and NOD2 detect the bacterial peptidoglycan (PGN) subunit muramyl dipeptide (MDP). Ligands binding to NOD1 or NOD2 result in the activation of nuclear

factor (NF)- κ B and the subsequent expression of proinflammatory cytokines [6].

Haidl et al. [7] analyzed the release of pro- and anti-inflammatory mediators using cord blood-derived mast cells following treatment with bacterial-derived PGN, NLR agonists, TLR2 activator triacyl lipopeptide Pam₃CSK₄, and a combination of NLR and TLR agonists. The release of IL-1 β , IL-6, CXCL-8, IL-10, and leukotriene C₄ was affected by PGN and Pam₃CSK₄ without inducing degranulation, but not by NLR agonists. It is important to note that NLR agonists selectively enhanced the TLR2-mediated release of IL-6 whereas the release of other cytokines was not increased. The enhancement of IL-6 levels was clear but less than 2-fold, slightly limiting this important observation. The authors report that PGN and Pam₃CSK₄-induced IL-6 production is dependent on adenylyl cyclase activity and NF- κ B activation. However, the question of how the NLR agonists enhance TLR2-mediated IL-6 production remains unanswered. The finding that NF- κ B and adenylyl cyclase inhibition reduced IL-6 production following TLR2 agonist stimulation alone to a similar degree as a combined stimulation with NLR agonists argues against the existence of separate pathways induced by TLR and NLR agonists. Thus, it can be speculated that the activation of NLR agonists

alone is not sufficient to initiate IL-6 production, but amplifies the TLR-mediated signaling pathways. Several questions need to be addressed in further studies. For example, why and how is cytokine release selectively enhanced for IL-6?

Haidl et al. [7] conclude that an increased IL-6 production in response to combined TLR2 and NLR activation could play a role in protection against bacterial infection, but could potentially exacerbate inflammation-dependent conditions. Indeed, the corecognition of pathogens by different pattern recognition receptor family members is required to trigger certain responses. For instance, NLR agonists interact with TLR signaling in dendritic cells, resulting in an augmentation of TLR-induced cytokine production [8]. In mast cells, dectin-1 and TLR2 cooperate to initiate leukotriene production in response to zymosan [9].

However, the expression of TLR and, in particular, the responsiveness of mast cells to different TLR ligands may differ between mast cells of different origins. Mast cells generated from sterile environments such as bone mar-

row or cord blood respond well to different TLR ligands such as LPS or PGN, whereas mast cells derived from primarily unsterile sites like the intestine respond less efficiently to such stimuli [10]. Possibly, this difference reflects a kind of tolerance mast cells acquire at sites constantly challenged with bacterial products. Interestingly, the quality of the response of mast cells to TLR ligands is different to that induced by allergens and other nonbacterial triggers. Whereas allergens primarily induce degranulation and the release of proinflammatory mediators such as histamine and eicosanoids, bacterial products hardly induce such mediators but instead cytokines needed for the initiation of innate and adaptive immune responses [11]. Thus, the findings of Haidl et al. [7] support a regulatory role of the corecognition of pathogens by different pattern recognition receptor family members in mast cells. Selective IL-6 production may be of importance in modulating innate and adaptive immune responses but needs to be analyzed in tissue-derived mast cells as well.

References

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