



Microbes taming mast cells: Implications for allergic inflammation and beyond

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ABSTRACT

There is increasing awareness of a relationship between our microbiota and the pathogenesis of allergy and other inflammatory diseases. In investigating the mechanisms underlying microbiota modulation of allergy the focus has been on the induction phase; alterations in the phenotype and function of antigen presenting cells, induction of regulatory T cells and shifts in Th1/Th2 balance. However there is evidence that microbes can influence the effector phase of disease, specifically that certain potentially beneficial bacteria can attenuate mast cell activation and degranulation. Furthermore, it appears that different non-pathogenic bacteria can utilize distinct mechanisms to stabilize mast cells, acting locally though direct interaction with the mast cell at mucosal sites or attenuating systemic mast cell dependent responses, likely through indirect signaling mechanisms. The position of mast cells on the frontline of defense against pathogens also suggests they may play an important role in fostering the host–microbiota relationship. Mast cells are also conduits of neuro-immuno-endocrine communication, suggesting the ability of microbes to modulate cell responses may have implications for host physiology beyond immunology. Further investigation of mast cell regulation by non-pathogenic or symbiotic bacteria will likely lead to a greater understanding of host microbiota interaction and the role of the microbiome in health and disease.

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1. Introduction

The mast cell, long regarded as a key effector of human allergic disease and immune responses to helminthic parasites is now considered a primary inducer and amplifier of both innate and adaptive immune responses (Vliagoftis and Befus, 2005).

The presence of mast cells in particularly high numbers in the skin, airway and gut mucosa is indicative of a role as important gatekeepers/sentinels for fighting infectious organisms at these portals of entry. Mast cells express a complement of Toll-like and other microbe associated pattern recognition receptors and activation by bacteria leads to signals that modulate both innate and adaptive immune responses that protect against infection. Mast cells participate in direct killing of organisms by phagocytosis and reactive oxygen species production and can produce anti-microbial peptides such as cathelicidins (St. John and Abraham, 2013). Furthermore, mast cells have been found to produce extracellular traps that encompass and kill organisms in a similar manner to

neutrophils (von Kockritz-Blickwede et al., 2008). Mast cells also protect against infection indirectly, processing and presenting bacterial antigens to T cells and recruiting other inflammatory cells through the release of proinflammatory mediators (Moon et al., 2010).

Increased understanding of the importance of the microbiota, particularly the gut microbiota, to the normal physiology of mammals has lead to a paradigm shift in immunology. The idea that the relationship between immunity and microbes is purely adversarial has been supplanted by an appreciation that the immune system not only evolved to protect against pathogens but, perhaps largely, to promote and encourage a healthy microbiota. Under this paradigm the position of mast cells on the frontline of defense against pathogens suggests they may also play an important role in fostering the host–microbiota relationship and regulating the dynamic ecosystem of the holobiont.

There is an emerging evidence that the mast cell plays an important role in microbiota–host communication and in particular, that certain non-pathogenic microbes and components of the microbiota can influence the development and severity of allergic disease by modulating mast cell function. Beyond allergy, mast cells translate signals between the nervous, immune and endocrine systems (Forsythe and Bienenstock, 2012; Theoharides, 1996)

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to modulate biological responses including intestinal permeability, pain perception, HPA axis activation, allergen avoidance and anxiety-like behaviors. Thus microbial modulation of mast cell function has the potential to influence a broad range of physiological parameters, suggesting mast cells may be important hubs of inter-kingdom communication.

2. Microbiota and allergy: a role for mast cells

The “microbiome hypothesis” proposes that perturbations in microbiota, because of dietary changes and increased antibiotic use in ‘industrialized’ countries, leads to disruption of the normal microbiota-mediated mechanisms of immunological tolerance in the mucosa. Consequently, this dysregulation leads to an increased susceptibility to immunological disorders including allergy (Noverr and Huffnagle, 2005; Shreiner et al., 2008). Recent studies utilizing gnotobiotic mice have identified that key bacterial classes within the microbiota, single bacterial strains, or isolated components of these strains, can strongly influence the development of T cell phenotypes in the intestine (Atarashi et al., 2011; Round and Mazmanian, 2010). Overall, evidence suggests that the microbiota of various tissue sites play a central role in governing susceptibility to the Th2 biased inflammatory response associated with allergy. Certain components of the microbiota are immunomodulatory, and colonization of specific subsets of microbes can induce immune signals that are either proinflammatory or tolerogenic in nature. Studies in animal models also lend support to the microbiota hypothesis. In particular, a recent study by Noval Rivas et al. (2013) identified that mice genetically predisposed to food allergy (IL4raF709) exhibit a specific gut microbiota signature distinct from sensitization-resistant wild-type mice. Strikingly, adoptive transfer of microbiota from IL4raF709 but not wild type mice into germ-free recipients lead to up-regulation of OVA-specific TH₂ and IgE responses and promoted anaphylaxis. Furthermore, treatment of neonatal mice with vancomycin, demonstrated to decrease microbial diversity and increase the population of firmicutes, was associated with increased severity of allergic airway inflammation in the adult animal (Russell et al., 2013). Taken together such studies strongly suggest that dysbiosis provides one mechanism that can contribute to the pathogenesis of allergy. Furthermore, there is now evidence of a role for mast cells in linking microbiota to allergy.

A causal relationship between specific microbiota changes and allergy is indicated in studies of the skin and allergic dermatitis. Overall, the skin of atopic dermatitis patients has been demonstrated to have greatly reduced microbial diversity relative to the same skin area of healthy controls. *Staphylococcus aureus*, rarely present on healthy skin is found on the skin in more than 90% of atopic dermatitis patients and some treatments to reduce *S. aureus* colonization decrease disease severity (Leung et al., 2008). Furthermore, a recent analysis of the microbiota composition of lesional skin of moderate-to-severe pediatric atopic dermatitis patients revealed temporal shifts associated with disease flares and treatment (Kong et al., 2012). Specifically, the relative abundance of *S. aureus* and the skin commensal *Staphylococcus epidermidis* was increased with disease severity, whilst *Streptococcus*, *Propionibacterium*, and *Corynebacterium* genera were increased following therapy (Kong et al., 2012). Significantly, another recent study by Nakamura et al. (2013) identifies mast cells as a mechanistic link between *S. aureus* and atopic dermatitis. These investigators identified that δ -toxin, produced by *S. aureus*, was a mast cell degranulating factor and that *S. aureus* isolates recovered from patients with atopic dermatitis produced large amounts of δ -toxin. Furthermore, IgE enhanced δ -toxin-induced mast cell degranulation in the absence of antigen. Skin colonization with *S. aureus*, but

not a mutant deficient in δ -toxin, increased IgE and interleukin-4 production and promoted inflammatory skin disease. Crucially, the enhancement of IgE production and dermatitis by δ -toxin was abrogated in KitW^{sh}/W^{sh} mast-cell-deficient mice and restored by mast cell reconstitution (Nakamura et al., 2013). Thus it appears that *S. aureus* infection drives a Th2 type immune response with associated IgE and inflammatory cytokine production through direct action on mast cells. This study identifies a role for mast cells in mediating the detrimental effects of changes in the microbiota on allergic disease development but there is also evidence that action on mast cells may also contribute to the efficacy of microbe based therapeutic approaches to allergy.

3. Mast cell suppression by beneficial microbes

It has emerged in recent years that microbial exposure either naturally in the environment or through dietary supplementation in the form of probiotics, may protect against allergic disease. For example, there is evidence that the protective effect of the farming environment on development of atopic sensitization, hay fever, and asthma is related to the wider range of microbial exposures in children living on farms compared to urban dwelling peers (Riedler et al., 2001). This is supported by animal studies demonstrating that specific bacteria that are abundant in cowsheds, *Acinetobacter lwoffii* F78 and *Lactococcus lactis* G121, can attenuate allergic responses in mice (Debarry et al., 2007).

Clinical trials indicate that feeding mothers with *Lactobacillus rhamnosus* GG in the pre and early post-natal period may be effective in the treatment and prevention of early atopic disease in children (Kalliomaki et al., 2001, 2003). In a similar vein, *Lactobacillus fermentum* was shown to be beneficial in improving the extent and severity of atopic dermatitis in young children (Weston et al., 2005). However, it should be noted that there have also been a number of clinical trials showing no effect of the same bacterial strains on the incidence or severity of allergic disease (Vliagoftis et al., 2008) and a greater understanding of host-microbe interactions will be required to identify the true therapeutic potential of probiotics in allergy.

Animal models have provided strong evidence indicating that oral administration of certain microbes can have systemic effects on immune responses, it has been shown that perinatal treatment with *L. rhamnosus* GG suppresses the development of experimental allergic asthma in adult mice (Blumer et al., 2007; Feleszko et al., 2007). *L. rhamnosus* JB-1, could attenuate an allergen induced allergic airway response in adult mice (Forsythe et al., 2007; Karimi et al., 2009) and others have since confirmed these anti-allergic effects in the airway using a variety of bacteria (Lim et al., 2009; Adam et al., 2010; Li et al., 2010). In addition, several strains of lactobacillus have been shown to attenuate allergic dermatitis when administered orally to mice (Inoue et al., 2007; Hacini-Rachinel et al., 2009; Won et al., 2011). A number of mechanisms have been identified that may contribute to the ability of these bacteria to attenuate allergic inflammation including altered antigen presentation by dendritic cells (Hart et al., 2004; Stagg et al., 2004), Th1 polarization (Adel-Patient et al., 2005; Hisbergues et al., 2007) or the induction of regulatory T cells (Karimi et al., 2009, 2012). More recently there has been evidence that certain Lactobacilli may influence the effector phase of adaptive inflammation (Schiffer et al., 2011). Specifically, it is emerging that inhibition of mast cell responses is a component of the immunomodulatory effects of certain bacteria and may be a contributing factor to the ability of candidate probiotic organisms to attenuate allergic inflammation (Kim et al., 2008; Magerl et al., 2008; Oksaharju et al., 2011; Forsythe et al., 2012).

Early evidence that commensal bacteria communicate with

mast cells came from the observations that nonpathogenic *Escherichia coli* strains could inhibit mast cell activation following direct co-culture *in vitro* and *ex vivo* following injection of the bacteria into the peritoneal cavity of mice (Magerl et al., 2008). More recently (Wesolowski and Paumet, 2014) it was identified that *E. coli* disrupts the sequence of events leading to secretory granule fusion with the cell membrane. Specifically, the interaction between IKK β and SNAP23 is inhibited resulting in the hypophosphorylation of SNAP23. Subsequent formation of the ternary SNARE complex between SNAP23, Syntaxin4 and VAMP8 is strongly reduced leading to impaired VAMP8-dependent granule release (Wesolowski and Paumet, 2014).

Lactobacilli have also been demonstrated to directly inhibit mast cell activation *in vitro*, however this ability appears to be highly strain specific (Kawahara, 2010; Oksaharju et al., 2011; Schiffer et al., 2011; Forsythe et al., 2012). Overnight incubation with a strain of *Lactobacillus casei* inhibits IgE-dependent mouse mast cell and human basophil activation (Schiffer et al., 2011). Inhibition could be induced by both viable and irradiated *L. casei*, suggesting the no involvement of secreted metabolites. A role for a structural component of the bacteria, rather than a secreted metabolite, is further supported by the observation that inhibition was also prevented when mouse mast cells were separated from bacteria by a semipermeable membrane, indicating a requirement for *L. casei*/mast cell contact (Schiffer et al., 2011). However, the mechanism underlying the ability of lactobacilli to inhibit mast cell function is unknown and it may be that different strains employ distinct approaches to suppress cell activity. This is supported by observations that *L. casei* induced inhibition of mast cells was not mediated by TLR or NOD1/2 receptors, while another study demonstrated that inhibition of IgE mediated mast cell activation by a strain of *Lactobacillus reuteri* was at least partially mediated by TLR2 (Schiffer et al., 2011).

It is important to note that while evidence suggests that direct inhibition of mast cells by non-pathogenic bacteria *in vitro* requires cell contact with the microbe, many of these bacteria when delivered orally, or into the peritoneal cavity, can inhibit systemic mast cell dependent responses. For example the requirement for direct bacteria mast cell interaction cannot readily explain the ability of *L. casei* to inhibit IgE mediated passive systemic anaphylaxis when delivered i.p. (Schiffer et al., 2011). There is also direct evidence to suggest systemic mast cell suppression may be mediated by a mechanism independent of contact between mast cells and bacteria. The *L. rhamnosus* strain JB-1 does not inhibit mast cell degranulation following direct *in vitro* co-culture (Forsythe et al., 2012). However, feeding this *L. rhamnosus* strain to rats inhibited peritoneal mast cell response to stimulation *ex vivo* and attenuated passive cutaneous anaphylaxis, strongly implying an indirect mechanism of action involving additional cell types (Forsythe et al., 2012). Overall, studies indicate that certain bacteria, many regarded as putative probiotics, can attenuate mast cell responses to stimuli and open the possibility that these abilities could be harnessed to provide novel strategies for reducing the severity of allergic responses and other inflammatory conditions. However to fully realize their therapeutic potential it will be important to understand the strategies employed by mast cell suppressing microbes.

4. Microbial mechanisms of mast cell suppression

It is clear that microbes, both pathogenic and beneficial/symbiotic, have evolved a number of approaches to modulate mast cell function and, in particular, to suppress degranulation. As with immunology in general, until recently the majority of studies in this area have focused on pathogen/host interactions, where

pathogens utilize these mechanisms to aid virulence by neutralizing the anti-microbial activity of the mast cell. Little is known about the mechanisms employed by normal components of the microbiota and putative probiotics, however it seems probable that they are similar to those utilized pathogens. Indeed, it may be that pathogens have co-opted strategies initially evolved to facilitate symbiotic relationships.

4.1. Direct suppression

Mast cells express a complement of pattern recognition receptors including TLRs, NOD-Like receptors and carbohydrate binding proteins. The sialic acid-binding immunoglobulin-type lectins (Siglecs) are a class of carbohydrate receptor involved largely in the suppression of immune responses. A number of Siglec receptors are expressed by mast cells and activation of these receptors has been demonstrated to inhibit IgE mediated mast cell degranulation (Jenner et al., 2006; Bochner, 2009; Mizrahi et al., 2014). It is thought the role of Siglecs is to recognize sialic acid as a “self-associated molecular pattern” (SAMPs) and deliver inhibitory signals to innate immune cells to help maintain the baseline non-activated state and dampen reactivity following an immune response (Varki, 2011). However, a range of commensals and pathogens have evolved SAMP molecular mimics to take advantage of the immunosuppressive action. A number of human pathogens are coated with N-acetylneuraminic acid (Neu5Ac), a sialic acid commonly found in humans, and these sialoglycan mimics dampen immune responses by ligating inhibitory Siglecs (Carlin et al., 2009). It seems likely that non-pathogenic organisms have also adopted SAMP mimicry to allow them to establish a niche within the commensal microbiota.

In addition to interactions with inhibitory receptors on host cells, bacteria can directly modulate mast cell signaling pathways. After penetrating the gut epithelium, the highly invasive pathogen *Salmonella typhimurium* eludes a neutrophil response by disabling local mast cells. *Salmonella* utilizes a type III secretion system to inject *Salmonella* Protein Tyrosine Phosphatase (SptP) into the mast cell cytosol (Choi et al., 2013). This potent phosphatase acts on multiple signaling targets involved in mast cell degranulation, including preventing the phosphorylation of Syk. The plague bacteria, *Yersinia pestis*, produces a structurally similar phosphatase, YoPH, that also imbues this pathogen with the ability to inactivate mast cells (Choi et al., 2013). Certain microbes, including fungi, produce toxins that modulate mast cell function. Gliotoxin, a metabolite of the pathogenic fungus *Aspergillus fumigatus* suppresses Fc ϵ RI-dependent and -independent mast cell responses, including degranulation, leukotriene C4 secretion, and TNF and IL-13 production (Niide et al., 2006; Urb et al., 2009).

Bacteria communicate with each other through a cell density dependent signaling system, termed quorum sensing (Walters and Sperandio, 2006; Kendall and Sperandio, 2007). These signals are mediated by small hormone-like molecules and allow a population of bacteria to co-ordinate their gene expression and activities. It is becoming evident that certain components of the quorum sensing system can also influence the behavior of eukaryotic cells (Rumbaugh, 2007; Lowery et al., 2008).

Gram-negative bacteria appear to use several types of small molecules. Of these, the best-described signaling system is the N-acyl-homoserine lactone (AHL) system. AHLs are fatty-acid-based signaling molecules and mediate bacterial processes by interacting with inducible transcriptional regulators (Walters and Sperandio, 2006; Subramoni and Venturi, 2009). These molecules differ significantly only in the constituents of their fatty acid derived acyl chains. Homologs of the AHL synthase (LuxI-type synthase) and AHL receptor (LuxR-type receptor) regulate responses to the structurally distinct AHL.

It has been demonstrated that AHSL, and in particular N-(3-oxododecanoyl)-L-homoserine lactone (3OC12-HSL) which functions as a transcriptional regulator in *Pseudomonas aeruginosa*, can also alter mammalian cell responses. 3OC12-HSL can promote the upregulation of pro-inflammatory cytokines and chemokines in lung epithelial cells, induce apoptosis of neutrophils and macrophages and inhibit lymphocyte proliferation and TNF production (Ritchie et al., 2003, 2007; Vikstrom et al., 2006; Zimmermann et al., 2006). There have been somewhat contradictory reports regarding the effect of AHSL on mast cell function suggesting that 3OC12-HSL may attenuate mast cell responses by inducing apoptosis or enhance mast cell degranulation (Wu et al., 2001; Li et al., 2009). These differential effects may depend on the phenotype of the mast cell and the concentration of AHSL. Gram-positive bacteria use a range of small peptides to coordinate their activities (Jimenez and Federle, 2014). However, to date there is little information regarding the effect of these peptides on regulating host cells. Nevertheless, inter-kingdom communication, with bacteria derived small signaling molecules influencing mast cell activity, is clearly a potential means through which specific microbes may influence allergy development or disease severity and deserves further investigation.

4.2. Indirect suppression

In addition to direct action on mast cells, regulatory effects may be mediated indirectly via modulation of other host cells. The exact nature of such mechanisms and the potential intermediary cells are currently unknown. However, de Kivit et al. (2012) conducted studies suggesting galectins may play a role in the mechanism through which modulation of gut bacteria leads to systemic alteration in mast cell function. Galectins are secreted by keratinocytes, intestinal epithelial cells and various immune cells, including dendritic cells, macrophages and mast cells (Hirashima et al., 2004; Rabinovich and Toscano, 2009; Larsen et al., 2011; Smetana et al., 2013). Galectins have been described to be involved in many physiological processes, including cell signaling, cell adhesion, chemotaxis and apoptosis. A diet containing prebiotic galacto- and fructo-oligosaccharides and a strain of *Bifidobacterium breve* protected against acute allergic symptoms and suppressed mast cell degranulation in whey-sensitized mice. The anti-allergic effects of the synbiotic treatment were correlated with increased galectin-9 expression by intestinal epithelial cells and increased levels of galectin-9 in serum (de Kivit et al., 2012). Crucially, serum derived from whey-sensitized synbiotic-treated mice was able to suppress IgE-mediated mast cell degranulation and the extent of this suppression was correlated with serum galectin-9 (de Kivit et al., 2012). *In vitro*, studies of mast cell degranulation involving RBL-2H3 cells demonstrated that galectin-9 suppressed IgE mediated degranulation. This inhibitory effect was completely abrogated in the presence of lactose, indicating lectin activity of galectin-9 is critical. It is known that galectin-9 strongly and specifically binds IgE, a heavily glycosylated immunoglobulin, and that this interaction blocks IgE-antigen complex formation thus preventing degranulation. Whether galectin-9 or other galectins, such as galectin-1 (Rabinovich et al., 2000) contribute universally to probiotic and prebiotic stabilization mast cells remains to be determined, as does the characteristics of specific bacteria that trigger galectin production.

The indirect stabilization of peritoneal mast cells in rats following feeding with *L. rhamnosus* JB-1 was associated with inhibition of a specific K^+ channel (Forsythe et al., 2012). The KCa3.1 channel current is critical to the function of many immune cells (Beeton et al., 2001; Wulff et al., 2003, 2004; Chandy et al., 2004) KCa3.1 opening, while not required for mast cell mediator secretion, potentiates degranulation (Mark Duffy et al., 2004; Shumilina

et al., 2008). The KCa3.1 opener 1-EBIO enhances IgE-dependent Ca^{2+} influx and degranulation in response to a submaximal stimulus (Mark Duffy et al., 2004), while cells from KCa3.1 deficient (KCa3.1^{-/-}) mice demonstrate attenuated degranulation in response to FcεR1 mediated activation (Shumilina et al., 2008). Indeed the degree of attenuation in response to IgE mediated activation of mast cells following *L. rhamnosus* feeding was similar to that observed in KCa3.1 deficient mice (Shumilina et al., 2008). While the mechanism through which oral treatment with *L. rhamnosus* leads to inhibition of the ion channel is unknown, the activation of a range of G_s-coupled receptors including β₂-adrenoceptors, A_{2A} adenosine receptors and EP2 prostaglandin receptors can lead to inhibition of the KCa3.1 current (Duffy et al., 2005, 2007, 2008). It is possible that other G_s-coupled receptors may also inhibit KCa3.1 opening and a variety of immune or neuronal derived mediators could be responsible for the effects of *L. rhamnosus* on the ion channel.

4.3. Immunomodulation of mast cells

There is strong evidence linking the immunomodulatory function of certain commensal bacteria, and components thereof, to induction of Treg and their associated cytokines (Karimi et al., 2009; Feleszko et al., 2007; Round and Mazmanian, 2010). Mazmanian et al. (2008) demonstrated that oral ingestion of polysaccharide A (PSA) derived from *Bacteroides fragilis* protects animals from experimental colitis through induction of IL-10-producing CD4⁺ T cells. *Bifidobacterium infantis* induces expression of Foxp3⁺ T cells that protect mice against *S. typhimurium* infection (O'Mahony et al., 2008), while early life treatment of mice with *L. Rhamnosus* GG leads to an attenuated allergic airway response in adult animals that is also associated with an increase in Foxp3⁺ T cells (Feleszko et al., 2007). *L. Rhamnosus* JB-1 significantly increases the proportion of CD4⁺CD25⁺Foxp3⁺ Treg cells in the mesenteric lymph nodes and spleen of non-sensitized adult mice (Karimi et al., 2009). In OVA-sensitized mice challenged with inhaled antigen this increase in Foxp3 was also observed in the mediastinal lymph nodes indicating that *L. rhamnosus* induced Treg can migrate to the airways in response to inflammation. Although the suppressive activity of Treg cells requires prior activation through their T-cell receptor, once activated, Treg cells can suppress in an antigen-nonspecific way called "bystander suppression" (Tang and Bluestone, 2008). Recently, it has been shown that constitutive Foxp3⁺ Treg can control mast cell activation and IgE-dependent anaphylaxis in mice (Kanjarawi et al., 2013). Inhibition of mast cell degranulation by Tregs appears to require OX40/OX40 ligand interactions. It is known from *in vivo* transfer studies that a population of Treg cells can create conditions that promote the outgrowth of new populations of Treg cells with antigen specificities distinct from those of the original Treg population (Tang and Bluestone, 2008). The stabilization of mast cells and reduction of mast cell dependent systemic responses following exposure to specific bacteria or shifts in microbiota composition may be a consequence of such a T cell driven regulatory milieu.

5. Microbiota–mast cell communication beyond allergy

In addition to being at the frontline of host defense mast cells can translate signals between the nervous, immune and endocrine systems (Theoharides, 1996; Forsythe and Bienenstock, 2012). A range of neurotransmitters and hormones can activate mast cells, in turn, a variety of molecules, including histamine and serotonin, synthesized and released by mast cells can influence neuronal activity and endocrine function (Frieling et al., 1991, 1993).

Similarly, mast cell derived cytokines including TNF and growth factors, such as NGF, modulate the threshold for activation of local neurons and promote nerve fiber growth (Leon et al., 1994; van Houwelingen et al., 2002; Arnett et al., 2003; Kakurai et al., 2006).

Such bi-directional interaction between mast cells and neuroendocrine systems plays an important role in maintaining homeostasis and host defense including the instigation of behavioral changes leading to avoidance of allergens and other noxious stimuli (Costa-Pinto and Basso, 2012). Mast cell may also play a role in mediating behavior in normal animals, as deficiency in mice results in a more anxious phenotype (Nautiyal et al., 2008), and participate in regulation of the HPA axis (Matsumoto et al., 2001). There is also strong evidence for mast cells as important participants in visceral hypersensitivity and pain perception, particularly in irritable bowel syndrome (Barbara et al., 2007; Wood, 2007). While causal relationships have not been established, there are marked parallels between the contribution of mast cells to neural and endocrine responses and the physiological effects described following exposure to certain non-pathogenic bacteria. These include decreased intestinal permeability, myenteric nerve activation, anti-nociception, HPA regulation, and changes in anxiety-like behavior (Kamiya et al., 2006; Kunze et al., 2006; Wang et al., 2010; Bravo et al., 2011). This opens the possibility that mast cell/microbe interactions can influence aspects of host biology beyond allergy and inflammation and raises the question of how much mast cells contribute to the broader physiological effects of symbionts/beneficial bacteria.

6. Conclusion

Given the position of mast cells as immune sentinels, concentrated in the skin and mucosal surfaces, it is not surprising that these cells are involved in both defense against pathogens and in maintaining the beneficial relationship between host and microbiota. It is clear that organisms have, both pathogenic and commensal, have developed diverse mechanisms for modulating mast cell activity. Most emphasis to date has been focused on the ability of certain bacteria to inhibit mast cell degranulation but it may be that microbes modulate a number of aspects of mast cell phenotype and function, such as differential mediator release or shifts to a more immunoregulatory phenotype. Such questions have yet to be addressed in detail. However, studies aimed at identifying characteristics of mast cell regulating microbes and elucidating their mechanism of action could provide important new strategies to tackle allergy and other inflammatory disorders and could potentially provide insight into the broader physiological effects of our microbiota.

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References

- Adam, E., Delbrassine, L., Bouillot, C., Reynders, V., Mailleux, A.C., Muraille, E., Jacquet, A., 2010. Probiotic *Escherichia coli* Nissle 1917 activates DC and prevents house dust mite allergy through a TLR4-dependent pathway. *Eur. J. Immunol.* 40, 1995–2005.
- Adel-Patient, K., Ah-Leung, S., Creminon, C., Nouaille, S., Chatel, J.M., Langella, P., Wal, J.M., 2005. Oral administration of recombinant *Lactococcus lactis* expressing bovine beta-lactoglobulin partially prevents mice from sensitization. *Clin. Exp. Allergy* 35, 539–546.
- Arnett, H.A., Wang, Y., Matsushima, G.K., Suzuki, K., Ting, J.P., 2003. Functional genomic analysis of remyelination reveals importance of inflammation in oligodendrocyte regeneration. *J. Neurosci.* 23, 9824–9832.
- Atarashi, K., Tanoue, T., Shima, T., Imaoka, T., Kuwahara, T., Momose, Y., Cheng, G., Yamasaki, S., Saito, T., Ohba, Y., Taniguchi, T., Takeda, K., Hori, S., Ivanov, I.I., Umesaki, Y., Itoh, K., Honda, K., 2011. Induction of colonic regulatory T cells by indigenous Clostridium species. *Science* 331, 337–341.
- Barbara, G., Wang, B., Stanghellini, V., de Giorgio, R., Cremon, C., Di Nardo, G., Trevisani, M., Campi, B., Geppetti, P., Tonini, M., Bunnett, N.W., Grundy, D., Corinaldesi, R., 2007. Mast cell-dependent excitation of visceral-nociceptive sensory neurons in irritable bowel syndrome. *Gastroenterology* 132, 26–37.
- Beeton, C., Wulff, H., Barbara, J., Clot-Faybesse, O., Pennington, M., Bernard, D., Cahalan, M.D., Chandy, K.G., Beraud, E., 2001. Selective blockade of T lymphocyte K(+) channels ameliorates experimental autoimmune encephalomyelitis, a model for multiple sclerosis. *Proc. Natl. Acad. Sci. USA* 98, 13942–13947.
- Blumer, M., Sel, S., Virna, S., Patrascu, C.C., Zimmermann, S., Herz, U., Renz, H., Garn, H., 2007. Perinatal maternal application of *Lactobacillus rhamnosus* GG suppresses allergic airway inflammation in mouse offspring. *Clin. Exp. Allergy* 37, 348–357.
- Bochner, B.S., 2009. Siglec-8 on human eosinophils and mast cells, and Siglec-F on murine eosinophils, are functionally related inhibitory receptors. *Clin. Exp. Allergy* 39, 317–324.
- Bravo, J.A., Forsythe, P., Chew, M.V., Escaravage, E., Savignac, H.M., Dinan, T.G., Bienenstock, J., Cryan, J.F., 2011. Ingestion of *Lactobacillus* strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. *Proc. Natl. Acad. Sci. USA* 108, 16050–16055.
- Carlin, A.F., Uchiyama, S., Chang, Y.C., Lewis, A.L., Nizet, V., Varki, A., 2009. Molecular mimicry of host sialylated glycans allows a bacterial pathogen to engage neutrophil Siglec-9 and dampen the innate immune response. *Blood* 113, 3333–3336.
- Chandy, K.G., Wulff, H., Beeton, C., Pennington, M., Gutman, G.A., Cahalan, M.D., 2004. K+ channels as targets for specific immunomodulation. *Trends Pharmacol. Sci.* 25, 280–289.
- Choi, H.W., Brooking-Dixon, R., Neupane, S., Lee, C.J., Miao, E.A., Staats, H.F., Abraham, S.N., 2013. *Salmonella typhimurium* impedes innate immunity with a mast-cell-suppressing protein tyrosine phosphatase, SptP. *Immunity* 39, 1108–1120.
- Costa-Pinto, F.A., Basso, A.S., 2012. Neural and behavioral correlates of food allergy. *Chem. Immunol. Allergy* 98, 222–239.
- de Kivit, S., Saeland, E., Kraneveld, A.D., van de Kant, H.J., Schouten, B., van Esch, B.C., Knol, J., Sprickelman, A.B., van der Aa, L.B., Knippels, L.M., Garssen, J., van Kooyk, Y., Willemsen, L.E., 2012. Galectin-9 induced by dietary synbiotics is involved in suppression of allergic symptoms in mice and humans. *Allergy* 67, 343–352.
- Debarry, J., Garn, H., Hanuszkiewicz, A., Dickgreber, N., Blumer, N., von Mutius, E., Bufer, A., Gatermann, S., Renz, H., Holst, O., Heine, H., 2007. *Acinetobacter lwoffii* and *Lactococcus lactis* strains isolated from farm cowsheds possess strong allergy-protective properties. *J. Allergy Clin. Immunol.* 119, 1514–1521.
- Duffy, S.M., Cruse, G., Brightling, C.E., Bradding, P., 2007. Adenosine closes the K+ channel KCa3.1 in human lung mast cells and inhibits their migration via the adenosine A2A receptor. *Eur. J. Immunol.* 37, 1653–1662.
- Duffy, S.M., Cruse, G., Cockerill, S.L., Brightling, C.E., Bradding, P., 2008. Engagement of the EP2 prostanoid receptor closes the K+ channel KCa3.1 in human lung mast cells and attenuates their migration. *Eur. J. Immunol.* 38, 2548–2556.
- Duffy, S.M., Cruse, G., Lawley, W.J., Bradding, P., 2005. Beta2-adrenoceptor regulation of the K+ channel iKCa1 in human mast cells. *FASEB J.* 19, 1006–1008.
- Feleszko, W., Jaworska, J., Rha, R.D., Steinhilber, S., Avagyan, A., Jaudszus, A., Ahrens, B., Gronenberg, D.A., Wahn, U., Hamelmann, E., 2007. Probiotic-induced suppression of allergic sensitization and airway inflammation is associated with an increase of T regulatory-dependent mechanisms in a murine model of asthma. *Clin. Exp. Allergy* 37, 498–505.
- Forsythe, P., Bienenstock, J., 2012. The mast cell-nerve functional unit: a key component of physiologic and pathophysiologic responses. *Chem. Immunol. Allergy* 98, 196–221.
- Forsythe, P., Wang, B., Khambati, I., Kunze, W.A., 2012. Systemic effects of ingested *Lactobacillus rhamnosus*: inhibition of mast cell membrane potassium (IKCa) current and degranulation. *PLoS One* 7, e41234.
- Forsythe, P., Inman, M.D., Bienenstock, J., 2007. Oral treatment with live *Lactobacillus reuteri* inhibits the allergic airway response in mice. *Am. J. Respir. Crit. Care Med.* 175, 561–569.
- Frieling, T., Cooke, H.J., Wood, J.D., 1991. Serotonin receptors on submucous neurons in guinea pig colon. *Am. J. Physiol.* 261, G1017–G1023.
- Frieling, T., Cooke, H.J., Wood, J.D., 1993. Histamine receptors on submucous neurons in guinea pig colon. *Am. J. Physiol.* 264, G74–G80.
- Hacini-Rachinel, F., Gheit, H., Le Ludec, J.B., Dif, F., Nancey, S., Kaiserlian, D., 2009. Oral probiotic control skin inflammation by acting on both effector and regulatory T cells. *PLoS One* 4, e4903.
- Hart, A.L., Lammers, K., Brigidi, P., Vitali, B., Rizzello, F., Gionchetti, P., Campieri, M., Kamm, M.A., Knight, S.C., Stagg, A.J., 2004. Modulation of human dendritic cell phenotype and function by probiotic bacteria. *Gut* 53, 1602–1609.
- Hirashima, M., Kashio, Y., Nishi, N., Yamauchi, A., Imaizumi, T.A., Kageshita, T., Saita, N., Nakamura, T., 2004. Galectin-9 in physiological and pathological conditions. *Glycoconj. J.* 19, 593–600.
- Hisbergues, M., Magi, M., Rigaux, P., Steuve, J., Garcia, L., Goudercourt, D., Pot, B., Pestel, J., Jacquet, A., 2007. In vivo and in vitro immunomodulation of Der p 1 allergen-specific response by *Lactobacillus plantarum* bacteria. *Clin. Exp. Allergy* 37, 1286–1295.
- Inoue, R., Nishio, A., Fukushima, Y., Ushida, K., 2007. Oral treatment with probiotic

- Lactobacillus johnsonii* NCC533 (La1) for a specific part of the weaning period prevents the development of atopic dermatitis induced after maturation in model mice, NC/Nga. *Br. J. Dermatol.* 156, 499–509.
- Jenner, J., Kerst, G., Handgretinger, R., Muller, I., 2006. Increased alpha2,6-sialylation of surface proteins on tolerogenic, immature dendritic cells and regulatory T cells. *Exp. Hematol.* 34, 1212–1218.
- Jimenez, J.C., Federle, M.J., 2014. Quorum sensing in group A *Streptococcus*. *Front. Cell Infect. Microbiol.* 4, 127.
- Kakurai, M., Monteforte, R., Suto, H., Tsai, M., Nakae, S., Galli, S.J., 2006. Mast cell-derived tumor necrosis factor can promote nerve fiber elongation in the skin during contact hypersensitivity in mice. *Am. J. Pathol.* 169, 1713–1721.
- Kalliomaki, M., Kirjavainen, P., Eerola, E., Kero, P., Salminen, S., Isolauri, E., 2001. Distinct patterns of neonatal gut microflora in infants in whom atopy was and was not developing. *J. Allergy Clin. Immunol.* 107, 129–134.
- Kalliomaki, M., Salminen, S., Poussa, T., Arvilommi, H., Isolauri, E., 2003. Probiotics and prevention of atopic disease: 4-year follow-up of a randomised placebo-controlled trial. *Lancet* 361, 1869–1871.
- Kamiya, T., Wang, L., Forsythe, P., Goettsche, G., Mao, Y., Wang, Y., Tougas, G., Bienenstock, J., 2006. Inhibitory effects of *Lactobacillus reuteri* on visceral pain induced by colorectal distension in Sprague–Dawley rats. *Gut* 55, 191–196.
- Kanjarawi, R., Dy, M., Bardel, E., Sparwasser, T., Dubois, B., Mecheri, S., Kaiserlian, D., 2013. Regulatory CD4+Foxp3+ T cells control the severity of anaphylaxis. *PLoS One* 8, e69183.
- Karimi, K., Kandiah, N., Chau, J., Bienenstock, J., Forsythe, P., 2012. A *Lactobacillus rhamnosus* strain induces a heme oxygenase dependent increase in Foxp3+ regulatory T cells. *PLoS One* 7, e47556.
- Karimi, K., Inman, M.D., Bienenstock, J., Forsythe, P., 2009. *Lactobacillus reuteri*-induced regulatory T cells protect against an allergic airway response in mice. *Am. J. Respir. Crit. Care Med.* 179, 186–193.
- Kawahara, T., 2010. Inhibitory effect of heat-killed *Lactobacillus* strain on immunoglobulin E-mediated degranulation and late-phase immune reactions of mouse bone marrow-derived mast cells. *Anim. Sci. J.* 81, 714–721.
- Kendall, M.M., Sperandio, V., 2007. Quorum sensing by enteric pathogens. *Curr. Opin. Gastroenterol.* 23, 10–15.
- Kim, J.Y., Choi, Y.O., Ji, G.E., 2008. Effect of oral probiotics (*Bifidobacterium lactis* AD011 and *Lactobacillus acidophilus* AD031) administration on ovalbumin-induced food allergy mouse model. *J. Microbiol. Biotechnol.* 18, 1393–1400.
- Kong, H.H., Oh, J., Deming, C., Conlan, S., Grice, E.A., Beatson, M.A., Nomicos, E., Polley, E.C., Komarow, H.D., Murray, P.R., Turner, M.L., Segre, J.A., 2012. Temporal shifts in the skin microbiome associated with disease flares and treatment in children with atopic dermatitis. *Genome Res.* 22, 850–859.
- Kunze, W., Mao, Y., Forsythe, P., Bienenstock, J., 2006. Effect of *Lactobacillus* sp. (Lb) probiotic ingestion on membrane properties of intrinsic sensory neurons in rat colon. *Gastroenterology* 130, A401.
- Larsen, L., Chen, H.Y., Saegusa, J., Liu, F.T., 2011. Galectin-3 and the skin. *J. Dermatol. Sci.* 64, 85–91.
- Leon, A., Burianni, A., Dal Toso, R., Fabris, M., Romanello, S., Aloe, L., Levi-Montalcini, R., 1994. Mast cells synthesize, store, and release nerve growth factor. *Proc. Natl. Acad. Sci. USA* 91, 3739–3743.
- Leung, A.D., Schiltz, A.M., Hall, C.F., Liu, A.H., 2008. Severe atopic dermatitis is associated with a high burden of environmental *Staphylococcus aureus*. *Clin. Exp. Allergy* 38, 789–793.
- Li, C.Y., Lin, H.C., Hsueh, K.C., Wu, S.F., Fang, S.H., 2010. Oral administration of *Lactobacillus salivarius* inhibits the allergic airway response in mice. *Can. J. Microbiol.* 56, 373–379.
- Li, H., Wang, L., Ye, L., Mao, Y., Xie, X., Xia, C., Chen, J., Lu, Z., Song, J., 2009. Influence of *Pseudomonas aeruginosa* quorum sensing signal molecule N-(3-oxododecanoyl) homoserine lactone on mast cells. *Med. Microbiol. Immunol.* 198, 113–121.
- Lim, L.H., Li, H.Y., Huang, C.H., Lee, B.W., Lee, Y.K., Chua, K.Y., 2009. The effects of heat-killed wild-type *Lactobacillus casei* Shirota on allergic immune responses in an allergy mouse model. *Int. Arch. Allergy Immunol.* 148, 297–304.
- Lowery, C.A., Dickerson, T.J., Janda, K.D., 2008. Interspecies and interkingdom communication mediated by bacterial quorum sensing. *Chem. Soc. Rev.* 37, 1337–1346.
- Magerl, M., Lamm, V., Siebenhaar, F., Zuberbier, T., Metz, M., Maurer, M., 2008. Non-pathogenic commensal *Escherichia coli* bacteria can inhibit degranulation of mast cells. *Exp. Dermatol.* 17, 427–435.
- Mark Duffy, S., Berger, P., Cruse, G., Yang, W., Bolton, S.J., Bradding, P., 2004. The K+ channel *IKCA1* potentiates Ca2+ influx and degranulation in human lung mast cells. *J. Allergy Clin. Immunol.* 114, 66–72.
- Matsumoto, I., Inoue, Y., Shimada, T., Aikawa, T., 2001. Brain mast cells act as an immune gate to the hypothalamic–pituitary–adrenal axis in dogs. *J. Exp. Med.* 194, 71–78.
- Mazmanian, S.K., Round, J.L., Kasper, D.L., 2008. A microbial symbiosis factor prevents intestinal inflammatory disease. *Nature* 453, 620–625.
- Mizrahi, S., Gibbs, B.F., Karra, L., Ben-Zimra, M., Levi-Schaffer, F., 2014. Siglec-7 is an inhibitory receptor on human mast cells and basophils. *J. Allergy Clin. Immunol.* 134, 230–233.
- Moon, T.C., St. Laurent, C.D., Morris, K.E., Marcet, C., Yoshimura, T., Sekar, Y., Befus, A.D., 2010. Advances in mast cell biology: new understanding of heterogeneity and function. *Mucosal Immunol.* 3, 111–128.
- Nakamura, Y., Oscherwitz, J., Cease, K.B., Chan, S.M., Munoz-Planillo, R., Hasegawa, M., Villaruz, A.E., Cheung, G.Y., McGavin, M.J., Travers, J.B., Otto, M., Inohara, N., Nunez, G., 2013. *Staphylococcus delta*-toxin induces allergic skin disease by activating mast cells. *Nature* 503, 397–401.
- Nautiyal, K.M., Ribeiro, A.C., Pfaff, D.W., Silver, R., 2008. Brain mast cells link the immune system to anxiety-like behavior. *Proc. Natl. Acad. Sci. USA* 105, 18053–18057.
- Niide, O., Suzuki, Y., Yoshimaru, T., Inoue, T., Takayama, T., Ra, C., 2006. Fungal metabolite gliotoxin blocks mast cell activation by a calcium- and superoxide-dependent mechanism: implications for immunosuppressive activities. *Clin. Immunol.* 118, 108–116.
- Noval Rivas, M., Burton, O.T., Wise, P., Zhang, Y.Q., Hobson, S.A., Garcia Lloret, M., Chehoud, C., Kuczynski, J., DeSantis, T., Warrington, J., Hyde, E.R., Petrosino, J.F., Gerber, G.K., Bry, L., Oettgen, H.C., Mazmanian, S.K., Chatila, T.A., 2013. A microbiota signature associated with experimental food allergy promotes allergic sensitization and anaphylaxis. *J. Allergy Clin. Immunol.* 131, 201–212.
- Noverr, O.C., Huffnagle, G.B., 2005. The ‘microflora hypothesis’ of allergic diseases. *Clin. Exp. Allergy* 35, 1511–1520.
- O'Mahony, C., Scully, P., O'Mahony, D., Murphy, S., O'Brien, F., Lyons, A., Sherlock, G., MacSharry, J., Kiely, B., Shanahan, F., O'Mahony, L., 2008. Commensal-induced regulatory T cells mediate protection against pathogen-stimulated NF-kappaB activation. *PLoS Pathog.* 4, e1000112.
- Oksaharju, A., Kankainen, M., Kekkonen, R.A., Lindstedt, K.A., Kovanen, P.T., Korpela, R., Miettinen, M., 2011. Probiotic *Lactobacillus rhamnosus* downregulates FCER1 and HRH4 expression in human mast cells. *World J. Gastroenterol.* 17, 750–759.
- Rabinovich, G.A., Sotomayor, C.E., Riera, C.M., Bianco, I., Correa, S.G., 2000. Evidence of a role for galectin-1 in acute inflammation. *Eur. J. Immunol.* 30, 1331–1339.
- Rabinovich, G.A., Toscano, M.A., 2009. Turning ‘sweet’ on immunity: galectin-glycan interactions in immune tolerance and inflammation. *Nat. Rev. Immunol.* 9, 338–352.
- Riedler, J., Braun-Fahrlander, C., Eder, W., Schreuer, M., Waser, M., Maisch, S., Carr, D., Schierl, R., Nowak, D., von Mutius, E., 2001. Exposure to farming in early life and development of asthma and allergy: a cross-sectional survey. *Lancet* 358, 1129–1133.
- Ritchie, A.J., Whittall, C., Lazenby, J.J., Chhabra, S.R., Pritchard, D.I., Cooley, M.A., 2007. The immunomodulatory *Pseudomonas aeruginosa* signalling molecule N-(3-oxododecanoyl)-L-homoserine lactone enters mammalian cells in an unregulated fashion. *Immunol. Cell Biol.* 85, 596–602.
- Ritchie, A.J., Yam, A.O., Tanabe, K.M., Rice, S.A., Cooley, M.A., 2003. Modification of in vivo and in vitro T- and B-cell-mediated immune responses by the *Pseudomonas aeruginosa* quorum-sensing molecule N-(3-oxododecanoyl)-L-homoserine lactone. *Infect. Immunity* 71, 4421–4431.
- Round, J.L., Mazmanian, S.K., 2010. Inducible Foxp3+ regulatory T-cell development by a commensal bacterium of the intestinal microbiota. *Proc. Natl. Acad. Sci. USA* 107, 12204–12209.
- Rumbaugh, K.P., 2007. Convergence of hormones and autoinducers at the host/pathogen interface. *Anal. Bioanal. Chem.* 387, 425–435.
- Russell, S.L., Gold, M.J., Willing, B.P., Thorson, L., McNagny, K.M., Finlay, B.B., 2013. Perinatal antibiotic treatment affects murine microbiota, immune responses and allergic asthma. *Gut Microbes* 4, 158–164.
- Schiffer, C., Lallane, A.I., Cassard, L., Mancardi, D.A., Malbec, O., Bruhns, P., Dif, F., Daeron, M., 2011. A strain of *Lactobacillus casei* inhibits the effector phase of immune inflammation. *J. Immunol.* 187, 2646–2655.
- Shreiner, A., Huffnagle, G.B., Noverr, M.C., 2008. The ‘Microflora Hypothesis’ of allergic disease. *Adv. Exp. Med. Biol.* 635, 113–134.
- Shumilina, E., Lam, R.S., Wolbing, F., Matzner, N., Zemtsova, I.M., Sobiesiak, M., Mahmud, H., Sausbier, H., Biedermann, T., Ruth, P., Sausbier, M., Lang, F., 2008. Blunted IgE-mediated activation of mast cells in mice lacking the Ca2+-activated K+ channel *KCa3.1*. *J. Immunol.* 180, 8040–8047.
- Smetana, K.J., Andre, S., Kaltner, H., Kopitz, J., Gabius, H.J., 2013. Context-dependent multifunctionality of galectin-1: a challenge for defining the lectin as therapeutic target. *Expert Opin. Ther. Targets* 17, 379–392.
- St. John, A.L., Abraham, S.N., 2013. Innate immunity and its regulation by mast cells. *J. Immunol.* 190, 4458–4463.
- Stagg, A.J., Hart, A.L., Knight, S.C., Kamm, M.A., 2004. Microbial–gut interactions in health and disease. Interactions between dendritic cells and bacteria in the regulation of intestinal immunity. *Best Pract. Res. Clin. Gastroenterol.* 18, 255–270.
- Subramoni, S., Venturi, V., 2009. LuxR-family ‘solos’: bachelor sensors/regulators of signalling molecules. *Microbiology* 155, 1377–1385.
- Tang, Q., Bluestone, J.A., 2008. The Foxp3+ regulatory T cell: a jack of all trades, master of regulation. *Nat. Immunol.* 9, 239–244.
- Theoharides, T.C., 1996. The mast cell: a neuroimmunoendocrine master player. *Int. J. Tissue React.* 18, 1–21.
- Urb, M., Pouliot, P., Gravelat, F.N., Olivier, M., Sheppard, D.C., 2009. *Aspergillus fumigatus* induces immunoglobulin E-independent mast cell degranulation. *J. Infect. Dis.* 200, 464–472.
- van Houwelingen, A.H., Kool, M., de Jager, S.C.A., Redegeld, F.A.M., van Heuven-Nolsen, D., Kraneveld, A.D., Nijkamp, F.P., 2002. Mast cell-derived TNF- α primes sensory nerve endings in a pulmonary hypersensitivity reaction. *J. Immunol.* 168, 5297–5302.
- Varki, A., 2011. Since there are PAMPs and DAMPs, there must be SAMPs? Glycan “self-associated molecular patterns” dampen innate immunity, but pathogens can mimic them. *Glycobiology* 21, 1121–1124.
- Vikstrom, E., Tafazoli, F., Magnusson, K.E., 2006. *Pseudomonas aeruginosa* quorum sensing molecule N-(3-oxododecanoyl)-L-homoserine lactone disrupts epithelial barrier integrity of Caco-2 cells. *FEBS Lett* 580, 6921–6928.
- Vliagoftis, H., Befus, A.D., 2005. Rapidly changing perspectives about mast cells at mucosal surfaces. *Immunol. Rev.* 206, 190–203.
- Vliagoftis, H., Kouranos, V.D., Betsi, G.I., Falagas, M.E., 2008. Probiotics for the

- treatment of allergic rhinitis and asthma: systematic review of randomized controlled trials. *Ann. Allergy Asthma Immunol.* 101, 570–579.
- von Kockritz-Blickwede, M., Goldmann, O., Thulin, P., Heinemann, K., Norrby-Te-glund, A., Rohde, M., Medina, E., 2008. Phagocytosis-independent antimicrobial activity of mast cells by means of extracellular trap formation. *Blood* 111, 3070–3080.
- Walters, M., Sperandio, V., 2006. Quorum sensing in *Escherichia coli* and *Salmonella*. *Int. J. Med. Microbiol.* 296, 125–131.
- Wang, B., Mao, Y.K., Diorio, C., Wang, L., Huizinga, J.D., Bienenstock, J., Kunze, W., 2010. *Lactobacillus reuteri* ingestion and IK(Ca) channel blockade have similar effects on rat colon motility and myenteric neurones. *Neurogastroenterol. Motil.* 22 (98–107), e33.
- Wesolowski, J., Paumet, F., 2014. *Escherichia coli* exposure inhibits exocytic SNARE-mediated membrane fusion in mast cells. *Traffic* 15, 516–530.
- Weston, S., Halbert, A., Richmond, P., Prescott, S.L., 2005. Effects of probiotics on atopic dermatitis: a randomised controlled trial. *Arch. Dis. Child* 90, 892–897.
- Won, T.J., Kim, B., Lim, Y.T., Song, D.S., Park, S.Y., Park, E.S., Lee, D.I., Hwang, K.W., 2011. Oral administration of *Lactobacillus* strains from Kimchi inhibits atopic dermatitis in NC/Nga mice. *J. Appl. Microbiol.* 110, 1195–1202.
- Wood, J.D., 2007. Neuropathophysiology of functional gastrointestinal disorders. *World J. Gastroenterol.* 13, 1313–1332.
- Wu, H., Song, Z., Givskov, M., Doring, G., Worlitzsch, D., Mathee, K., Rygaard, J., Hoiby, N., 2001. *Pseudomonas aeruginosa* mutations in lasI and rhlI quorum sensing systems result in milder chronic lung infection. *Microbiology* 147, 1105–1113.
- Wulff, H., Beeton, C., Chandy, K.G., 2003. Potassium channels as therapeutic targets for autoimmune disorders. *Curr. Opin. Drug Discov. Dev.* 6, 640–647.
- Wulff, H., Knaus, H.G., Pennington, M., Chandy, K.G., 2004. K⁺ channel expression during B cell differentiation: implications for immunomodulation and autoimmunity. *J. Immunol.* 173, 776–786.
- Zimmermann, S., Wagner, C., Muller, W., Brenner-Weiss, G., Hug, F., Prior, B., Obst, U., Hansch, G.M., 2006. Induction of neutrophil chemotaxis by the quorum-sensing molecule N-(3-oxododecanoyl)-L-homoserine lactone. *Infect. Immunity* 74, 5687–5692.