ICMI 2009: all immunity is mucosal

Following his first and only electoral defeat, for a seat on the city council of Cambridge, MA, then-future Speaker of the House Tip O'Neill famously remarked, "All politics is local." Reflecting on the highly successful 14th International Congress of Mucosal Immunology (ICMI), held 5–9 July in Boston—just across the Charles River from O'Neill's home district—one could posit that this message applies just as well to the immune system: all immunity is local (i.e., mucosal). The theme of ICMI 2009, "reconciling immunity, tolerance and inflammation at the mucosal interface," highlights the concept that properly regulated mucosal immunity is critical to overall health and well-being. The cells that populate the mucosal surfaces of the body are confronted on a daily basis with local challenges from microbes, food antigens, and environmental pollutants, and must inform the systemic immune system about issues that affect the body as a whole. Immune homeostasis at the mucosal level allows the body to obtain nourishment from foreign substances and to develop a mutualistic relationship with its resident microbiota, without disrupting the balance of power. By contrast, mucosal unrest can lead to local damage in the form of an unregulated inflammatory response, with the potential to spread throughout the body in the form of autoimmune and allergic diseases and even cancer. The breadth of current research in mucosal immunology was evidenced by the diversity of topics of the morning plenary sessions at ICMI 2009, including microbe–host interactions, innate immunity, epithelial cells, B- and T-cell function and regulation, novel cytokines, mucosal diseases, and mucosal vaccines. These topics were expanded on at oral and poster sessions in the afternoons and discussed well into the evenings by immunologists from all corners of the globe who appreciate that *all immunity is mucosal.*

One theme that bridged the many topics addressed at ICMI 2009 is the dynamic interplay between the commensal microbiota and the mucosal immune system. While the crucial role of resident bacteria in the development, activation, and regulation of immunity has long been appreciated, far less is known about the roles of specific bacterial species and interactions among species.[1] Recent advances in metagenomics have greatly increased our knowledge of the composition of microbial communities at the mucosal surface[2] and have triggered new interest in unraveling the complexity of host immune interactions with commensal bacteria. Nowhere is the impact of the microbiota more evident than in the intestine, where upward of 15,000 individual bacterial species inhabit the mucosal surface. It is now clear that the microbial "signature" varies widely among individuals, and that alterations in the composition of the gut microbiota ("dysbiosis") are associated with local inflammation that can cause significant collateral damage and give rise to systemic disease. Apropos of the theme of microbe–host interactions, ICMI 2009 was kicked off by a pre-congress workshop, "Microbes and Mucosal Immunity," which Peter Ernst (University of Virginia) and I cochaired. At the conclusion of this workshop, ICMI 2009 opened with a keynote lecture by Brett Finlay (University of British Columbia), "Studying the Microbiome in Mucosal Tissues."

Among the many topics related to microbe–host interactions at ICMI 2009, three specific examples illustrate the contribution of microbes to immunopathology: inflammatory bowel disease (IBD), colorectal cancer, and type 1 diabetes.

In his presentation of the Tsuchiya Memorial Lecture, Charles Elson (University of Alabama at Birmingham) discussed his recent work on the interactions among the intestinal microbiota, regulatory T cells (Tregs), and immunoglobulin A (IgA) in the maintenance of intestinal homeostasis. Elson's research has implicated the flagellar antigen CBir1 in the etiology of Crohn's disease, a form of IBD.[3,4] He presented evidence that Tregs in the gut promote the production of secretory IgA specific for antigens such as CBir1, which in turn limits systemic T-cell exposure to potentially immunogenic microbial antigens. Specific depletion of Tregs was found to cause a decrease in intestinal anti-CBir1 IgA, accompanied by increased proliferation of pro-inflammatory CBir1 effector T cells. Elson concluded that the Treg–IgA–microbiota homeostatic pathway stabilizes the gut microbiota, prevents pro-inflammatory T-cell responses, and provides resistance to colonization by pathogenic microorganisms. Another example of regulation by the microbiota of intestinal inflammation was presented by Dan Littman (New York University) in the plenary session "Novel Cytokines at Mucosal Surfaces" (chaired by Jo Viney, Amgen). Littman's research has implicated specific species of segmented filamentous bacteria (SFB) in promoting the differentiation of pro-inflammatory helper T cells that produce interleukin (IL)-17 (Th17 cells).[5] He presented evidence that mice lacking SFB in their gut microbiota have high numbers of mucosal Tregs and virtually no Th17 cells. Co-housing these mice with mice colonized with SFB was sufficient to induce development of Th17 cells and to exacerbate experimental colitis. New data from Littman's group suggest that the balance of Tregs and Th17 cells in the gut is regulated by local concentrations of transforming growth factor-β, which at low levels promotes synthesis of the transcription factor RORγt and differentiation of Th17 cells, and at high levels promotes synthesis of the transcription factor FoxP3 and differentiation of Tregs. Other examples of bacteria that promote inflammation were presented in oral and poster sessions throughout the meeting, and it is clear that characterization of microbe–host interactions will be crucial to understanding and preventing IBD and other inflammatory diseases.

While certain types of bacteria promote intestinal inflammation, others appear to ameliorate inflammation and promote homeostasis in surprising ways. In the plenary session "Molecular Basis of Microbial–Immune Interactions at the Wet Surfaces of the Body" (chaired by Roy Curtiss, Arizona State University), Dennis Kasper (Brigham and Women's Hospital) discussed a novel mechanism by which bacterial capsular polysaccharides can ameliorate inflammation. Kasper's group recently reported that polysaccharide A (PSA) from *Bacteroides fragilis* protects mice from experimental colitis induced by *Helicobacter hepaticus*, a widespread commensal bacterium that can act as an opportunistic pathogen in immunocompromised hosts.[6] Kasper presented evidence that PSA, either as part of intact *B. fragilis* or as a purified polysaccharide, ameliorates colitis through a mechanism requiring IL-10-producing helper T cells. Another example of an anti-inflammatory bacterial product was described by Brent Polk (Vanderbilt University) in the plenary session "Mucosal Epithelium." Polk's group has reported that soluble products from the probiotic bacterium *Lactobacillus rhamnosus* GG (LGG) regulate intestinal epithelial cell survival and growth, thereby enhancing barrier function and limiting exposure of bacterial antigens to the systemic immune system.[7] Polk presented new data suggesting that the beneficial effects of a soluble 40-kDa protein from LGG involve stimulation of the kinase activity of the epidermal growth factor receptor in intestinal epithelial cells. Exciting new research on the anti-inflammatory effects of probiotic bacteria and their products was presented in many sessions at ICMI 2009, offering the hope that new probiotic-based therapies for inflammatory diseases will emerge in the near future.

Uncontrolled intestinal inflammation is a risk factor for epithelial neoplasia in mice with experimental colitis as well as in humans with IBD, and recent evidence has suggested that the gut microbiota may contribute to cancer development.[8] In the Distinguished Keynote Lecture, "Transmissible Ulcerative Colitis and Colorectal Cancer Driven by T-bet in Dendritic Cells," Laurie Glimcher (Harvard School of Public Health) presented convincing evidence that alterations in the colonic microbiota can contribute directly to intestinal inflammation and subsequent development of colorectal cancer. Recent work from Glimcher's group revealed an unexpected function for the transcription factor T-bet in regulating intestinal inflammation and the composition of the colonic microbiota.[9] Immunodeficient ($Rag^{-/-}$) mice with a concurrent deletion in the T-bet gene spontaneously developed intestinal inflammation similar to that seen in humans with ulcerative colitis (UC), a form of IBD, and were hence termed TRUC mice. Genetically normal mice housed with TRUC mice developed colitis, suggesting that colitis is "communicable" via the gut microbiota. Glimcher presented new evidence that TRUC mice spontaneously develop epithelial neoplasia, recapitulating key features of UC-associated colorectal cancer. The TRUC epithelium was found to be hyperproliferative, with elevated expression of antiapoptotic proteins. A key role for dendritic cells (DCs) was evidenced by the findings that deletion of DCs ablated colitis and that re-expression of T-bet specifically in DCs blunted both colitis and neoplasia. Although the specific bacterial species that contribute to communicable TRUC colitis and neoplasia have not yet been identified, this exciting avenue of research offers the promise to increase our understanding of the etiology of IBD and colitis-associated cancer as well as the potential development of therapies that target the colonic microbiota.

A third example of a novel connection between the gut microbiota and inflammatory disease was presented by Alex Chervonsky (University of Chicago) in the plenary session "Molecular Basis of Microbial–Immune Interactions." Chervonsky's research has recently revealed an important contribution of innate immunity and the intestinal microbiota to the development of type 1 diabetes, which is characterized by autoimmune destruction of pancreatic islets.[10] Interestingly, deletion of the gene encoding the Toll-like receptor adaptor protein MyD88 was found to prevent the development of islet inflammation in non-obese diabetic (NOD) mice. Dependence of this effect on the gut microbiota was evidenced by the finding that germ-free $MyD88^{-/-}$ mice developed robust diabetes, which could be reversed by colonization of the mice with a defined microbial consortium of bacteria typically present in the human colon. Chervonsky presented data from metagenomic analyses demonstrating that MyD88 deficiency in and of itself leads to an alteration in the composition of the gut microbiota, which in turn can contribute to systemic inflammation. This example highlights the complex interplay between microbial and host cells, and offers an explanation for the synergy between genetic and environmental factors in the development of type 1 diabetes. Future identification of specific inflammatory and protective bacterial species could lead to the development of new preventive or therapeutic strategies for type 1 diabetes and other autoimmune diseases.

These three examples offer a taste of new developments in the emerging field of microbe–host interactions in mucosal immunity, but they represent only a portion of the exciting new research in this area that was presented at ICMI 2009. Hopefully, new insights and collaborations resulting from this meeting of like-minded scientists in Boston will provide a stimulus for this promising line of research. We should be vigilant, however, to avoid falling into a "host-centric" view of our interactions with our resident microbiota. As aptly described by Jorge Galán (Yale University) in the plenary session "Molecular Basis of Microbial–Immune Interactions," pathogens are continually coevolving with

our immune system and finding new ways to prevent or exploit inflammatory responses designed to promote their elimination. Even bacteria traditionally viewed as "commensal" may change their behavior in ways that promote their survival to our detriment, particularly in combination with host genetic predispositions and environmental pressures in the form of, for example, sanitation, vaccination, and antibiotic use. It is also well to remember the prescient admonition of Louis Pasteur: "*C'est les microbes qui auront le dernier mot*" (the microbes will have the last word).

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Book review: *The Big Necessity*

The Big Necessity: The Unmentionable World of Human Waste and Why It Matters
Rose George
Metropolitan Books, New York, 2008 (304 pp)

Lars Hanson's career in mucosal immunology has bridged his basic research characterizing secretory immunoglobulin A in human milk to the importance of breast-feeding for the improvement of human health. His advocacy provided scientific merit that helped redirect federal budgets in Costa Rica toward maternal–infant health, leading to dramatic reductions in infant mortality.[1]

In this book, Rose George describes global deficiencies in sanitation and does a favor for basic research by reminding readers of the social relevance of mucosal immunology. In a well-researched and referenced social commentary, she notes that 40% of humanity—2.6 billion people—have no alternative to open defecation. That means "no access to any latrine, toilet, bucket or box," just "bare bottoms doing what they must." The estimated tonnage in raw sewage is numbing (200,000 tons every day in India alone). The author points out that the vastness of the enteric microbiome causes numerous mucosal diseases when sewage is not handled properly: "Feces can get into fluid and onto fields, fingers, flies, and foods." The impact of contamination is reflected in the Bangladeshi slogan "A fly is deadlier than a thousand tigers." She notes that diarrhea "kills a child every 15 seconds"—more than 2.2 million per year. Clearly, there are limits to any protection attributable to the hygiene hypothesis.

George visits a range of strategies to protect people from contaminated water, including John Snow's removal of London's Broad Street pump handle to stem a cholera outbreak. She toured the world's grand sewers and observed open defecation in the worst slums imaginable. She interviewed politicians, functionaries, engineers, sewer workers, and defecators from China, Bangladesh, and India, as well as Europe and the United States. No relevant issue is left unexplored, including the economic, social, and cultural pressures that lead to the acceptance of or resistance to change.

The discussion carries on with great humor (she cites a joke told in Moscow: "How do you use a latrine in a Russian winter? Quickly.") and candor as George provides details that only someone interested in gastroenterology might appreciate. To say the text is indelicate is an understatement, but she points out that disgust is an effective motivation that encourages people to contain waste. Despite the existence of many euphemisms for excrement, the author observes that the absence of a conversational term contributes to the lack of meaningful discussion. She notes that the Greek word *skihzein*, the Latin *scindere*, and the Old English *scitan* are the noble relatives of "shit." The term is used throughout the book and, as she writes, "people who deal with things best are the ones not afraid of it."

While the infrastructure in wealthier countries is better, the author points out that many of our large cities allow sewage to run untreated into major waterways. As a result of shortcomings in infrastructure, rain runoff is mixed with sewage, forcing the discharge of untreated waste. This, along with agricultural runoff, causes outbreaks of diarrhea and death, even in the United States and Canada. Mucosal vaccines for foodborne illnesses and biodefense remain a huge need in our own health-care systems.

After spending nearly 30 years editing manuscripts and grant applications critically, I may be too sensitive to editorial errors, but a few exist that lead the reader to be wary of some of the statistics presented. Nonetheless, the case George makes is compelling.

The relevance of the book to those of us in the field of mucosal immunology is clear, as mucosal immunologists can have a positive impact in many areas. The biggest challenge may be the unchecked expansion of the global population. Mucosal vaccines targeted to the urogenital tract may yet be developed for birth control as well as for protection from sexually transmitted diseases, potentially reducing the devastating toll of HIV infection. Similarly, infections of the airway can be controlled through better sanitation as a complement to new mucosal vaccines.

Bathing in contaminated water and aerosol exposures can cause infections of the urogenital tract and airway, but enteric infection accounts for the overwhelming share of the health-care burden. As we are reminded in this book, "No act of terrorism generates economic devastation on the scale of the crisis in water and sanitation." In addition to the mortality, enteric infections cause substantial morbidity associated with frequent outbreaks of diarrhea. Increasingly, malnutrition is viewed as an enteric, infectious disease that leads to stunted growth and impaired cognitive development.[2] Mucosal vaccines for enteric infections may not work optimally without improvements in sanitation, because the overwhelming number of recurrent challenges may thwart the most innovative immunization protocols and limit herd immunity.

After reading this book, most people will wash their hands a little longer and think a little more before they flush. Given that many of us will never travel to these poorer countries, George's impassioned descriptions will give readers a better appreciation of the challenges. A mucosal immunologist will be even more inspired by the urgency for vaccine development. From Lars Hanson's perspective, this book describes issues that support advocacy by both scientists and nonscientists for greater funding of sanitation in order to reduce the infectious burden enough to allow new vaccines to succeed.

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