Gut reactions: immune pathways in the intestine in health and disease

During my biochemistry degree I became fascinated by the complexity and wonder of the immune system. How in the vast majority of us it steadfastly protects from pathogens but in others, it turns on our own tissues or innocuous environmental antigens leading to autoimmune and chronic inflammatory diseases. It is evident that on the one hand, the immune system is vital for human health but that when dysregulated also has the capacity to kill the host.

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We now know that alongside other mechanisms of self-tolerance functionally specialized regulatory T cells (Treg) play a non-redundant role in controlling the immune response to both self- and environmental antigens. In this perspective, I describe my early work that contributed to the discovery of Treg and our more recent focus on elucidation of their function in intestinal homeostasis.

Do not mention the S word

After a brief spell in the City of London as an accountant, I was lucky enough to land a PhD position in Don Masons’ Lab in the Cellular Immunology Unit, Sir William Dunn School of Pathology, University of Oxford. The CIU was headed by the dynamic and brilliant Alan Williams who, with Neil Barclay, discovered the Ig superfamily of leukocyte surface proteins. The Oxford group had produced a large series of monoclonal antibodies (mAbs) against cell surface proteins. These tools revolutionized the study of immune cells allowing the molecular characterization of cell surface proteins, as well as the description of markers that could distinguish functional immune subsets. With a mAb termed OX-22 (which recognized an isof orm of CD45) in hand, I was able to build on work ongoing in Don’s Lab to show that this antibody subdivided rat CD4+ T cells into functionally distinct populations. The most striking observation was that transfer of the OX-22high subset to nude rats led to a fatal inflammatory disease, which could be prevented by co-transfer of the reciprocal OX-22low population (Powrie & Mason, 1990). There was no debating the functional significance of an outcome of life or death. To us, these results provided clear evidence of the existence of a specialized CD4+ T-cell subset that regulated the function of other T cells.

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Similar results providing evidence for dominant mechanisms of immune tolerance had also emerged from several other labs including Shimon Sakughi, Antonio Coutinho and Nicole Ledouarin (reviewed in Maloy & Powrie, 2001).

The late eighties and early nineties was an exciting era in immunology with rapid advances in our understanding of the molecular basis of T-cell reactivity, thymic selection and cell intrinsic mechanisms of tolerance. The emphasis was on immune cell activation and interest in the concept of T-cell-mediated suppression, first postulated in the early 1970s, had declined as a result of poorly characterized mechanisms of action. Against this backdrop the re-emergence of dominant tolerance and immune suppression was treated with some scepticism. However, a small group of us pursued these studies and with advances in the area of CD4+ T-cell heterogeneity based on cytokine secretion, this led to the renaissance of the immune suppression field. Suppressor cells were reborn as Treg, a term which more accurately describes their function.

Cytokines, intercellular messengers of the immune response

To gain further insight into mechanisms of immune regulation, I joined Bob Coffman’s Lab at The DNAX Research Institute in Palo Alto, CA as a postdoctoral fellow. I arrived at DNAX during a golden era. Bob and Tim Mossman had described the influential Th1 and Th2 model for functional specialization of mouse CD4+ T cells based on the differential expression of cytokines (Mossman & Coffman, 1987). The corridors were buzzing as new cytokines were discovered and mapped to immune cell functions. My project was to analyze the role of T-cell subsets and cytokines in response to the intracellular protozoan Leishmania major. Somewhat serendipitously these studies took me back to my PhD work as transfer of CD4+ CD45RBlow T cells to T- and B-cell-deficient severe combined immune deficiency mice, resulted in a chronic colitis resembling aspects of inflammatory bowel disease (IBD) in humans. Although not the primary aim of my project, Bob encouraged me to pursue these findings. Our results revealed a pathogenic role for Th1 cells and the cytokines interferon gamma (IFN-γ) and tumour-necrosis factor (TNF)-α in driving experimental colitis (Powrie et al, 1994). Similar to the rat studies, T-cell transfer colitis could be inhibited by CD4+ CD45RBlow T cells. As Th2 cells had been shown to reciprocally regulate the Th1 response, it seemed likely that differential activation of Th2 responses might explain Treg activity. However, we found that Treg function was IL-4-inde-
ependent but required TGF-β production (Powrie et al., 1996). These results together with those from Howard Weiner’s Lab suggested that TGF-β producing Treg were functionally distinct from Th2 cells (Maloy & Powrie, 2001).

By the late nineties, interest in Treg cells and their fundamental role in immune homeostasis was increasing. The identification by Shimon Sakaguchi of CD25 as marker aided purification of these cells (Sakaguchi, 2005). However, there was much debate about their mechanism of action with evidence for cytokine-dependent and -independent functions. The identification of the transcription factor forkhead box P3 (Foxp3) as a key component of Treg cell selection in the thymus and function, cemented Treg cells as a bona fide T-cell subset with a non-redundant role in the immune system (Sakaguchi, 2005). Patients with loss of function, mutations in the FOXP3 gene develop a fatal inflammatory response with dysregulated mucosal immunity and autoimmune disease illustrating the pivotal role of this pathway in immune homeostasis in humans. Today the Treg field is thriving. Key advances in the molecular control of Treg function have shown that Treg cells adapt to environmental conditions and utilize a range of suppressive mechanisms that are tuned to the inflammatory responses they control.

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The importance of balance

The T-cell transfer model of colitis together with a number of genetic models of chronic intestinal inflammation, illustrated the importance of balance between inflammatory and regulatory pathways for intestinal health. These models showed us how genetic predisposition can render the host susceptible to the development of a deranged inflammatory response to our usually beneficial intestinal bacteria. The complex and poorly characterized interactions between the intestinal immune system and commensal bacteria captivated me and this area has become the focus of my current research. In 1996, I was awarded a Wellcome Trust Senior Research Fellowship in basic biomedical science to characterize immune pathways in the

Figure 1. Intestinal homeostasis and its breakdown in chronic colitis. Under homeostatic conditions RORγt expressing lymphoid cells including Th17 cells, γδ T cells and innate lymphoid cells promote host defence and repair. IL-10 secreting Treg cells are abundant and prevent pathological inflammatory responses. In colitis, sustained IL-23 production in response to colitogenic bacteria promote pathological Type 17 responses with elaboration of inflammatory cytokines and repression of the Treg response.
intestine in health and disease. These excellent awards allow early stage researchers the independence to establish their own labs and to compete internationally. I returned to Oxford initially to the Nuffield of Department of Surgery and then to the Sir William Dunn School of Pathology. Since establishing my own lab, we have focussed on understanding the specialized functions of immune cells in the intestine, how they act as an integrated unit and how the diverse and abundant intestinal microbiota influences their functions.

Our results have shown that Foxp3+ Treg cells are abundant in the intestine and produce high levels of the immune suppressive cytokine interleukin 10 (IL-10), which is required for the control of intestinal homeostasis (Asseman et al, 1999). We also found that the intestine is a specific site for the generation of Treg cells reactive with intestinal antigens through the actions of specialized dendritic cells, the vitamin A metabolite retinoic acid and TGF-β (Coombes and Powrie, 2008). Similar results were obtained by Howard Weiner, Juan Lafaille and Jasmine Belkaid and provided a cellular basis for the well-described phenomenon of oral tolerance. Indeed the capacity of the intestinal immune system to favour Treg induction and production of IL-10 may be an important component of host commensal mutualism, preventing deleterious inflammatory responses to intestinal bacteria.

Deficiencies in regulatory pathways in the presence of triggering intestinal bacteria can lead to chronic intestinal inflammation. Initially thought to be driven by an interleukin 12 (IL-12)-dependent Th1 response, Kevin Maloy and I made the unanticipated observation in collaboration with Dan Cua and colleagues at DNAX, of a functional role for the IL-12 family cytokine, interleukin 23 (IL-23), as key driver of T-cell transfer colitis (Ahern et al, 2008). Further analysis of this pathway led to the identification of a novel population of innate lymphoid cells (ILC) that mediate colitis through the production of Type-17 associated cytokines. Like Th17 cells, IL-23-driven ILC are dependent on the transcription factor retinoic acid receptor related orphan receptor gamma t (RORyt) indicating striking functional parallels between innate and adaptive lymphoid populations in the gut (Bonocore et al, 2010). Together these results highlight the multiple activities of IL-23 that mediate tissue inflammatory responses (Fig 1). Further understanding of the molecular signatures associated with interleukin 23 receptor (IL-23R) signalling in lymphoid cells may provide novel therapies in inflammatory disease.

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Challenges ahead—from the laboratory to the clinic

While we have made progress in identifying immune pathways that contribute to intestinal health and disease, we are only just beginning to unravel how these interface with the hundreds of species of commensal bacteria that inhabit the gastrointestinal tract. In IBD, genetically controlled malfunctions in a number of different pathways including intestinal barrier function, host defence and innate and adaptive inflammatory pathways, predispose to a dysregulated interplay between the microbiota and the intestinal immune system. The complex clinical and genetic subtypes in IBD, taken together with the individuality of the intestinal microbiota, raise formidable challenges ahead as we try to apply findings from experimental models to the development of novel therapies for IBD. Further understanding of individuality and commonality in IBD aetiology and pathogenesis is required to identify subgroups of patients that may benefit from more tailored therapeutic approaches. Towards this goal, in 2009 I was appointed as the Sidney Truelove Professor of Gastroenterology at Oxford to translate findings from fundamental mucosal immunology to the study of IBD. Advances in molecular microbiology, genetics and analysis of human clinical samples offer great hope that we can apply our growing knowledge of immune system bacterial interactions towards enhanced therapies for these devastating clinical conditions.

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Fiona Powrie
Experimental Medicine Division, Nuffield Department of Clinical Medicine, University of Oxford, John Radcliffe Hospital, Oxford, UK
E-mail: fiona.powrie@path.ox.ac.uk

Fiona Powrie is awarded the 2012 Louis Jeantet Prize for Medicine for her work on regulatory T cells and intestinal homeostasis. She is the Director of the Translational Gastroenterology Unit and head of the Experimental Medicine Division at the Nuffield Department of Clinical Medicine, University of Oxford, UK.

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