Preface

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The past several decades have witnessed great advances in our understanding of inflammatory bowel disease (IBD) in both its forms, Crohn's disease and ulcerative colitis. Some have arisen from bench research involving experimental models of intestinal inflammation or the study of tissues and cells obtained from patients, others from the clinical study of patients and their responses to various forms of treatment, and still others from environmental and genetic studies of large patient cohorts. These advances have led to a deeper understanding of the genetic basis of the disease, the relationship of the disease to the intestinal microflora, and the role of epithelial cells and the mucosal immune system in disease pathogenesis. Slowly, if fitfully, a general theory of disease causation is emerging that envisages IBD as a multifactorial disturbance of mucosal homeostasis leading to hyperresponsiveness of both the innate and the adaptive elements of the mucosal immune system.

In October of 2007 the Falk Foundation provided the resources to convene a workshop, entitled "Mechanisms of Intestinal Inflammation," that was dedicated to an in-depth review of current research focusing on the pathogenesis of IBD. Accordingly, scientists at the forefront of such research were brought together in the historic city of Dresden, Germany, to discuss their recent studies in this area and to submit these studies to the scrutiny of their peers. The work presented addressed each of the major areas of current IBD research. Taken together, it encapsulated many, if not all, of the significant advances in this field at the time of the meeting. Many of the invited speakers agreed to submit a written summary of their presentations for review and publication in *Mucosal Immunology*. This supplement to the journal contains the submitted papers and, as such, presents an excellent review of what is known about IBD.

The workshop was organized into segments reflecting the major research areas currently in play in the study of IBD. In an initial segment, the role of innate immune responses in IBD was the focus of discussion. Seth Rakoff-Nahoum discussed data showing that innate immune responses that could lead to inflammation are controlled by both passive and active mechanisms. The former consist of regulatory responses; the latter consist of physical barriers such as the epithelium, which shields immune elements from innate stimuli. These studies were nicely supportive of studies of CARD15 polymorphisms reported by Warren Strober. Dr. Strober provided strong evidence that the polymorphisms lead to increased susceptibility to Crohn's disease by impairing the capacity of the innate immune system to downregulate itself. Dr. Rakoff-Nahoum's concept also interdigitated with studies reported by

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Elke Cario showing that stimulation of epithelial cells via ligands for Toll-like receptor 2 greatly increase epithelial cell barrier function.

While innate immune responses induced by ligands in the intestinal microflora are an important component of IBD pathogenesis, adaptive responses to antigens associated with particular members of the microflora may also be important. In the next session of the workshop, Gerald Tannock reported on molecular techniques utilizing 16s ribosomal RNA identification by polymerase chain reaction and gel electrophoresis to characterize constituents of the microflora in IBD patients and controls. He showed that this technique distinguishes between the flora in ulcerative colitis and Crohn's disease patients, but, interestingly, the profiles do not distinguish between the flora associated with inflamed and non-inflamed tissue. In addition, he found that unclassified members of the phyla Bacteroidetes and Verrucomicrobia were more prevalent in patients with Crohn's disease than in those with ulcerative colitis, and it may be fruitful to determine whether these or other unclassified bacteria are important in the pathogenesis of IBD.

Reiner Duchmann, in related studies, has devised methods of obtaining conserved *Escherichia coli* proteins to determine whether patient responses to these proteins are dysregulated. Interestingly, IBD patients tended to respond to these proteins less frequently than controls did, perhaps indicating that there is in fact an imbalance in adaptive responses to bacterial antigens due to underlying defects in epithelial barrier or innate immune function. This approach holds promise for the identification of unique bacterial proteins that elicit dysregulated responses.

Recent studies of the cytokines that mediate inflammation in IBD have emphasized that underlying genetic and environmental factors in IBD are channeled through a defect in cytokine production. In a segment of the workshop devoted to this subject, Stefan Fichtner-Feigl reported on a chronic model of trinitrobenzene sulfonic acid colitis in which T helper type 1 (Th1) and Th17 cytokines dominate the inflammation in a sequential fashion and then are accompanied by the appearance of interleukin (IL)-13 and transforming growth factor (TGF)-β1 secretion, which induces a fibrotic reaction. This model is of great interest because it may replicate the march of cytokine events in the inflammation of Crohn's disease.

Markus Neurath discussed the IL-12 family of cytokines that dominates the inflammation of Crohn's disease. These include IL-12p70 and IL-23, the two cytokines that drive the Th1 and Th17 responses, respectively, and cross-regulate each other. He also described recent studies of other IL-12 family members, IL-27 and IL-35, which play important roles in regulatory T-cell development and function. Because these various cytokines signal through key intracellular molecules such as T-bet (T-box expressed in T cells) and various STAT (signal transducer and activator of transcription) proteins, Dr. Neurath suggested that future therapy of IBD will be focused on targeting these signaling molecules rather than the cytokines themselves. Finally, Ivan Fuss spoke about the cytokines that drive ulcerative colitis. He described studies that establish that this form of IBD, in contrast to Crohn's disease, is mediated by IL-13 produced by natural killer T (NKT) cells. He assembled data showing that IL-13 induces injury by directly affecting epithelial cell function and by

activating cytotoxic NKT cells that can "kill" epithelial cells.

In a session devoted to immunoregulatory defects in IBD, Fiona Powrie offered an update on her extensive work on the role of "natural" Foxp3$^+$ T cells in the pathogenesis of IBD. She reported on new findings showing that such regulatory T cells are induced by a particular population of dendritic cells that bear the CD103 marker and produce key regulatory T-cell–inductive factors, namely, TGF-β1 and retinoic acid. These studies provide a cellular and molecular basis for the phenomenon of oral tolerance and therefore provide a roadmap for unraveling the possible immune dysregulation existing in IBD. Atsushi Kitani continued the discussion of regulatory T cells by presenting data showing that they can paradoxically become Th17 effector cells under the influence of IL-6. This introduces the possibility that the effector and regulatory–T-cell responses in the gut are "plastic" or interconvertible. Thus, inflammation and control of inflammation by regulatory T cells can potentially be manipulated by changing the cytokine milieu of the gut.

Giovanni Monteleoni emphasized the role of TGF-β1 in regulatory activity in the gut by reporting on studies showing that the ability of gut cells to express Smad 7 limits immunoregulation in the gut by downregulating TGF-β1 signaling. Conversely, downregulation of Smad7 by delivery of a Smad7 antisense oligonucleotide facilitates TGF-β1 regulatory function. Such delivery thus protects mice from various forms of experimental colitis and is a potential therapy for patients with IBD. The importance of regulatory T cells in gut homeostasis was also evident in recent studies by Monica Boirivant. She showed that controlled breakdown of the epithelial barrier led to the generation of Foxp3$^-$, membrane TGF-β1$^+$ regulatory cells that protect mice from the induction of experimental colitis. This finding indicates that the mucosal immune system normally responds to the gut microflora with regulatory cell induction and that mild breaches of the epithelial barrier lead to reduced rather than increased inflammation.

Richard Blumberg reported on a new type of regulatory cell, one that expresses CEACAM1 on its cell surface and thereby recognizes CEACAM1 on other cells through homophilic interactions. It functions as a regulatory cell by activating inhibitory programs during cell–cell interaction mediated by CEACAM1 and, in fact, inhibits a broad range of immune responses due to its effects on proximal components of the signaling complex immediately downstream of the T-cell receptor/CD3 complex. This work emphasizes that regulatory cell function in the gastrointestinal tract is multifaceted and complex.

In the final segment of the workshop, investigators discussed the emerging role of the epithelium in mucosal homeostasis. Manolis Pasparakis reported on mice with a conditional deletion of *Iffg* (NEMO) in epithelial cells. NEMO is a key scaffolding protein in the NF-κB signaling pathway, and its deletion results in a broad defect in epithelial cell signaling via this pathway. Dr. Pasparakis showed that in the absence of such signaling, TNF-α induces epithelial cell apoptosis and ulcer formation. This, in turn, results in severe colonic inflammation. These studies thus emphasize the importance of epithelial barrier function in the prevention of inflammation. Jörg Schulzke sounded a similar theme in studies of the effects of IL-13 on epithelial cell barrier function. In studies of epithelial monolayers, Dr. Schulzke showed that IL-13 induced epithelial cell apoptosis, reduced epithelial

monolayer resistance, and induced pore-forming claudin-2 at tight junctions. In this manner, IL-13 disrupts the epithelial barrier and sets the stage for ulcerative colitis as alluded to above.

Finally, Jan Wehkamp reported on the role of epithelial defensins in IBD. He outlined his recent studies showing that patients with Crohn's disease have reduced Paneth cell α-defensin production, particularly patients with CARD15 abnormalities. In addition, patients manifest reduced β-defensin formation in the colon. Dr. Wehkamp suggests that this reduced defensin production leads to impaired bacterial killing and thus sets the stage for the inflammatory response in Crohn's disease.

It is apparent from this brief summary of the Dresden meeting that the participants delved into a majority of the major facets of current IBD research and in many instances defined its cutting edge. The workshop succeeded in providing outstanding scientific stimulation for the participants while the beauty of the restored center of Dresden succeeded in enhancing their appreciation of European culture and history.