Microbe-host interactions in the alimentary tract: the gateway to understanding inflammatory bowel disease

Inflammatory bowel disease (IBD), typified by ulcerative colitis and Crohn’s disease, has an aetiology that appears to possess both genetic and environmental components. A number of mouse models of intestinal inflammation have been identified. For example, the interleukin (IL)-10 knockout mouse develops inflammation that is histologically similar to Crohn’s disease while the IL-2 and T cell receptor α knockout animals develop inflammation that resembles ulcerative colitis. Together with other genetic mutant mouse models that develop IBD, these reports strongly support the view that genetic defects can predispose an individual to IBD. To our knowledge, however, the genetic defect models that have been described to date do not develop overt IBD if they are kept in a pathogen free environment, implying that the mucosal microflora plays a role in the initiation and/or perpetuation of the disease process. Despite the uncertain aetiology of IBD, the symptoms of the disease are associated with overproduction of proinflammatory cytokines and a commonly held view is that the disease is primarily a consequence of a deregulated adaptive immune system.

Transcriptional control of many inflammatory cytokines (including IL-4, tumour necrosis factor α (TNF-α), etc) is mediated by the transcription factor NF-κB, a key component in the inducible transcription of proinflammatory cytokines. NF-κB is normally retained in the cytoplasm by binding to its inhibitor protein, IκB, which masks the NF-κB nuclear localisation signal (NLS). A broad range of external stimuli that lead to activation of NF-κB set off signalling cascades that ultimately converge on the IκB kinase (IKK) complex. Activated IKK specifically and directly phosphorylates IκB and this phosphorylation event targets IκB for degradation. As a consequence, NF-κB NLS is uncovered and nuclear translocation occurs. External stimuli that can activate NF-κB include IL-1β, TNF-α, and bacterial lipopolysaccharide (LPS), the major constituent of Gram negative bacterial cell walls. Until recently the eukaryotic receptor for LPS remained elusive but a huge advance in this field was made when a mammalian homologue of Drosophila Toll was shown to transduce signals in response to LPS (including signals from Yersinia pseudotuberculosis and Y. enterocolitica), can infect a host without inducing a robust immune response. All three strains harbour a virulence plasmid that encodes a type III secretion system and this mediates secretion of different Yersinia effector proteins (Yops). On cell contact, Yops are translocated into eukaryotic cells where they interfere with cellular responses and ensure bacterial adherence. For example, through the action of YopH, Yersinia targets focal adhesion structures and can resist phagocytosis by macrophages. Another effector protein, YopJ, abrogates signalling pathways that lead to activation of NF-κB, the cyclic AMP response element binding protein (CREB), and activator protein 1 (AP-1) and it has recently been shown to have substrate specificity for several mitogen activated protein (MAP) kinase kinases. MAP kinase kinases (MAPKKs) are a conserved family of proteins that phosphorylate and activate specific downstream MAP kinases that in turn activate a variety of immediate early response genes critical for the production of cytokines and growth factors. The target of YopJ in signalling pathways that activate NF-κB is IKKβ and it appears to block the ability of IKK to phosphorylate IκB. As IKK is the converging point for the majority of extracellular stimuli that activate NF-κB (including signals from the TLRs), Yersinia has evolved an extremely efficient mechanism to counter inflammatory responses.

As mentioned above, YopJ can also interfere with CREB signalling, presumably by incapacitating the upstream MAPKKs that signal via p38 mitogen activated protein kinase (MAPK) through to CREB. One well documented target for CREB is AP-1, a transcription factor that is intimately involved in cell growth. YopJ can consequently affect the mitogenic potential of infected cells and is capable of inhibiting LPS induced clonal expansion in primary B cells.

Abbreviations used in this paper: IBD, inflammatory bowel disease; IKK, IκB kinase; LPS, lipopolysaccharide; TLR, toll-like receptor; PRR, pattern recognition receptor; MAP, mitogen activated protein; MAPK, mitogen activated protein kinase; IL, interleukin; NLS, nuclear localisation signal; TNF-α, tumour necrosis factor α; Yops, Yersinia effector proteins; CREB, cyclic AMP response element binding protein; AP-1, activator protein 1.
lymphocytes (Meijer et al, unpublished observations). The observation that p38 MAPK appears to be required for the development and activity of Th1 cells highlights an additional inhibitory potential of YopP. Therefore, it seems that YopP can counter inflammatory responses at multiple levels by interfering with both innate and adaptive immune responses.

A question arises as to whether the effects attributed to YopP are unique to Yersinia or can be thought of as a more generalised evolutionary trait of bacteria. Considering the huge bacterial load that the gastrointestinal tract receives—in a human individual this amounts to 2 kg of bacteria—the potential to activate TLRs (and thus NF-kB) is manifest. It is tempting to speculate that YopP-like proteins (or proteins that can perform the same role as YopP) have evolved in all commensal bacteria to help counter the induction of widespread inflammatory responses. Database comparisons of YopP protein sequence do indeed uncover a number of homologous proteins. The capacity to modulate inflammatory responses in animals or to interfere with hypersensitive responses in plants may therefore be evolutionarily conserved.

As well as having evolved mechanisms to control mammalian cell translocation via the type III secretion system, bacteria use additional tricks to modulate an inflammatory response. For example, the endotoxic activity of LPS resides in the lipid A portion of the molecule and alterations in the structure of lipid A can change the biological activity of LPS. Differences in LPS structure are presumably detected by TLRs that signal induction of distinct transcription factors. One could therefore simply envisage the commensal milieu as bacterial colonies that express endotoxin displaying a low biological activity with respect to mammalian cells and targets focal adhesions. An alternative and intriguing view is that different expression patterns of TLRs on different mucosal surfaces determine the inflammatory response. Indeed, recent studies have shown that bladder and intestinal epithelial cells display different TLR expression patterns (Richter-Dahlfors, unpublished observations) and this may go some way to explaining why certain uropathogenic Escherichia coli strains exist as commensal flora in the gut. Other bacterial surface molecules/structures such as intimin and fimbriae can also influence host responses.

A deregulated innate immune system. If we are to draw a greater understanding as to why certain bacteria are inflammation inducing pathogens, others are pathogens that evade inflammatory reactions, but the great majority exist in a peaceful symbiotic relationship with the host.

Research efforts that have been brought to bear on adaptive immunity over the past 20 years have revealed a number of dysfunctonal adaptive immune mechanisms that can predispose towards IBD. Good correlations have also been drawn between patients suffering from different forms of IBD and upregulated Th1 or Th2 driven immune responses. Innate immunity is now recognised as the bridge between the recognition of an invading microbial infection and mounting of an efficient adaptive immune reaction that can overcome the infection. It will surely not be long before genetic defects in innate immune mechanisms join those of its adaptive counterpart as predisposing factors in IBD. Although provocative, one could therefore view the upregulated Th1/Th2 responses in certain patients as a normal adaptive immune response (albeit a destructive one) to a deregulated innate immune system. If we are to understand pathological processes within the alimentary tract (typified by IBD) it is clear that the fundamental aspects of microbe-host interactions need to be examined in greater detail. By doing so, we will find novel therapeutic approaches in the treatment of chronic inflammation.