Published in final edited form as:
Clin Rev Allergy Immunol. 2010 February ; 38(1): 20–31. doi:10.1007/s12016-009-8133-2.

Crohn's Disease: an Immune Deficiency State

Daniel J. B. Marks, **Farooq Z. Rahman**, **Gavin W. Sewell**, and **Anthony W. Segal**
Department of Medicine, University College London, London, WC1E 6JJ, UK

Abstract

Crohn's disease is a chronic inflammatory disorder primarily affecting the gastrointestinal tract. Its clinical manifestations arise from a substantial infiltration of the intestinal mucosa by activated leukocytes and the downstream consequences of chronic inflammation. The underlying cause driving this immunological reaction remains poorly understood. A number of hypotheses have been proposed, most of which postulate a primary over-activation of the immune response, based on the pathological appearances of active Crohn's lesions. Interestingly, none of these theories have been mechanistically proven. It is possible that the immunological events responsible for disease initiation are quite different from those contributing to its persistence and propagation. A substantial body of data has emerged in recent years to suggest that the primary defect in Crohn's disease is actually one of relative immunodeficiency. This review considers the evidence for such a phenomenon in contrast to alternative prevailing hypotheses and attempts to address some of the potential paradoxes that it generates.

Keywords

Crohn's disease; Immunodeficiency; Macrophage; Neutrophil; Cytokine

Introduction

The underlying cause of the chronic intestinal inflammation that characterizes Crohn's disease remains heavily contested. While early theories focussed on potential infective etiologies, over the past three decades emphasis has shifted onto abnormalities of T cell function [1, 2]. A number of differences from healthy individuals have been described, but none proven to arise as primary phenomena. In marked contrast, in the 1970s, it was proposed that Crohn's disease resulted instead from a weak acute inflammatory response [3]. This view has been bolstered recently by novel immunological and clinical studies that have confirmed gross aberrations in this early response [4], consistent with subsequent genetic studies that highlighted molecules important for innate immune function [5]. The suggestion therefore is that Crohn's pathogenesis actually results from partial immunodeficiency, a theory that coincides with the frequent recognition of a virtually identical, non-infectious inflammatory bowel disease arising in patients with congenital monogenic disorders impairing phagocyte function [6]. The mechanisms responsible for these abnormalities in Crohn's disease are still being elucidated, but have substantial

D. J. B. Marks d.marks@ucl.ac.uk.

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

repercussions for its therapeutic management and broader implications for understanding the pathogenesis of other chronic inflammatory disorders.

Theories of disease pathogenesis

What is undisputed is that there is a clear requirement for the intestinal luminal contents for the development of Crohn's lesions. This is elegantly demonstrated by a series of clinical experiments in patients with active colonic disease in whom the fecal stream was diverted by creation of a proximal ileostomy. This led to rapid resolution of inflammation [7, 8]. Reintroduction of the bowel luminal contents, either by surgical re-anastomosis or experimentally infusing ileostomy effluent, provoked relapse of disease activity. Whether the stimulus to inflammation is an abnormal constituent of the fecal stream (possibly microbial) or an aberrant immune reaction to the normal bowel contents remains strongly contested.

Infectious etiology

The first formal case series of the syndrome now recognized as Crohn's disease was published in 1916 by T. Kennedy Dalziel [9]. It contained a clear clinicopathological description of the disorder and likened these appearances to those of mycobacterial infection of the gastrointestinal tract. A particular parallel was drawn to Johne's disease, a granulomatous ileitis in cattle caused by *Mycobacterium paratuberculosis* (MAP). There was therefore considerable excitement in the 1980s, when spheroplasts were isolated from Crohn's tissues, which in long-term culture developed Ziehl–Neelsen-positive cell walls and contained a MAP genome [10]. A number of studies using genetic and serological methodologies subsequently demonstrated that MAP was more prevalent in Crohn's patients [11].

Although a strong candidate, there are several pitfalls with the mycobacterial theory of pathogenesis [12]. Firstly, despite the superficial similarities to Johne's disease, there are a number of epidemiological, clinical, and pathological differences (Table 1) [13]. Secondly, rates of detection of MAP in Crohn's disease are highly variable, ranging from 0% to 100%, often with similar frequencies in healthy individuals [11]. Finally, a primary role for mycobacteria appears inconsistent with the effects of newer pharmacological agents. Inhibitors of tumor necrosis factor (TNF)-α are highly efficacious at suppressing inflammation in Crohn's patients, yet well-established to increase susceptibility to other mycobacteria [1]. Furthermore, a double-blind randomized controlled trial of anti-mycobacterial chemotherapy in Crohn's disease failed to provide any evidence of sustained benefit or cure [14]. While the latter has been criticized, mostly in terms of the doses of antibiotics employed and its failure to obtain microbiological confirmation of MAP elimination, it contributes to a growing body of evidence that primary infection with this organism does not represent the root cause of disease.

Numerous other microbiological agents have been advocated over the years as causative of Crohn's disease (Table 2). It is interesting that no obvious shared characteristics bind these together as a cohesive group. One that has attracted considerable interest recently is adherent-invasive *Escherichia coli* [15]. This organism was also first isolated from Crohn's

tissues and its candidacy advanced by observations of its effects in vitro. It is capable of invading both enterocytes and mononuclear phagocytes through the endocytic pathway, from which it subsequently escapes to exert a number of effects potentially relevant to Crohn's pathogenesis. These include the release of pro-inflammatory cytokines (including TNF-α and interleukin (IL)-8) and inducing macrophage differentiation into multinucleated giant cells that then aggregate into structures reminiscent of developing granulomata [16–18].

In general, the evidence for any one organism as the primary etiology of Crohn's disease is limited to individual small studies that report its isolation or detection at greater frequencies in Crohn's patients than healthy controls [19]. In no case has Koch's postulates been fulfilled. Many proponents of microbial hypotheses are now examining a different concept, that of dysbiosis [20]. This purports that subtle variations in the proportions of the normal bowel flora constituents disturb the homeostatic balance between pro-inflammatory and anti-inflammatory mechanisms. While the bowel bacterial contents do differ between patients and healthy individuals, it remains unknown as to what degree this is of primary pathogenic relevance and how much is secondary to a disease characterized by chronic diarrhea and long-term treatment with antibiotics and immunosuppressants.

Increased intestinal permeability

The normal intestinal mucosa constitutes a physical barrier, preventing the luminal contents from gaining access to the tissues of the bowel wall. A number of studies have demonstrated that the permeability of this layer is elevated in both Crohn's patients and their first degree relatives [21, 22], potentially caused by disruption of intercellular tight junctions [23]. Alterations in the overlying mucus barrier are also implicated both by association of polymorphisms in mucin genes with Crohn's disease [5, 24] and abnormal expression [25] and post-translational modification [26, 27] of their encoded proteins. A consequent reduction in mucosal integrity could predispose to increased exposure of the mucosal immune system to the bowel contents, stressing its capacity to degrade and remove exogenous material.

Excessive adaptive immune response

The prevailing dogma, however, is that Crohn's disease arises from an overly exuberant adaptive immune reaction. This is predominantly based on the observation that established lesions are replete with activated lymphocytes of a Th1 phenotype [1] and that current efficacious treatment largely consists of general immunosuppressants or more specific TNF-α antagonists such as infliximab [2].

Nonetheless, the initiating events behind this chronic inflammation remain unresolved. The evidence that Crohn's disease is an autoimmune disorder is not strong and it certainly fails to meet standard criteria for classification as such [19]. Although autoreactive T cells and antibodies have been reported, their pathogenic relevance is not proven. There is no animal model that accurately recapitulates all the clinical and pathological features of the human diseases, including those employing adoptive transfer techniques, nor is there strong association to any HLA haplotype. This contrasts markedly to the repertoire of

incontrovertibly established autoimmune disorders such as type 1 diabetes mellitus, myasthenia gravis, and Hashimoto's thyroiditis. It is therefore possible that all the abnormalities taken as evidence of a hyper-inflammatory etiology are secondary to a different underlying pathogenic process.

Genetic susceptibility to Crohn's disease

A hereditary component to Crohn's disease has long been recognized, with early epidemiological studies demonstrating approximately 50% disease concordance in monozygotic twins and familial clustering in up to 20% of patients [1]. It is also clear, however, that it is not transmitted in a simple Mendelian fashion and that a complex polygenic inheritance defines a susceptible genetic background upon which environmental factors exert influence.

Genome-wide linkage analyses in the 1990s revealed a number of chromosomal susceptibility loci, the strongest of which was *IBD1* on 16q [28]. Progressive refinement of the region by single nucleotide polymorphism (SNP) mapping identified polymorphisms in the *CARD15* gene, encoding the NOD2 protein, as the responsible variants [29, 30]. These results have been extended, such that up to 32 loci have now been characterized as predisposing to Crohn's disease (Table 3) [5]. The major and consistent theme to have emerged from these analyses is the central importance of the early innate immune response to bacteria, with distinct genes participating in functionally similar cellular processes such as pathogen recognition, the IL-12/IL-23 axis and autophagy.

CARD15

In 2001, two groups simultaneously discovered three SNPs in *CARD15* that were associated with Crohn's disease, thereby delineating the first definitive susceptibility gene [29, 30]. In Caucasian populations, approximately 30% of Crohn's patients carry one of these variants on a single allele compared to 15% of healthy individuals. In contrast, approximately 15% of Crohn's patients are homozygous or compound heterozygous for these variants, as opposed to less than 1% of healthy controls. A meta-analysis of 39 studies of European cohorts described odds ratios of 2.4 for simple heterozygosity and 17.1 with carriage of two polymorphisms [5]. These variants appear to predispose specifically to disease involving the small bowel [31].

The encoded protein, NOD2, is constitutively expressed by mononuclear phagocytes, neutrophils, and intestinal epithelial and Paneth cells [32–34]. It has a cytoplasmic localization, where it is thought to function as a sensor of muramyl dipeptide, the minimal bioactive motif of peptidoglycan, an important constituent of bacterial cell walls [35, 36]. Its recognition by the normal protein triggers activation of NF-κB and induction of pro-inflammatory cytokines, a function that is abrogated in the presence of disease-associated polymorphisms [37, 38].

IL-23R/IL-12B

Strong association between protective variants in the gene for the IL-23 receptor and Crohn's disease have been reported by several independent groups [5, 39–41]. This is a key

cytokine involved in crosstalk between the innate and adaptive immune systems, released from mononuclear phagocytes and polarizing T lymphocytes towards the Th17 phenotype [42]. It is further bolstered by reports of susceptibility polymorphisms in the *IL-12B* gene [5], which encodes the p40 subunit shared by IL-12 and IL-23. The mechanism of predisposition to Crohn's disease remains unclear, but may relate to orchestration of initial inflammatory responses following exposure to bacteria.

Autophagy—A major recent advance is the identification of an important role for autophagy in Crohn's disease, related to polymorphisms in three genes: *ATG16L1*, *IRGM*, and *LRRK2* [5, 39]. Autophagy is a fundamental biological process of cytoplasmic homeostasis, by which cells recycle redundant organelles [43]. It is essential for the clearance of long-lived proteins and serves a complementary function to that of the ubiquitin-proteasome system (that principally degrades short-lived proteins). Perhaps more importantly for Crohn's disease, it is also now understood to play a key role in the defense against intracellular microorganisms, targeting bacteria that enter the cytoplasm either by direct invasion or escape from endocytic or phagocytic vesicles. While the precise mechanisms have yet to be resolved, both functional knockdown and the Crohn's-associated variant of *ATG16L1* abrogate autophagy of the intracellular pathogen *Salmonella typhimurium* and post-translational processing of antimicrobial digestive enzymes in model systems [39, 44]. Similarly, knockdown of *IRGM* in mice or human macrophages impairs their ability to eliminate the intracellular pathogens *Toxoplasma gondii*, *Listeria monocytogenes*, and *Mycobacterium tuberculosis* [45].

OCTN/DLG5—Polymorphisms in two further genes have been identified as potentially associated with Crohn's disease: *OCTN* and *DLG5* [46]. These were reported as underlying susceptibility at the *IBD5* locus on chromosome 5q31. This remains slightly contentious, given the large number of genes within the region and its proximity to a cytokine gene cluster with which there might be linkage disequilibrium [47]. Nonetheless, if the associations are genuine, they might be mechanistically important in terms of their effects on intestinal epithelial permeability. *OCTN* polymorphisms alter transcription and the carnitine transport function of the OCT1 and OCT2 transporters [48], while those in *DLG5* impair its ability to maintain epithelial polarity [49]. Mutations in either could lead to disrupted mucosal barrier function, thus increasing exposure of the underlying immune system to luminal bacterial products and other antigenic material.

Missing heritability—Although exciting and providing several clues as to mechanisms of pathogenesis, there is a caveat to these genetic studies. The polymorphisms are very common in the healthy population, their penetrance limited and effect sizes at any one locus extremely limited. Even for *CARD15*, the gene with the strongest association and largest effect size, examining absolute rather than relative risks, it can be calculated that for every simple heterozygous Crohn's patient there are approximately 500 healthy individuals with the same genotype. Likewise, for every compound heterozygous or homozygous patient, there are approximately 25 healthy individuals with no evidence of bowel inflammation, emphasizing that the variants are neither sufficient nor necessary for the development of Crohn's disease [4]. Additionally, these variants, and those in *ATG16L1*, appear to

predispose only to ileal inflammation and not colonic disease. Taken together, all 32 genes identified to date account for less than 20% of the genetic risk [5], leading to the concept of missing heritability [50].

In marked contrast, profound phenotypic abnormalities can be consistently identified in Crohn's patients in vivo and in vitro when the immune system is functionally stressed.

Immunodeficiency

Despite the prevailing theories that Crohn's disease results from a primary hyper-inflammatory state, we postulated the novel hypothesis that the underlying defect might be one of an impaired acute inflammatory response. The first indication that this could be the case derived from the observation of frequent granuloma formation in these patients. Although most reports suggest that these develop in only 50%, this may be an underestimate related to sampling error. In routine clinical practice, usually fewer than 12 intestinal biopsies are taken for analysis. In contrast, postmortem studies in which the entire bowel has been step-sectioned revealed granulomata in all patients [51]. These structures occur in numerous other disorders. In all of the latter for which the etiology is known, for example tuberculosis or berylliosis, they form in response to the failure of the immune system to remove exogenous material from the body [52]. This suggested a defect in the clearance of antigenic material from the bowel wall in Crohn's disease, either due to the presence of some unique indigestible material or from a failure of the cellular phagocytic response [3].

Crohn's-like disease in primary immunodeficiencies

This concept is consistent with the very similar, non-infectious bowel inflammation that arises in the context of primary disorders of phagocyte function (Table 4). These comprise a collection of congenital immunodeficiencies in which well-defined genetic mutations are inherited in a Mendelian fashion, resulting in gross attenuation or abrogation of the ability of neutrophils to not only kill microbes but also degrade phagocytosed material [6]. The latter is due to suboptimal biochemical conditions such as pH within the phagocytic vacuole that impede digestive enzyme activation and function [53]. The prototypic disorder is chronic granulomatous disease (CGD), in which mutations in the NADPH oxidase complex render cells unable to mount a respiratory burst [54]. Approximately half of these patients develop inflammatory bowel disease in the absence of a clear microbial infection. While this gastrointestinal inflammation has been previously anecdotally likened to Crohn's disease, we recently evaluated its clinical and pathological features and found that all those with intestinal involvement met the best established diagnostic criteria for the latter [55]. Interestingly, only 50% of these patients were documented to have granulomata on routine intestinal biopsy, reminiscent of the figures quoted for idiopathic Crohn's disease. Similar findings in the Chediak–Higashi [56] and Hermansky–Pudlak [57] syndromes, caused by abnormalities in the cytoskeleton leading to aberrant phagosome and vesicle trafficking, are also reminiscent of the recent links between Crohn's disease and defects in autophagy.

In contrast therefore to the genetic loci identified in population-based association studies, mutations in NADPH oxidase predispose to Crohn's-like enteritis with much stronger penetrance. Despite the magnitude of these effects, however, they would not be identified by

Europe PMC Funders Author Manuscripts

screening an unselected population because of their rarity, occurring in approximately only one in 250,000 live births.

Defective acute inflammation in Crohn's disease

Based on these observations, we first investigated the innate inflammatory response in Crohn's disease in the 1970s. A major abnormality was described, whereby these patients failed to recruit neutrophils to the sites of new acute inflammatory responses induced by trauma, in this case skin windows created by dermal abrasion of the forearm [3]. The cells displayed normal chemotaxis in vitro [58] and therefore an abnormality of the inflammatory environment was postulated. Other neutrophil functions, including the respiratory burst, were subsequently investigated. Although some contradictory results were published, these were largely found to be normal.

The hypothesis propounded at the time was that in all individuals, through everyday minor damage to the gastrointestinal mucosal lining, the luminal contents including bacteria might gain access to the tissues of the bowel wall. In order to prevent the accumulation and collateral spread of likely infectious material, a physiological acute inflammatory response would be required with recruitment of phagocytes to remove and degrade debris. Should this process prove inefficient or ineffective, neutrophil-based phagocytosis would be overwhelmed, leading to persistence of potentially noxious agents. As a compensatory mechanism, these would instead be surrounded and engulfed by macrophages, cells with high phagocytic but much less digestive capacity than neutrophils, with granuloma formation as a protective response. These leukocytes, however, would then be chronically activated, acting as a source of pro-inflammatory cytokines driving a secondary, chronic immune reaction as seen in active disease.

Although attracting considerable early interest, the immunodeficiency hypothesis was subsequently dropped, followed by the ascendancy of theories focusing on T cell dysfunction. This was largely due to reports that defective neutrophil recruitment could be explained by a circulating inhibitor of chemotaxis [59]. These observations derived from ex vivo experiments in which neutrophil migration was measured following incubation with serum from healthy individuals, or patients with Crohn's disease or ulcerative colitis. The latter is a clinically and pathogenetically distinct type of chronic inflammatory bowel disease [60], often used as a disease control. In this model, serum from Crohn's patients was shown to decrease stimulated neutrophil chemotaxis, which was suggested to account for the abnormalities previously demonstrated in vivo. This, however, overlooked two inconsistencies. Firstly, the same effect was demonstrated with serum from ulcerative colitis patients, although neutrophil recruitment to skin windows was normal in these subjects. Secondly, the magnitude of the inhibition correlated strongly with disease activity, whereas the in vivo defects were present in patients with quiescent Crohn's disease.

We recently revisited this concept in a new series of experiments, which confirmed diminished neutrophil recruitment into skin windows and blisters [38, 61]. By developing a novel serial biopsy technique, the phenomenon was also shown to extend to epithelial injuries to the small and large bowel, the primary sites of involvement of Crohn's disease. It was possible to demonstrate that impaired chemotaxis correlated with decreased secretion of

pro-inflammatory cytokines, including IL-1β, IL-8, and TNF-α, with the likely site of the lesion at the level of resident tissue macrophages (Fig. 1). These experiments were also important as they were performed in patients with the disease in question rather than animal models, none of which accurately reproduce the clinicopathological features of the human disease [62]. The findings were also consistent with subsequent genetic studies that highlighted genes likely to affect innate immune function, phagocyte biology, and cytokine production.

The phenomenon was explored in depth using skin windows, a crude but highly informative model that allowed us to witness the progression of a newly induced acute inflammatory response [38]. We found that neutrophil accumulation was grossly impaired in all Crohn's patients, regardless of their clinical phenotype or *CARD15* genotype. It could, however, be corrected in all patients by topical application of exogenous recombinant IL-8, confirming that Crohn's neutrophils will migrate in the presence of an appropriate stimulus. In subsequent studies, we treated skin windows with MDP, the NOD2 ligand, which augmented chemokine production and neutrophil numbers in *CARD15* wild-type patients but not those carrying two disease-associated polymorphisms. This indicated that the failure of acute inflammation was a generic problem in Crohn's disease not attributable to any single genetic lesion. Systems such as NOD2 can normally augment the inflammatory response when presented with their ligand, including MDP in the small bowel [63] and possibly Toll-like receptor agonists in the large bowel [64]. They can therefore be considered as compensatory mechanisms in the face of suboptimal initial responses to epithelial damage [4, 38]. We postulate that it is the combination of a weak generic reaction to mucosal breach together with a failure of secondary protective mechanisms that predisposes to Crohn's disease.

The physiological relevance of this impaired acute inflammation was subsequently evaluated by determining responses to the introduction of gut bacteria (in the form of heat-killed *E. coli*) into the subcutaneous tissues of the forearm [38]. Local inflammatory responses were quantified by measuring changes in blood flow at inoculation sites using laser Doppler. In healthy individuals, massive increases were seen following injection, maximum within 24 h and returning to baseline by 48 h. The responses were considerably dampened in Crohn's patients, with a more profound defect in patients with colonic than ileal disease. These were very different again from the reaction seen in ulcerative colitis, in whom initiation of acute inflammation was normal but resolution delayed [65]. Interestingly, serum IL-6 and acute phase reactants C-reactive protein (CRP) and serum amyloid A (SAA) were also measured during these experiments, and found to be highest in colonic patients at 48 h following injection, an immunological pattern strikingly reminiscent of that seen in established active Crohn's disease. IL-6 is predominantly produced by macrophages and signals to the liver to secrete CRP and SAA [66]. These increased concentrations likely reflect defective neutrophil recruitment leading to a greater involvement of macrophages in phagocytosing bacteria. They also definitively illustrate the concept that weak local acute inflammatory reactions can engender a systemic pro-inflammatory state.

Environmental influences

The immunodeficiency hypothesis is consistent with the role of environmental influences known to modify susceptibility to Crohn's disease. The most strongly established is cigarette smoking, which imparts a fivefold increased risk of developing disease and a stormier clinical course [67]. Although classically thought of as pro-inflammatory based on its irritant effects to the lungs and bronchial mucosa, the systemic effects of cigarette smoking are predominantly immunosuppressive [68]. Furthermore, immunological responses in the intestinal mucosa have been studied in smokers, who are less able to generate pro-inflammatory cytokines including IL-8 compared to non-smoking matched controls [69].

Crohn's disease is also a condition that becomes more prevalent with improved standards of sanitation [70]. It remains rare in the tropics and its incidence rose dramatically towards the end of the last century, theoretically accounted for by the hygiene hypothesis [71]. The latter proposes that exposure to infection early in life establishes immunological tolerance and protects against subsequent development of autoimmune diseases. It is equally possible, however, that in regions where intestinal infection and infestation remains endemic, the immune system of the bowel is constantly primed [72]. In this state, it would be able to mount more vigorous acute inflammatory reactions whenever the mucosal barrier is breached. Such a mechanism might explain the reported efficacy of helminth therapy in Crohn's patients [73].

Challenges to the immunodeficiency hypothesis

Despite the above observations, the immunodeficiency hypothesis has been contested based upon apparent contradictions with clinical experience. The two seeming paradoxes relate to the absence of an obvious phenotype of recurrent infections and the efficacy of immunosuppressive medications. These criticisms can, however, be addressed and are not mutually exclusive with the proposed mechanism.

Predisposition to infection

If Crohn's patients possess defective innate immune responses, why do they not manifest susceptibility to severe or recurrent infections? The latter is certainly true of the congenital neutrophil disorders, such as CGD, in which patients present with frequent bacterial and fungal disease [54]. The issue is complicated by the fact that the abnormality in Crohn's disease is partial, whereas CGD patients typically have a completely abrogated respiratory burst. Furthermore, there are a number of confounding influences, including but not limited to the long-term use of immunosuppressive medications, coexistent malnutrition, and a more frequent requirement for surgery.

Whether Crohn's patients should be more predisposed to infection is not itself clear. These individuals are able to recruit a proportion of neutrophils to sites of acute tissue insult and once present these appear able to kill bacteria and fungi effectively. Furthermore, even patients with the far more severe phenotype of CGD may go many years without significant intercurrent infection and are not infrequently only diagnosed with immunodeficiency in adolescence or later life [55]. The bacterial contents of the normal human bowel reach as high as 10^{12} organisms/gram of fecal material [74] and will effectively be presented to the

mucosal immune system in a large bolus. In contrast, most exogenous infections such as those sporadically affecting the respiratory tract will arise from relatively small inoculates of inhaled bacteria. It is probable that there is a threshold beyond which the innate immune response becomes overwhelmed. In Crohn's patients, this may be sufficient to enable them to suppress most infections, but inadequate when confronted by the enormous microbial load in the bowel. This would also explain why a defect that is evident systemically leads to disease primarily affecting the gastrointestinal tract.

Nonetheless, there is some evidence that Crohn's patients may be more prone to developing infections. A number of studies suggest that gastroenteritis has a higher prevalence in this group [75] and that they incur more postoperative infections than control subjects [76, 77]. There are also indications that this predisposition is not site-specific, with greater incidences of urinary tract infection [78] and all-cause infective mortality [79, 80].

Why are immunosuppressants and TNF-α inhibitors clinically effective?

Should the underlying problem in Crohn's disease be one of an immunodeficiency, why is active disease associated with high serum and mucosal concentrations of pro-inflammatory cytokines such as TNF-α? Furthermore, why are immunosuppressant medications that antagonize these mediators effective in controlling disease?

Under the immunodeficiency hypothesis, disease pathogenesis occurs in two phases [4]. The primary abnormality is an initial failure of acute inflammation when bacteria or other organic debris penetrate the bowel mucosal lining. In healthy individuals, this would lead to an immediate and potent release of cytokines, resulting in removal of offending material. Counter-regulatory mechanisms would then come into play to terminate the inflammatory response in a timely fashion [81]. Should this process prove ineffective, bacteria persisting in the mucosa will be phagocytosed instead by macrophages, forming granulomata and heralding the second phase of pathogenesis. As these structures consist of activated leukocytes in direct contact with bacterial products, it is not surprising that some pro-inflammatory cytokines, including TNF-α, should be released.

When drawing inferences about the levels of TNF-α in active Crohn's disease, it is important to recognize that the appropriate comparison is not healthy or non-inflamed mucosa. Instead, it is intestinal mucosa of otherwise healthy individuals in which granuloma formation has been induced, for example in gastrointestinal tuberculosis. This control has not yet been properly analyzed.

In fact, it is not entirely clear that raised a TNF-α concentration is the critical factor in Crohn's disease. Interest started to focus on this cytokine predominantly after the successful use of infliximab for ameliorating bowel inflammation [82]. This largely followed from its translation for suppression of chronic inflammation in rheumatoid arthritis rather than hypotheses postulating a primary role of TNF-α in Crohn's disease itself. Although concentrations of the cytokine do appear raised in active disease [83–86], this is mostly based on detection of mRNA transcripts rather than active protein. The mechanism of action of infliximab in Crohn's disease is also not clear cut. TNF-α antagonists can be broadly divided into neutralizing antibodies (infliximab and adalimumab) and recombinant receptors

(such as etanercept). Both classes have similar TNF-α blocking activity and are equally clinically efficacious in rheumatoid arthritis. In contrast in Crohn's disease, recombinant receptors were ineffective in clinical trials [87]. The proposition is that the benefits of infliximab and adalimumab come not from direct binding of TNF-α but cross-linking of membrane-bound forms and induction of leukocyte apoptosis [88].

Animal models provide additional support for differing roles of TNF-α in early and established mucosal injury. Contrary to expectations, mice deficient in the cytokine are actually more susceptible to bowel inflammation in the dextran sodium sulfate (DSS) model of colitis, manifesting more florid mucosal injury and higher mortality [89]. Conversely, TNF-α inhibition is effective for ameliorating established DSS colitis. There are also now a number of case reports of patients developing Crohn's disease following the administration of TNF-α antagonists for the treatment of other chronic inflammatory diseases [90, 91]. Furthermore, despite their undoubted ability to ameliorate established inflammatory reactions, immunosuppressants are far less potent in maintaining disease remission, with effects no greater than use of an elemental diet [92]. We therefore propose that pro-inflammatory cytokines are crucial in the acute inflammatory response to effect rapid clearance of exogenous material penetrating the bowel wall and that the efficacy of immunosuppressants and biological agents targeting these cytokines is limited to compensation in the secondary maladaptive phase.

Summary

Prevailing theories advocating a central role for T cell dysfunction in the pathogenesis of Crohn's disease have been challenged in recent years, with renewed focus on a primary deficiency of innate immune function. The confirmation of substantial defects in acute inflammation in these patients, followed by the identification of multiple genetic variants associated with disease susceptibility, has highlighted a central role for abnormalities in phagocyte function. Our hypothesis puts forward a mechanism that not only explains the clinical and pathological appearances of Crohn's lesions, but can also encompass many of the observations that led to previous suggestions regarding microbial agents, heightened mucosal permeability, and T cell dysfunction as etiological factors. Thus it is not infection with any specific pathogen that gives rise to Crohn's disease, but the presence of sufficient numbers of viable microbes to overwhelm the initial inflammatory response and provoke a chronic granulomatous reaction with secondary T lymphocyte activation. The wealth of microbiological data reporting higher frequencies of various bacteria in Crohn's patients could equally result from a generic failure of bacterial clearance instead of elevated infection rates, with their increased detection as a marker of the underlying disease process rather than the primary pathogenic event. Disruption of the gut epithelial and mucus barrier will contribute by increasing the numbers of bacteria gaining access to the underlying tissues, and environmental influences can act synergistically with inherited factors to further attenuate acute inflammatory responses.

The principal criticisms leveled at the immune insufficiency theory are the lack of an obvious susceptibility to infection and therapeutic efficacy of immunosuppressive

medications. Neither of these apparent paradoxes, however, is mutually exclusive with the failure of acute inflammation described in Crohn's disease.

The case for an immunodeficiency origin for Crohn's disease is being constantly strengthened, with profound implications for the clinical management of this disorder. Whereas current therapy directed at suppressing inflammation is effective in the proposed secondary phase of disease, it may in fact exacerbate the underlying abnormality and potentially convert a sporadic disorder into a chronic relapsing-remitting condition. It may be that providing a low level of immune stimulation in patients with quiescent disease may help maintain remission and prevent intercurrent flares.

References

1. Shanahan F. Crohn's disease. Lancet. 2002; 359(9300):62–69. [PubMed: 11809204]
2. Podolsky DK. Inflammatory bowel disease. N Engl J Med. 2002; 347(6):417–429. [PubMed: 12167685]
3. Segal AW, Loewi G. Neutrophil dysfunction in Crohn's disease. Lancet. 1976; 2(7979):219–221. [PubMed: 59239]
4. Marks DJ, Segal AW. Innate immunity in inflammatory bowel disease: a disease hypothesis. J Pathol. 2008; 214(2):260–266. [PubMed: 18161747]
5. Barrett JC, et al. Genome-wide association defines more than 30 distinct susceptibility loci for Crohn's disease. Nat Genet. 2008; 40(8):955–962. [PubMed: 18587394]
6. Rahman FZ, et al. Phagocyte dysfunction and inflammatory bowel disease. Inflamm Bowel Dis. 2008; 14(10):1443–1452. [PubMed: 18421761]
7. Rutgeerts P, et al. Effect of faecal stream diversion on recurrence of Crohn's disease in the neoterminal ileum. Lancet. 1991; 338(8770):771–774. [PubMed: 1681159]
8. Harper PH, et al. Role of the faecal stream in the maintenance of Crohn's colitis. Gut. 1985; 26(3): 279–284. [PubMed: 3972275]
9. Dalziel TK. Chronic intestinal enteritis. BMJ. 1913; ii:1068–1070.
10. Chiodini RJ, et al. Possible role of mycobacteria in inflammatory bowel disease. I. An unclassified *Mycobacterium* species isolated from patients with Crohn's disease. Dig Dis Sci. 1984; 29(12): 1073–1079. [PubMed: 6499624]
11. Feller M, et al. *Mycobacterium avium* subspecies paratuberculosis and Crohn's disease: a systematic review and meta-analysis. Lancet Infect Dis. 2007; 7(9):607–613. [PubMed: 17714674]
12. Quirke P. Antagonist. *Mycobacterium avium* subspecies paratuberculosis is a cause of Crohn's disease. Gut. 2001; 49(6):757–760. [PubMed: 11709507]
13. Van Kruiningen HJ. Lack of support for a common etiology in Johne's disease of animals and Crohn's disease in humans. Inflamm Bowel Dis. 1999; 5(3):183–191. [PubMed: 10453375]
14. Selby W, et al. Two-year combination antibiotic therapy with clarithromycin, rifabutin, and clofazimine for Crohn's disease. Gastroenterology. 2007; 132(7):2313–2319. [PubMed: 17570206]
15. Darfeuille-Michaud A, et al. High prevalence of adherent-invasive *Escherichia coli* associated with ileal mucosa in Crohn's disease. Gastroenterology. 2004; 127(2):412–421. [PubMed: 15300573]
16. Glasser AL, et al. Adherent invasive *Escherichia coli* strains from patients with Crohn's disease survive and replicate within macrophages without inducing host cell death. Infect Immun. 2001; 69(9):5529–5537. [PubMed: 11500426]
17. Berin MC, et al. Role of EHEC O157:H7 virulence factors in the activation of intestinal epithelial cell NF-kappaB and MAP kinase pathways and the upregulated expression of interleukin 8. Cell Microbiol. 2002; 4(10):635–648. [PubMed: 12366401]
18. Meconi S, et al. Adherent-invasive *Escherichia coli* isolated from Crohn's disease patients induce granulomas in vitro. Cell Microbiol. 2007; 9(5):1252–1261. [PubMed: 17223928]

19. Marks DJ, et al. Can unresolved infection precipitate autoimmune disease? Curr Top Microbiol Immunol. 2006; 305:105–125. [PubMed: 16724803]
20. Frank DN, Pace NR. Gastrointestinal microbiology enters the metagenomics era. Curr Opin Gastroenterol. 2008; 24(1):4–10. [PubMed: 18043225]
21. Ainsworth M, et al. Intestinal permeability of 51Cr-labelled ethylenediaminetetraacetic acid in patients with Crohn's disease and their healthy relatives. Scand J Gastroenterol. 1989; 24(8):993–998. [PubMed: 2512633]
22. Hollander D, et al. Increased intestinal permeability in patients with Crohn's disease and their relatives. A possible etiologic factor. Ann Intern Med. 1986; 105(6):883–885. [PubMed: 3777713]
23. Marin ML, et al. A freeze fracture study of Crohn's disease of the terminal ileum: changes in epithelial tight junction organization. Am J Gastroenterol. 1983; 78(9):537–547. [PubMed: 6613965]
24. Kyo K, et al. Associations of distinct variants of the intestinal mucin gene MUC3A with ulcerative colitis and Crohn's disease. J Hum Genet. 2001; 46(1):5–20. [PubMed: 11289722]
25. Buisine MP, et al. Mucin gene expression in intestinal epithelial cells in Crohn's disease. Gut. 2001; 49(4):544–551. [PubMed: 11559653]
26. Clamp JR, Fraser G, Read AE. Study of the carbohydrate content of mucus glycoproteins from normal and diseased colons. Clin Sci (Lond). 1981; 61(2):229–234. [PubMed: 7261546]
27. Pullan RD, et al. Thickness of adherent mucus gel on colonic mucosa in humans and its relevance to colitis. Gut. 1994; 35(3):353–359. [PubMed: 8150346]
28. Hugot JP, et al. Mapping of a susceptibility locus for Crohn's disease on chromosome 16. Nature. 1996; 379(6568):821–823. [PubMed: 8587604]
29. Hugot JP, et al. Association of NOD2 leucine-rich repeat variants with susceptibility to Crohn's disease. Nature. 2001; 411(6837):599–603. [PubMed: 11385576]
30. Ogura Y, et al. A frameshift mutation in NOD2 associated with susceptibility to Crohn's disease. Nature. 2001; 411(6837):603–606. [PubMed: 11385577]
31. Cuthbert AP, et al. The contribution of NOD2 gene mutations to the risk and site of disease in inflammatory bowel disease. Gastroenterology. 2002; 122(4):867–874. [PubMed: 11910337]
32. Ogura Y, et al. Nod2, a Nod1/Apaf-1 family member that is restricted to monocytes and activates NF-kappaB. J Biol Chem. 2001; 276(7):4812–4818. [PubMed: 11087742]
33. Gutierrez O, et al. Induction of Nod2 in myelomonocytic and intestinal epithelial cells via nuclear factor-kappa B activation. J Biol Chem. 2002; 277(44):41701–41705. [PubMed: 12194982]
34. Lala S, et al. Crohn's disease and the NOD2 gene: a role for paneth cells. Gastroenterology. 2003; 125(1):47–57. [PubMed: 12851870]
35. Girardin SE, et al. Nod2 is a general sensor of peptidoglycan through muramyl dipeptide (MDP) detection. J Biol Chem. 2003; 278(11):8869–8872. [PubMed: 12527755]
36. Inohara N, et al. Host recognition of bacterial muramyl dipeptide mediated through NOD2. Implications for Crohn's disease. J Biol Chem. 2003; 278(8):5509–5512. [PubMed: 12514169]
37. Li J, et al. Regulation of IL-8 and IL-1beta expression in Crohn's disease associated NOD2/CARD15 mutations. Hum Mol Genet. 2004; 13(16):1715–1725. [PubMed: 15198989]
38. Marks DJ, et al. Defective acute inflammation in Crohn's disease: a clinical investigation. Lancet. 2006; 367(9511):668–678. [PubMed: 16503465]
39. Rioux JD, et al. Genome-wide association study identifies new susceptibility loci for Crohn disease and implicates autophagy in disease pathogenesis. Nat Genet. 2007; 39(5):596–604. [PubMed: 17435756]
40. Borgiani P, et al. Interleukin-23R Arg381Gln is associated with susceptibility to Crohn's disease but not with phenotype in an Italian population. Gastroenterology. 2007; 133(3):1049–1051. [PubMed: 17854611]
41. Weersma RK, et al. Confirmation of multiple Crohn's Disease susceptibility loci in a large Dutch-Belgian cohort. Am J Gastroenterol. 2009; 104(3):630–638. [PubMed: 19174780]
42. Maloy KJ. The interleukin-23/interleukin-17 axis in intestinal inflammation. J Intern Med. 2008; 263(6):584–590. [PubMed: 18479257]

43. Stuart LM, Ezekowitz RA. Phagocytosis: elegant complexity. Immunity. 2005; 22(5):539–550. [PubMed: 15894272]
44. Kuballa P, et al. Impaired autophagy of an intracellular pathogen induced by a Crohn's disease associated ATG16L1 variant. PLoS ONE. 2008; 3(10):e3391. [PubMed: 18852889]
45. Singh SB, et al. Human IRGM induces autophagy to eliminate intracellular mycobacteria. Science. 2006; 313(5792):1438–1441. [PubMed: 16888103]
46. Torok HP, et al. Polymorphisms in the DLG5 and OCTN cation transporter genes in Crohn's disease. Gut. 2005; 54(10):1421–1427. [PubMed: 15955786]
47. Rioux JD, et al. Genetic variation in the 5q31 cytokine gene cluster confers susceptibility to Crohn disease. Nat Genet. 2001; 29(2):223–228. [PubMed: 11586304]
48. Peltekova VD, et al. Functional variants of OCTN cation transporter genes are associated with Crohn disease. Nat Genet. 2004; 36(5):471–475. [PubMed: 15107849]
49. Nakamura H, et al. Identification of a novel human homolog of the *Drosophila* dlg, P-dlg, specifically expressed in the gland tissues and interacting with p55. FEBS Lett. 1998; 433(1–2): 63–67. [PubMed: 9738934]
50. Maher B. Personal genomes: the case of the missing heritability. Nature. 2008; 456(7218):18–21. [PubMed: 18987709]
51. Kuramoto S, et al. Granulomas of the gut in Crohn's disease. A step sectioning study. Dis Colon Rectum. 1987; 30(1):6–11. [PubMed: 3803110]
52. James DG. A clinicopathological classification of granulomatous disorders. Postgrad Med J. 2000; 76(898):457–465. [PubMed: 10908370]
53. Reeves EP, et al. Killing activity of neutrophils is mediated through activation of proteases by K+ flux. Nature. 2002; 416(6878):291–297. [PubMed: 11907569]
54. Thrasher AJ, et al. Chronic granulomatous disease. Biochim Biophys Acta. 1994; 1227(1–2):1–24. [PubMed: 7918677]
55. Marks DJ, et al. Inflammatory bowel disease in CGD reproduces the clinicopathological features of Crohn's disease. Am J Gastroenterol. 2009; 104(1):117–124. [PubMed: 19098859]
56. Ishii E, et al. Chediak-Higashi syndrome with intestinal complication. Report of a case. J Clin Gastroenterol. 1987; 9(5):556–558. [PubMed: 3680907]
57. Grucela AL, et al. Granulomatous enterocolitis associated with Hermansky-Pudlak syndrome. Am J Gastroenterol. 2006; 101(9):2090–2095. [PubMed: 16848805]
58. O'Morain C, Segal AW, Levi AJ. Elemental diet as primary treatment of acute Crohn's disease: a controlled trial. Br Med J (Clin Res Ed). 1984; 288(6434):1859–1862. [PubMed: 6428577]
59. Rhodes JM, et al. Serum inhibitors of leukocyte chemotaxis in Crohn's disease and ulcerative colitis. Gastroenterology. 1982; 82(6):1327–1334. [PubMed: 6978274]
60. Farrell RJ, Peppercorn MA. Ulcerative colitis. Lancet. 2002; 359(9303):331–340. [PubMed: 11830216]
61. Harbord MW, et al. Impaired neutrophil chemotaxis in Crohn's disease relates to reduced production of chemokines and can be augmented by granulocyte-colony stimulating factor. Aliment Pharmacol Ther. 2006; 24(4):651–660. [PubMed: 16907898]
62. Strober W, Fuss IJ, Blumberg RS. The immunology of mucosal models of inflammation. Annu Rev Immunol. 2002; 20:495–549. [PubMed: 11861611]
63. Vavricka SR, et al. hPepT1 transports muramyl dipeptide, activating NF-kappaB and stimulating IL-8 secretion in human colonic Caco2/bbe cells. Gastroenterology. 2004; 127(5):1401–1409. [PubMed: 15521010]
64. Doyle SL, O'Neill LA. Toll-like receptors: from the discovery of NFkappaB to new insights into transcriptional regulations in innate immunity. Biochem Pharmacol. 2006; 72(9):1102–1113. [PubMed: 16930560]
65. Marks DJ, et al. An exuberant inflammatory response to *E. coli*: implications for the pathogenesis of ulcerative colitis and pyoderma gangrenosum. Gut. 2006; 55(11):1662–1663. [PubMed: 17047113]
66. Castell JV, et al. Interleukin-6 is the major regulator of acute phase protein synthesis in adult human hepatocytes. FEBS Lett. 1989; 242(2):237–239. [PubMed: 2464504]

67. Bridger S, et al. In siblings with similar genetic susceptibility for inflammatory bowel disease, smokers tend to develop Crohn's disease and non-smokers develop ulcerative colitis. Gut. 2002; 51(1):21–25. [PubMed: 12077086]
68. Sopori M. Effects of cigarette smoke on the immune system. Nat Rev Immunol. 2002; 2(5):372–377. [PubMed: 12033743]
69. Sher ME, et al. The influence of cigarette smoking on cytokine levels in patients with inflammatory bowel disease. Inflamm Bowel Dis. 1999; 5(2):73–78. [PubMed: 10338374]
70. Hugot JP, et al. Crohn's disease: the cold chain hypothesis. Lancet. 2003; 362(9400):2012–2015. [PubMed: 14683664]
71. Liu AH, Murphy JR. Hygiene hypothesis: fact or fiction? J Allergy Clin Immunol. 2003; 111(3): 471–478. [PubMed: 12642824]
72. Elliott DE, et al. Does the failure to acquire helminthic parasites predispose to Crohn's disease? FASEB J. 2000; 14(12):1848–1855. [PubMed: 10973934]
73. Summers RW, et al. Trichuris suis therapy in Crohn's disease. Gut. 2005; 54(1):87–90. [PubMed: 15591509]
74. Farthing MJ. Bugs and the gut: an unstable marriage. Best Pract Res Clin Gastroenterol. 2004; 18(2):233–239. [PubMed: 15123066]
75. Porter CK, et al. Infectious gastroenteritis and risk of developing inflammatory bowel disease. Gastroenterology. 2008; 135(3):781–786. [PubMed: 18640117]
76. Bednarz W, et al. Analysis of results of surgical treatment in Crohn's disease. Hepatogastroenterology. 2008; 55(84):998–1001. [PubMed: 18705315]
77. Scammell BE, Keighley MR. Delayed perineal wound healing after proctectomy for Crohn's colitis. Br J Surg. 1986; 73(2):150–152. [PubMed: 3947907]
78. Kyle J. Urinary complications of Crohn's disease. World J Surg. 1980; 4(2):153–160. [PubMed: 7405253]
79. Ambrose NS, Alexander-Williams J, Keighley MR. Audit of sepsis in operations for inflammatory bowel disease. Dis Colon Rectum. 1984; 27(9):602–604. [PubMed: 6468201]
80. Hutfless SM, et al. Mortality by medication use among patients with inflammatory bowel disease, 1996–2003. Gastroenterology. 2007; 133(6):1779–1786. [PubMed: 18054550]
81. Gilroy DW, et al. Inflammatory resolution: new opportunities for drug discovery. Nat Rev Drug Discov. 2004; 3(5):401–416. [PubMed: 15136788]
82. Nahar IK, et al. Infliximab treatment of rheumatoid arthritis and Crohn's disease. Ann Pharmacother. 2003; 37(9):1256–1265. [PubMed: 12921510]
83. Cui G, et al. Improvement of real-time polymerase chain reaction for quantifying TNF-alpha mRNA expression in inflamed colorectal mucosa: an approach to optimize procedures for clinical use. Scand J Clin Lab Invest. 2006; 66(3):249–259. [PubMed: 16714253]
84. Dionne S, et al. Quantitative PCR analysis of TNF-alpha and IL-1 beta mRNA levels in pediatric IBD mucosal biopsies. Dig Dis Sci. 1997; 42(7):1557–1566. [PubMed: 9246063]
85. Stallmach A, et al. Cytokine/chemokine transcript profiles reflect mucosal inflammation in Crohn's disease. Int J Colorectal Dis. 2004; 19(4):308–315. [PubMed: 14605835]
86. Plevy SE, et al. A role for TNF-alpha and mucosal T helper-1 cytokines in the pathogenesis of Crohn's disease. J Immunol. 1997; 159(12):6276–6282. [PubMed: 9550432]
87. Sandborn WJ, et al. Etanercept for active Crohn's disease: a randomized, double-blind, placebo-controlled trial. Gastroenterology. 2001; 121(5):1088–1094. [PubMed: 11677200]
88. Van den Brande JM, et al. Infliximab but not etanercept induces apoptosis in lamina propria T-lymphocytes from patients with Crohn's disease. Gastroenterology. 2003; 124(7):1774–1785. [PubMed: 12806611]
89. Naito Y, et al. Enhanced intestinal inflammation induced by dextran sulfate sodium in tumor necrosis factor-alpha deficient mice. J Gastroenterol Hepatol. 2003; 18(5):560–569. [PubMed: 12702049]
90. Oh J, Arkfeld DG, Horwitz DA. Development of Crohn's disease in a patient taking etanercept. J Rheumatol. 2005; 32(4):752–753. [PubMed: 15801037]

91. Charach G, Grosskopf I, Weintraub M. Development of Crohn's disease in a patient with multiple sclerosis treated with copaxone. Digestion. 2008; 77(3–4):198–200. [PubMed: 18607107]

92. Saverymuttu S, Hodgson HJ, Chadwick VS. Controlled trial comparing prednisolone with an elemental diet plus nonabsorbable antibiotics in active Crohn's disease. Gut. 1985; 26(10):994–998. [PubMed: 3902590]

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

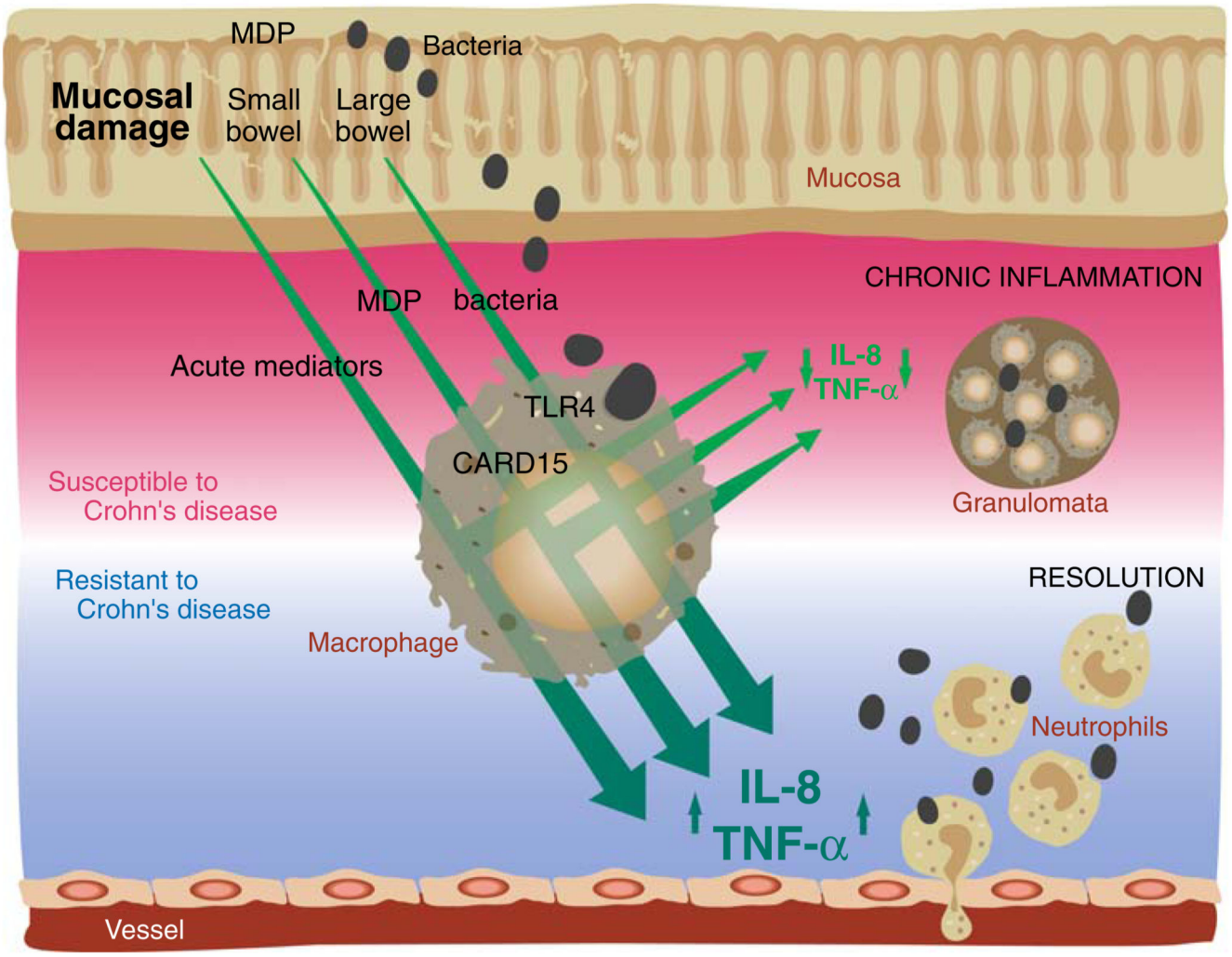

Fig. 1.

Schematic representation of the proposed mechanisms involved in the pathogenesis of Crohn's disease. Damage to the mucosa allows penetration of gut contents including bacteria (*brown ovals*) into the bowel wall. The outcome depends upon the subsequent inflammatory response. A vigorous response leads to the secretion of high levels of IL-8 and TNF-α attracting large numbers of neutrophils, which phagocytose and digest the bacteria and foreign material. A weak inflammatory response predisposes to Crohn's lesions because the foreign material is taken up by macrophages to form granulomata and foci of chronic inflammation. A naturally weak response can be boosted in the small bowel by MDP signaling through the CARD15 pathway of macrophages to induce them to produce IL-8. In the large bowel a similar role might be performed by Toll-like receptor-4 (TLR4). The predisposition to Crohn's disease is greatly increased by a combination of a low innate inflammatory response coupled to failure of one of the compensatory mechanisms

Europe PMC Funders Author Manuscripts

Table 1

Comparison of the clinicopathological features of Johne's disease and Crohn's disease

	Johne's disease	Crohn's disease
Epidemiology		
Organisms infected	Ruminants	Human
Geographical distribution	Global	Westernized countries
Intraspecies transmission	Yes	No
Clinical features		
Intestinal involvement	Ileocaecal	Global
Extraintestinal manifestations	Rare	25%
Predominant extraintestinal sites	Hepatic	Skin, eyes, joints
Pathology		
Continuity of inflammation	Continuous	Skip lesions
Ulceration	Minor	Common
Stenosis	Rare	Yes
Fibrosis	No	Yes
Fistulation	No	Yes
Histologic extent	Mucosa only	Transmural
Non-caseating granulomata	Yes	Yes
Visible acid-fast bacilli	100%	0%
Response to therapeutic agents		
Effect of anti-mycobacterial chemotherapy	Induces remission	Ineffective
Effect of TNF-α blockade	Not known, but exacerbates human mycobacterial diseases	Induces remission

Europe PMC Funders Author Manuscripts

Table 2

Microorganisms that have been proposed to play aetiological roles in Crohn's disease

Organism	Illustrative references
Bacteria	
Gram positive	
Streptococcus sp	Liu et al. (1995) Gastroenterology 108(5):1396–1404
Listeria monocytogenes	Liu et al. (1995) Gastroenterology 108(5):1396–1404
Clostridium sp	Bolton (1980) Lancet 1(8165):383–384
Gram negative	
Escherichia coli	Darfeuille-Michaud et al. (1998) Gastroenterology 115(6):1405–1413
Yersinia enterocolitica	Lamps et al. (2003) Am J Surg Pathol 27(2):220–227
Helicobacter sp	Puspok et al. (1999) Am J Gastroenterol 94(11):3239–3244
Bacteroides fragilis	Prindiville et al. (2000) Emerg Infect Dis 6(2):171–174
Pseudomonas sp	Wei et al. (2002) Infect Immum 70(12):6567–6576
Chlamydia trachomatis	Schuller et al. (1979) Lancet 1(8106):19–20
Coxiella burnetti	Kangro et al. (1990) Gastroenterology 98(3):549–553
Klebsiella pneumoniae	Tiwana (2001) Rheumatology 40(1):15–23
Mycobacteria	
Mycobacterium paratuberculosis	Chiodini et al. (1984) J Clin Microbiol 20(5):966–971
Mycobacterium kansasii	
Atypical	
Mycoplasma pneumoniae	Kangro et al. (1990) Gastroenterology 98(3):549–553
L-forms	Belsheim et al. (1983) Gastroenterology 85(2):364–369
Viruses	
Paramyxomavirus	
Measles	Wakefield et al. (1993) J Med Virol 39(4):345–354
Herpersvirus	
Epstein-Barr	Yanai et al. (1999) Am J Gastroenterol 94(6):1582–1586
Cytomegalovirus	Dimitroulia et al. (2006) Inflamm Bowel Dis 12(9):879–884
Yeasts	
Candida albicans	Standaert-Vitse et al. (2006) Gastroenterology 130(6):1764–1775
Saccharomyces cerevisiae	Main et al. (1988) BMJ 297(6656):1105–1106

Europe PMC Funders Author Manuscripts

Table 3

Genes with polymorphisms known to predispose to Crohn's disease and their putative functions (after Barrett et al. [5])

Gene	Putative functions
Odds ratio <4	
NOD2	Pathogen recognition
IL23R	IL-12/IL-23 pathway
Odds ratio <1.5	
ATG16L1	Autophagy
IRGM	Autophagy
LRRK2	Autophagy, cell signaling
IL12B	IL-12/IL-23 pathway
JAK2	JAK-STAT pathway
STAT3	JAK-STAT pathway
TNFSF15	TNF superfamily
MST1	Macrophage stimulation, promotes apoptosis
NKX2-3	Transcription factor, leukocyte migration
CCR6	Chemokine receptor
MUC19	Mucin
ITLN1	Stabilizes intestinal antimicrobial peptides
PTGER4	Tumor suppressor
PTPN2	Cell signaling
PTPN22	Cell signaling
ORMDL3	Protein folding in endoplasmic reticulum
ICOSLG	T cell co-stimulation
ZNF365	Not known
CDKAL1	Not known
C11orf30	Not known

Many of these relate to innate immune function. Genes that were not convincingly verified following Bonferroni correction are omitted

Europe PMC Funders Author Manuscripts

Table 4

Congenital disorders of phagocyte function associated with Crohn's-like inflammatory bowel disease (after Rahman et al. [6])

Disorder	Mechanism
Diminished neutrophil numbers	
Congenital neutropaenia	Completely arrested myelopoeisis
Cyclical neutropaenia	Transiently arrested myelopoeisis
Autoimmune neutropaenia	Anti-neutrophil antibodies
Impaired phagocyte migration	
Leukocyte adhesion deficiency-1	Integrin deficiency abrogating endothelial transmigration
Impaired respiratory burst	
Chronic granulomatous disease	Absent or attenuated NADPH oxidase enzyme
Glycogen storage disease-1b	Lack of substrate
Impaired delivery of digestive enzymes	
Chediak-Higashi syndrome	Aberrant vesicle trafficking
Hermansky-Pudlak syndrome	Aberrant vesicle trafficking