

# Innate immunity and adaptive immunity in Crohn's disease

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Crohn's disease (CD) is systemic immune disorder affecting the gastrointestinal tract with frequent extraintestinal manifestations. Generally, CD is considered as a polygenic immune disorder with complex multifactor etiology. Specifically, CD mainly occurs in susceptible individuals in whom upon environmental and commensal microbiota triggers a sustained disturbed mucosal immune reaction. And the chronic unrestrained inflammatory response in CD is mainly driven by a disintegrated host immune regulatory network.

An interesting phenomenon is that large areas of apparently healthy mucosa lie adjacent to ulcerated intestine in CD. Parikh et al. used kinome profiling to generate comprehensive descriptions of signal transduction pathways in inflamed and non-inflamed colonic mucosa in a cohort of CD patients, and compared the results to non-CD controls (1). They have found that p21Rac1 guanosine triphosphatase (GTPase) signaling was strongly suppressed in non-inflamed colonic mucosa in CD. And they concluded that suppression of p21Rac activity assists innate immunity in bactericidal activity and may induce remission in CD. It is very significant that an understanding of the mechanisms that sustain the non-inflamed intestinal phenotype may prove useful for developing improved therapies in CD.

Whether innate immunity or adaptive immunity involved in the pathogenesis of CD is an important issue. Some scientists proposed a hypothesis that CD is an immunodeficiency disease (2,3). Contral to this hypothesis were the observations of diminished neutrophil accumulation in patients with CD and consequent impaired clearance of pathogens from the tissues. The underlying problem appeared to be a primary immunodeficiency of the macrophage, which secreted insufficient concentrations

of proinflammatory cytokines on bacterial challenge. The precise molecular mechanisms involved are difficult to describe. Some genetic and environmental factors are known to modulate susceptibility to patients with CD. And the secondary deleterious adaptive immune response will determine the clinical significance of the innate immunodeficiency.

Now the three phase model for the generation of CD were developed based on the penetration of gut luminal contents into the bowel wall, impaired clearance of this material by the innate immune response and propagation of a secondary inflammatory reaction by the adaptive immune system (4). Specifically, in phase I, bowel luminal contents breach the mucosal barrier gaining access to the underlying tissues. In phase II, resident tissue macrophages attempt to initiate clearance by secreting cytokines to attract neutrophils, as well as activating autophagy. In phase III, if innate immune responses have been ineffective, macrophages aggregate around the foreign material to form protective granulomata. Lymphocyte activation ensues, generating the chronic inflammation seen in active Crohn's lesions. In fact, the phase of chronic inflammation is temporally and functionally distinct from the initial abnormal acute inflammatory response that occurs upon primary exposure to bowel luminal contents or intestinal bacteria. In the absence of adequate neutrophil recruitment, residual uncleared debris is phagocytosed by macrophages that subsequently form granulomata. Secondary macrophage activation will then result in a second wave of proinflammatory cytokine production, driving lymphocyte recruitment and polarization to the characteristic Th1 phenotype. At this later stage, even if net production of cytokine by each immune cell were lower than from a

healthy individual, the overall numbers of immune cells would generate sufficient concentrations of cytokines to result in local tissue damage and systemic inflammation.

The occurrence of CD in congenital immunodeficiencies provides strong support for the hypothesis of defective innate immunity. Inflammation was particularly common in the oral cavity and large bowel, and every patient exhibited perianal manifestations. This suggests a possible role for local trauma damaging the mucosa in lesion initiation, because of food in the mouth and solid faeces in the lower gastrointestinal tract. Bowel inflammation of CD responds to the biological treatment, including anti-TNF- $\alpha$  therapies. The characterization of CD as a form of immunodeficiency has important sequelae for its management. Current therapies that suppress inflammation, although beneficial during periods of disease activity, may be detrimental in the long term.

The recognition of innate immunodeficiency in CD raises the question of the extent to which similar mechanisms are responsible for other chronic inflammatory disorders, particularly the granulomatous diseases. The identical gastrointestinal pathology observed in congenital disorders of phagocyte function supports the role of conserved pathogenetic processes in their generation. A role for perturbed neutrophil function has also recently been identified in the clinical expression of tuberculosis. There is little evidence to suggest innate immunodeficiency in the nongranulomatous disorders. Many studies in patients with CD were conducted with contemporaneous chronic inflammatory disease controls, particularly patients with ulcerative colitis (UC). In fact, the phenotype in UC was markedly different: the initial response to bacterial challenge was normal but subsequently failed to terminate promptly.

At the same time, much of the previous work on adaptive immunity in patients with CD has been descriptive. The role of lymphocytes in modulating and perpetuating Crohn's lesions following a failure of the acute inflammatory

response merits reexamination.

There are two main directions for future research in CD. The first is a continuation of the examination of the basis of an innate immune defect as it relates to CD. This involves the more complete description of innate immune defects and the broad role of the innate immune system in CD. In conjunction, factor that may influence the development of impaired innate immunity in CD are important as well, as the central factor to investigate is the intestinal bacteria in possibly impairing or interacting with innate immunity. Environmental influences also should be further investigated. The other direction is how these insights will culminate in therapy. In addition, biomarkers should be identified for CD, to identify patients with CD who are more likely to respond to these therapies rather than biologic therapies or other approaches that downregulate the T-cell.

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