

What Is “Physiological” Intestinal Inflammation and How Does It Differ from “Pathological” Inflammation?

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The gastrointestinal tract is unique when compared to other organs of the body because it is in direct contact with the external environment and continuously exposed to antigens derived from foods and the enteric flora. To provide a balanced response (homeostasis) to these massive antigenic challenges and still allow the selective absorption of essential nutrients, the intestine has developed a series of powerful defense mechanisms that comprise both physical and biological controls. Physical controls include peristalsis, mucus secretion, and an uninterrupted monolayer of epithelial cells regulated by tight junctions. Biological controls include secretion of antibacterial molecules like defensins, lactoferrin, and lysozyme, trafficking of immune cells in and out of the gut, and a highly specialized immunological system that utilizes both innate and adaptive immune components. The integrated response of these combined defense systems is reflected by the accumulation of an enormous amount of immune cells that are scattered all along the mucosal surface of the gastrointestinal tract, distributed as either organized structures (Peyer's patches in the small bowel and lymphoid follicles in the colon) or diffusely in the epithelium and lamina propria (intraepithelial lymphocytes and lamina propria mononuclear cells, respectively).¹ Thus, when examined histologically, the intestinal mucosa appears to be “inflamed” compared to other mucosal surfaces that are devoid of immune cells or sparsely populated by them. Hence, the term “physiological” intestinal inflammation has been coined.² Three obvious questions follow this definition of physiological intestinal inflammation: What are the mechanisms underlying its existence? What is its functional significance? What happens when physiological inflammation goes awry?

During the last decade major advances in our understanding of the cellular, molecular, and functional mechanisms of physiological intestinal inflammation have occurred. Most of these advances are due to a substantially improved appreciation of the interactions between the normal commensal flora and the mucosal immune system.³ For a long time it has been known that animals kept in a germ-free environment

only develop a very rudimentary mucosal immune system, a phenomenon primarily due to the lack of antigenic exposure to the bacteria that normally reside in the intestinal lumen. We know now that bacterial antigens are sampled by mucosal dendritic cells, critical antigen-presenting cells that initiate and control innate immune responses.⁴ There is recognition that bacterial antigen is mediated by Toll-like receptors (TLRs), NOD-like receptors (NLRs), and RIG-1-like receptors (RLRs)^{5,6} that discriminate between molecular patterns expressed by commensal or pathogenic bacteria, with subsequent presentation to and activation of effector cells of the adaptive immune system, primarily T and B cells, and development of an immune response that maintains mucosal immune homeostasis. Anatomically, the establishment of this homeostasis is translated by the presence of physiological intestinal inflammation.

The functional significance of developing physiological inflammatory reactions in the gut is that they enable the body to recognize foreign and bacterial commensal antigens, and mount an appropriate immune response that is highly regulated and “controlled.” This way, intestinal tissue damage is prevented. The ability of responding to an antigenic challenge without causing injury or disease is what is defined as “tolerance,” or “oral tolerance” in the case of the gastrointestinal tract, and endows the essential ability of continuously adapt to the surrounding environment by creating a limited degree of inflammation that does not cause disease.⁷

The balance that controls intestinal homeostasis is delicate but, in most individuals, sturdy enough to withstand the challenges of qualitative or quantitative changes of dietary and microbial antigens, and physiological intestinal inflammation is preserved. If an acute infection occurs, as in salmonellosis or shigellosis, physiological inflammation transforms into pathological inflammation, which, however, is self-limited and followed by complete resolution. In contrast, in individuals destined to develop inflammatory bowel disease (IBD), the transformation of physiological into pathological inflammation never results in complete resolution, and overt chronic intestinal inflammation ensues, as typically observed in patients with Crohn's disease (CD) or ulcerative colitis (UC).^{8,9} In individuals with an enhanced genetic risk of developing gut inflammation, like first-degree relatives of CD patients, there is a high prevalence of subclinical intestinal inflammation,¹⁰ which could be viewed as an intermediate

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state between physiological and pathological inflammation. Depending on life events, these subjects may remain symptom-free even in the face of pathological intestinal inflammation, or become fully symptomatic and develop signs and symptoms of overt intestinal inflammation.

In summary, physiological intestinal inflammation is a normal response that prevents gut injury through its ability to flawlessly adapt to multiple proinflammatory challenges, and is therefore essential to health. When the capacity to develop or maintain physiological intestinal inflammation is lost, pathological inflammation takes over, resulting in disease.

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