Chronic gastrointestinal inflammation

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Abstract

Chronic gastrointestinal inflammation is one of the most common types of inflammatory process which affects humans. It is diverse in aetiology, pathogenesis and manifestation. There are also features of chronic inflammation at different sites within the gastrointestinal tract which provide a common thread in terms of the approaches which may be used in investigating these intriguing processes. This paper provides an overview of the mucosal changes in chronic gastrointestinal inflammation. Conserved and variable features of inflammation at different sites extending from the oral cavity to the rectum are highlighted. The involvement of different inflammatory cell types within any diagnostic entity is considered and the progression from an acute to chronic inflammatory condition explored. Important issues in the maintenance of a chronic inflammatory state are the balance between pro- and anti-inflammatory pressures, the driving force behind the inflammation and immune response that is occurring and the mechanisms for curtailment of unwanted or harmful responses which may damage the host. Thus inflammation is likely to result when there is persistence of a driving force and/or imbalance in the pro- and anti-inflammatory mechanisms in the tissue involved. © 1999 Federation of European Microbiological Societies. Published by Elsevier Science B.V. All rights reserved.

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1. Introduction

Inflammation is part of the host’s response to damage to all or part of its tissues. An inflammatory response generally follows an initial insult resulting in recognition by the host of potential or actual harm. In response to this recognition defences are recruited to the area of damage. The inflammatory cells that constitute these defences are attracted to the area by a variety of factors released or produced by damaged cells in response to the initial insult. The nature of the cellular response can vary considerably in different circumstances with varying proportions of neutrophils, eosinophils, basophils, lymphocytes (both T and B cells), natural killer (NK) cells and cells of the monocyte macrophage lineage. In the normal course of events inflammation will resolve, the cause of the insult will be eliminated and repair will take place. If this does not occur, if damage continues, the host response continues with persistent recruitment of inflammatory cells to the area and further damage ensues. Thus chronic inflammation will occur when acute inflammation fails to resolve. The mechanisms of harm recognition and response contribute to whether an insult results in inflammation.
2. Inflammation occurs throughout the gastrointestinal tract

The gastrointestinal tract (GIT) extends from the mouth to the anus. Inflammation can occur at any site in the GIT and may have a variety of aetiologies. One of the most common inflammatory processes is that associated with periodontal disease. Here bacteria in the gingival crevice initiate and drive an inflammatory response resulting in cell activation, cytokine production and eventual tissue damage [1,2]. At all levels in this tract an epithelial barrier separates the external environment from the tissues of the body. This epithelial barrier varies in nature and specialised function in different parts of the tract. When chronic inflammation occurs in the gastrointestinal mucosa there are consequences for the tissue involved. In many situations epithelial damage occurs. This may be visible or gross loss of the epithelium such as is seen in peptic ulcer disease, the ulceration seen throughout the GIT in Crohn’s disease or the colonic and rectal ulceration seen in ulcerative colitis. Microscopic damage to the gastrointestinal mucosa with epithelial breaches is a well recognised feature of aphthous ulceration in Crohn’s disease and often extends well into the mucosa. Any breach in the epithelium will undoubtedly affect the local barrier. Barrier function has been recognised to be impaired in gastrointestinal inflammation even without obvious or microscopic loss of epithelial integrity.

In situations where there is impairment of epithelial function this may be due to increased epithelial cell loss or reduced division and cell renewal. This has been examined in Helicobacter pylori gastritis using both cell lines and specialist techniques such as the terminal deoxynucleotidyl transferase-mediated dUTP-biotin nicked-end labelling (TUNEL) assay to examine mucosal biopsies. It has been shown that there is increased epithelial cell apoptosis in the stomach of H. pylori-infected individuals compared with uninfected subjects [3]. Increased apoptosis has also been demonstrated in gastric epithelial cell lines in response to challenge with H. pylori, and this is greatly increased by interferon-γ, a cytokine which is known to be increased in the gastric mucosa during H. pylori infection [4]. Thus it is clear that there can be reduced epithelial cell survival due to increased apoptosis in chronic gastrointestinal inflammation. There is also evidence of increased production or cell division [5–7]. In many situations where there is increased cell division alterations in cellular phenotype may also occur. Metaplasia is well recognised in H. pylori infection. This can be intestinal metaplasia in the stomach as well as gastric metaplasia in the duodenum [8–10]. Likewise metaplastic changes may occur in inflammatory bowel disease. Dysplasia is generally believed to be a precursor of malignancy in gastrointestinal epithelial tissues [7,11,12].

3. Chronic inflammation

It is relevant then to consider how chronic inflammation differs from an acute inflammatory process that would normally resolve. Firstly it lasts longer. While this is an obvious statement it is necessary to differentiate this as a persistent process, rather than one following an acute event such as infectious gastroenteritis which might be slowly abating. Despite this, in many of the diseases associated with chronic inflammation in the GIT there is considerable variation over time in the level of inflammation observed. This is particularly true where clinical symptoms are concerned. The severity of inflammatory bowel disease can range from one where the individual feels relatively normal to one that is life-threatening and disabling with severe systemic manifestations. In asthma, another disease involving mucosal inflammation, exacerbations and remissions are also recognised. From examinations of cytokine levels and airway inflammation it is known that during remission periods there is a considerable degree of activity of inflammatory processes when clinical signs are minimal [13]. A situation analogous to this may be observed in gastrointestinal inflammation. It is recognised that there may be little correlation between gastric inflammation associated with H. pylori and upper gastrointestinal symptoms. Rectal biopsies from individuals during remission of ulcerative colitis show increased inflammatory infiltrate and mucosal thinning despite thickening of the muscularis mucosa part. Thus clinical symptoms, while indicative of more gross changes, are not necessarily a true reflection of the level of the underlying inflammation.
Chronic gastrointestinal inflammation involves many different cell types. Generally the greater the proportion of neutrophils the greater the current activity of the inflammatory process. Neutrophil infiltration is seen in the gastric mucosa in response to H. pylori, particularly those strains that produce vacuolating cytotoxin (Vac) A and are often also cytokine-associated gene (Cag) A-positive [10,14–17]. This is associated with higher levels of interleukin (IL)-8 in the tissues and thus may be due to increased neutrophil chemotaxis in this group [14]. A neutrophil response is an important part of the inflammation seen in inflammatory bowel disease. In ulcerative colitis crypt abscesses where histological sections demonstrate masses of neutrophils in the crypt lumen are common. In some individuals lymphocytes, including both T and B cells, play a more prominent role in the inflammatory process [8,18–20]. Germinal centres can be found throughout the gastrointestinal tract where chronic mucosal inflammation occurs. While the aetiology may be different in different parts of the GIT the cellular response in the stomach, small bowel, colon and rectum may demonstrate considerable similarities.

Comparison of the mucosal response in different parts of the GIT is both interesting and useful [21,22]. It is also important to look at various parameters using different methods. Examples of this type of approach include investigation of the T cell subsets in gastrointestinal disease. CD8+ cells are prominent in the normal undiseased intestinal mucosa; they are also considerably increased in the presence of inflammation [23]. It is interesting that different methods, e.g. immunocytochemistry and flow cytometry, produce different results for the proportions of CD4- and CD8-positive cells in gastric mucosal inflammation [23,24].

The surface area of the intestinal mucosa is very large. It would be surprising therefore if there were no systemic effects of extensive inflammation of this organ. In H. pylori infection the demonstration of systemic effects has been controversial. It appears that there is an effect on growth, particularly of prepubescent females [25,26]. There is interest in a variety of chronic inflammatory disorders as contributory factors to an increased risk of cardiovascular events. Despite this, it remains unclear exactly what role H. pylori infection plays in this area [27].

In inflammatory bowel disease systemic effects are well recognised. These may be due to a variety of processes including poor nutrition due to disrupted mucosal function. They may also be manifestations of a misdirected immune response with a significant autoimmune component, e.g. the arthropathies which are associated with these disorders. Systemic effects are also related to the production of inflammatory mediators such as tumor necrosis factor (TNF)-α and IL-6. TNF-α, a predominantly macrophage cytokine, causes fever and cachexia as well as inducing the production of acute phase proteins, an effect also caused by IL-6 [22,28].

One of the most fundamental questions to ask when studying any chronic inflammation is, why does the inflammation persist? There are a number of different possibilities. There may be a failure or dysfunction in processes involved in resolution of inflammation. One way this could occur is through mechanisms such as Fas-Fas ligand (FasL)-mediated control of apoptosis and activation induced cell death [29–31]. The inflammatory process could also be prolonged by a failure of tolerance or a mechanism that results in exposure of T cells to previously masked self-antigens [32,33]. There is considerable evidence for involvement of autoimmune mechanisms in H. pylori-related disease, but as yet the molecular mechanisms are speculative. In this situation there is persistence of a variety of foreign antigens some of which are known to cross-react with antigens on host tissues [34]. H. pylori gastritis does resolve after eradication of the infection with antimicrobial combinations. However, if atrophic gastritis has developed, resolution does not appear to occur. In other systems the inflammatory process appears to break down mechanisms which control autoreactive cells [33,35].

Increased recruitment of inflammatory cells to an area may also result in inflammation persisting in that tissue. Recruitment of inflammatory cells involves activation of the endothelium. This results in the expression of integrins that interact with adhesion molecules on the inflammatory cells thus attracting them to the area concerned. P-selectin is an integrin that is expressed early and lost 24 h after the endothelial cell activation process. P-selectin has been found to be raised in inflammatory bowel disease suggesting that activation is an ongoing process.
Interestingly blocking CD11b/CD18 reduces inflammation in an experimental model of rat colitis [37]. If once recruited to the area inflammatory cells expand within the tissues this will also contribute to the maintenance of the inflammatory process. The mucosa-associated lymphoid tissues (MALT) are intrinsically involved in immune responses in the GIT [38]. Tissue of this type is also present in other areas such as the respiratory and genitourinary tracts where a mucosal surface is the barrier between the body tissues and the external environment. At mucosal surfaces the predominant immunoglobulin (Ig) type is secretory IgA which is a major mediator of mucosal immunity. The MALT includes intraepithelial as well as lamina propria lymphocytes and associated accessory cells. In all parts of the GIT this can be observed as germinal centres with or without overlying specialised epithelium as seen in the Peyer’s patches of the small intestine. In the stomach these develop only in gastritis. In the small and large intestine they are more numerous in areas with chronic inflammation together with an increased inflammatory infiltrate.

One of the most likely explanations for continuing inflammation is the persistence of the initial insult. There have been a number of attempts to find an infectious aetiology for inflammatory bowel disease with little success. In the case of H. pylori gastritis however, there is very clear persistence of the infecting organism. This bacterium causes gastritis in 50–60% of the world’s population [39]. How is it that this infection is not eradicated by the host’s immune response? H. pylori inhabits a specialised niche with almost no competition from other flora. Has this specialisation included mechanisms to subvert the host response and so aid its survival? Is there an inappropriate level or type of response?

4. The pro- and anti-inflammatory balance

The control of gastrointestinal inflammatory responses is largely unknown. In recent years the balance between pro- and anti-inflammatory processes and the importance of investigating these in this context has been recognised. Cytokines, other mediators and their receptors play an important role in this balance. These may be measured in a variety of ways that directly or indirectly detect expressed, produced and secreted cytokine. Ideally one would like to know what each cell or cell type is producing or responding to in vivo. Pragmatically we investigate these processes using a variety of methods, tissues and models. One possibility is to use cell lines to investigate discrete aspects of a response to a particular stimulus. This type of approach has been used to investigate the response of various cell types to H. pylori. When the response of MonoMac 6 cells to H. pylori was investigated a peak in TNF-α was found 6 h after exposure. This was followed by a rise in IL-10 production. This relationship was consistent at different challenge combinations and when the investigation was extended to peripheral blood mononuclear cells (Bamford, unpublished; [40]). It is also possible to extract cells from tissues to examine their behaviour in different diseases compared with controls. Production of T cell clones and cells freshly isolated from the GIT have demonstrated that the predominant T cell phenotype in H. pylori infection is T-helper (Th) 1-like [41–43]. A similar T-helper response is recognised in inflammatory bowel disease although the antigen involved is not known [44]. Interferon-γ (IFN-γ) is a cytokine predominantly associated with a Th 1 phenotype. IFN-γ promotes the production of antibodies of the IgG2 subclass, the fixation of complement and Fc receptors on macrophages. Thus inflammation is further promoted. Complement deposition and activation is detectable...
in *H. pylori*-infected gastric mucosa as well as in the mucosa in inflammatory bowel disease [45–47].

When the relative levels of anti-*H. pylori* IgG subclasses were examined in *H. pylori*-positive individuals it was found that the predominant antibody response was of the IgG2 subclass [48].

Cytokines produced by Th1 and 2 cells exert a positive influence on the development of cells of their own particular phenotype. The development of T cells with this pattern is also under the control of cytokines produced by antigen-presenting cells (Fig. 1). Examination of gastric tissue has shown that in *H. pylori* infection there is a disproportionately large amount of the Th1 promoting cytokine IL-12 compared to IL-10. This is supported by the production of IL-12 by peripheral blood mononuclear cells in response to live *H. pylori* [48, 49].

Cytokine and immune knock-out models have been used to investigate the role of various mediators such as IL-2 and IL-10 and the development of the immune response in the induction of inflammatory bowel disease [50]. By investigating the role of the bowel flora in the development of disease the importance of persistent antigen (or infection) is also illustrated. IL-10 is an anti-inflammatory cytokine produced by macrophages and monocytes that promotes the development of a Th2 response and suppresses the development of Th1 cells. IL-10 knock-out (KO) mice kept in a germ-free environment were found to be free of bowel disease whereas if they had a specific pathogen-free flora they developed chronic bowel inflammation and had reduced growth (Fig. 2) [50].

Modulation of this control mechanism by administering IL-10 or anti-IL-12 abrogates tolerance to intestinal bacteria in mice resulting in the development of inflammation [51, 52]. This leads to questions

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**Fig. 2.** Effect of gene knock-out on the growth of specific pathogen free and germ free mice. The interaction between host and environment [23].
regarding the level of the pro- or anti-inflammatory response in individuals who develop inflammation of the GIT (Fig. 3).

It also helps when considering whether these findings support therapeutic interventions.

Thus in summary, chronic gastrointestinal inflammation extends throughout the GIT in different guises. In each area there are differences in how the tissues respond and in the normal flora. Despite this there are also similarities in the underlying response mechanisms and the cells involved. Application of modern methodologies to inflammation in different locations and with different underlying aetiologies can only improve our knowledge of this exciting area.

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References


