Inflammatory bowel disease: clinics and pathology

Do inflammatory bowel disease and periodontal disease have similar immunopathogeneses?

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Inflammatory bowel disease (IBD) comprises two chronic, tissue-destructive, clinical entities—Crohn disease (CD) and ulcerative colitis (UC)—both apparently caused by immunological overreaction (hypersensitivity) to commensal gut bacteria. Under normal conditions the intestinal immune system shows a down-regulating tone ('oral tolerance') against dietary antigens and the indigenous microbiota. This local homeostasis is disturbed in IBD, leading to hyperactivation of T helper 1 (Th1) cells with abundant secretion of interferon-γ and tumor necrosis factor (TNF) and production of IgG antibodies against commensal bacteria. In addition, UC includes genetically determined autoimmunity, particularly IgG1-mediated cytotoxic epithelial attack. Breaching of the epithelium is the best-defined event underlying abrogation of oral tolerance, but immune deviation caused by cytokines from irritated epithelial cells or subepithelial elements (for example, mast cells, natural killer cells, macrophages) may also be involved. Endogenous infection with local hypersensitivity likewise causes periodontal disease, reflecting 'frustrated' immune elimination mechanisms entertained by antigens from dental plaque. Altogether, perturbation of a tightly controlled cytokine network, with abnormal crosstalk between several cell types, apparently explains the progressive immunopathology of chronic inflammatory mucosal diseases in general. This adverse development will be influenced by numerous immunity genes, the dosage and potential pathogenicity of commensal bacteria, general health, nutritional status, and psychological factors. Several targets for new therapy have tentatively been identified to block immunopathological mechanisms in IBD, and inhibition of TNF has a striking beneficial effect in CD, supporting a central role of this cytokine.

☐ *Adhesion molecules; antibodies; cytokines; hypersensitivity; T cells*

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Inflammatory bowel disease (IBD) comprises two chronic, relapsing, and tissue-destructive clinical entities; whereas ulcerative colitis (UC) is limited to the large bowel, Crohn disease (CD) can strike anywhere along the alimentary canal, most commonly in the distal ileum as so-called regional enteritis. The inflammation in CD extends deep into the affected tissue, in contrast to UC, which causes inflammation and wide ulcers in the superficial tissue layers of the colon and rectum. Inflammation in CD is asymmetrical and segmental, with areas of both diseased and relatively healthy tissue (so-called 'skip' lesions), in contrast to UC, in which inflammation is symmetrical and uninterrupted from the rectum proximally. Some 10% to 12% of cases are not initially classifiable and are therefore referred to as 'indeterminate colitis'. Over time, about half of these patients are eventually classified as having CD or UC (1, 2).

Both CD and UC are chronic and relapsing, affect men and women rather equally, and are most common in northern Europe and North America. Approximately 20% of individuals with CD have a relative with some form of IBD. The age of IBD onset is usually between 15 and 30 years, but both younger and older individuals may be affected. Over the past decade several studies have reported an increase in the prevalence of CD in various geographic regions (3, 4).

Despite enormous efforts over many decades the etiologies of these severe wasting diseases remain enigmatic. Therefore, no rational cure or prevention can as yet be offered for IBD. Nevertheless, identification of critical events in the pathogenesis is important to develop efficient methods that may provide rational modulation of the disease process, with clinical benefits. Central in such efforts is the characterization of the participating mucosal effector cells, their biological mediators, and their recruitment to the lesions.

In this paper the immunopathogenesis of IBD will be discussed and compared with that of periodontal disease (PD). Both inflammatory disorders can apparently be explained by endogenous infection inducing hypersensitivity against commensal bacteria. A brief general account of immune mechanisms will first be given as a background for the discussion of IBD and PD pathogenesis.

Immune response, immune reaction, and hypersensitivity

An adaptive or acquired immune response refers to the cellular activation and biological mechanisms induced when active immunity is elicited by antigens (Fig. 1). Such specific stimulation depends primarily on antigen-presenting cells (APCs) expressing major histocompatibility

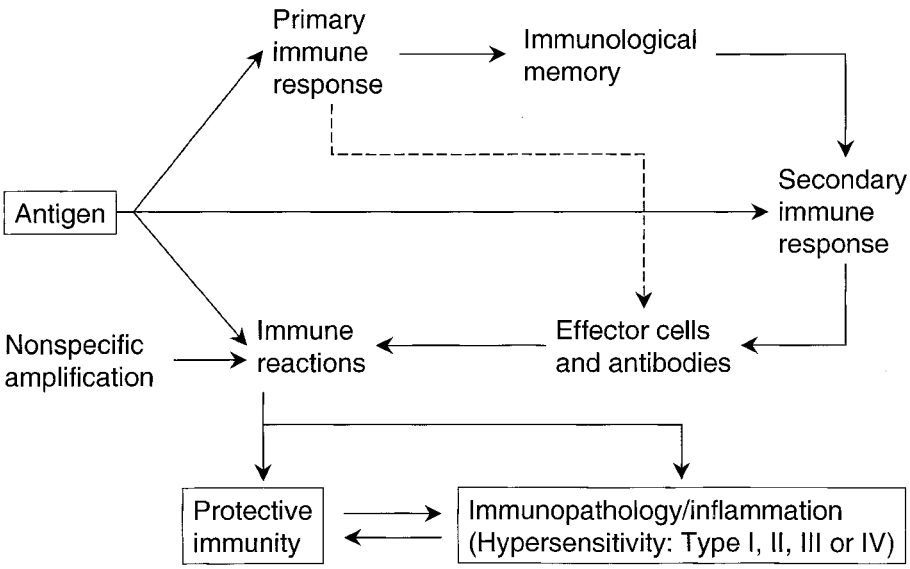

Fig. 1. Schematic representation of the relationships between immune response, immune reaction, protective immunity, and hypersensitivity (immunopathology).

complex (MHC) class-II determinants (in humans: HLA-DR, -DQ, and -DP) as genetically determined restriction elements for $CD4^+$ T helper (Th) cells. The response may also involve MHC class-I molecules and $CD8^+$ T cells with a cytotoxic and/or suppressive potential. All of these cell categories are present in the intestinal mucosa and inflamed gingiva, so an immune response to antigens from the indigenous microbiota can undoubtedly be mounted locally at both sites.

A long-lasting, secondary type of immune response gives rise to prominent differentiation to effector cells and release of biologically active substances aiming at neutralization and elimination of antigen. Such immunological effector mechanisms, and the nonspecific biological amplification often triggered by them, are collectively referred to as immune reactions (Fig. 1). Adaptive immunity is thus based on specific immune responses but is expressed by various cellular and humoral immune reactions. The effector cells of the B-cell system are the terminally differentiated immunoglobulin (Ig)-producing plasma cells that abound in normal and inflamed intestinal mucosa (5, 6) and in the established PD lesion (7–12). Progressive IBD and PD are both typical B-cell lesions, but the early lesions may nevertheless be determined by activated T cells (6, 13, 14). Although immune reactions are initially directed specifically against antigen(s), they usually engage extensive nonspecific events that may be considered variations on the theme of inflammation. When the result is judged clinically to be damaging, the underlying immune reactions are referred to as hypersensitivity, and the tissue-destructive effect is called immunopathology (Fig. 1).

For didactic reasons, hypersensitivity mechanisms are categorized into four main types (Fig. 2) in accordance with Coombs & Gell (15). These types rarely occur isolated, but one type may be dominant in a particular immunopathological lesion. It should also be emphasized that hypersensitivity is principally an expression of protective immune reactions, which, however, become tissue-damaging mainly when immune elimination for some reason is not successful within a reasonable time (Fig. 1). This may be due to continuous supply of antigen (for example, chronic virus infection, autoimmunity, or excessive exposure to the indigenous microflora such as in IBD and PD), often combined with an inefficient or exaggerated immune response on a polygenic background. The hypersensitivity mechanisms involved in IBD and PD have not been clearly defined, although circumstantial evidence points to types II, III, and IV—the latter especially in the initial lesions (6, 13, 14, 16, 17). A high degree of complexity is emerging as research is performed with steadily more sophisticated methods; even the mast cell may play a crucial initial role in the pathogenesis, apparently with some mimicry of a type-I reaction (18). Also, in the switch from acute to chronic persistent inflammation with a tissue repair potential, the fibroblast has been postulated to be a central player, contributing to retention and survival of leukocytes (19). Thus, chronic inflammation has been referred to as a 'foster home' for leukocytes (19).

Are both IBD and PD explained by endogenous bacterial hypersensitivity?

Bacteria in dental plaque produce various toxins and enzymes that may directly contribute as virulence factors in the pathogenesis of PD (20, 21). However, there is no reason to doubt that also immunopathological mechanisms are engaged, even by principally innocuous antigens. Numerous studies have reported that antibodies to various

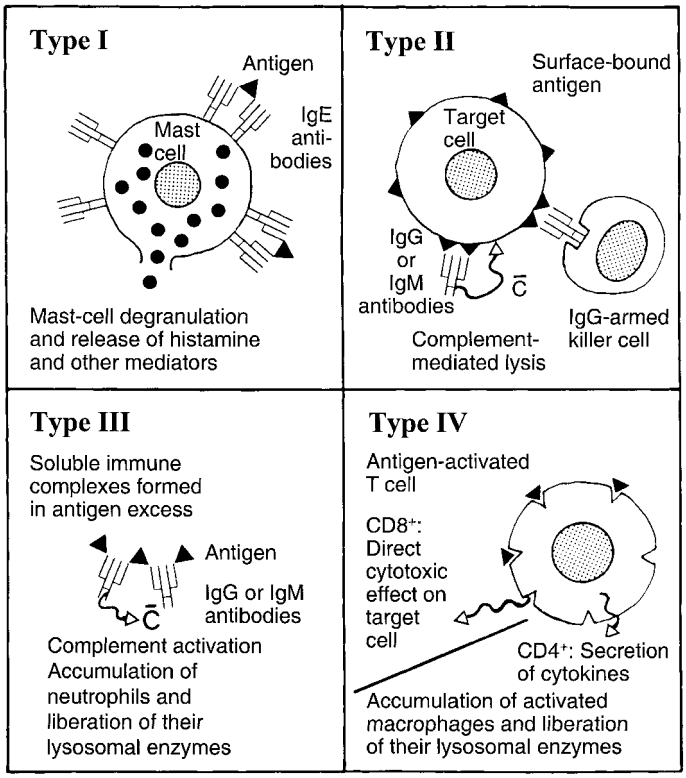

Fig. 2. Schematic representation of type-I (immediate, atopic, or anaphylactic), type-II (cytotoxic or lytic), type-III (immune complex-mediated), and type-IV (T-cell-mediated or delayed-type (DTH)) hypersensitivity mechanisms. This classification is used to describe, in mechanistic terms, how immunopathology develops, but the immune reactions involved principally do not differ from those defending the host by neutralization and elimination of foreign antigens.

plaque components are present in serum (22–27), and these antibodies, which are mainly of the IgG class, will with some 50% extravascular distribution be available to react against corresponding antigens in the gingival area (12). Such local immune reactions may increase the influx of bystander antigens as part of an inflammatory response (28, 29). The initial gingival lesion is probably an ideal situation for the development of an 'Auer phenomenon'—that is, aggravation of mild inflammation by local accumulation of serum antibodies combined with (systemic or) topical supply of the corresponding antigen(s) (10). Thus, type-III (immune complex-mediated) hypersensitivity has been shown to cause colitis in experimental animals (30). There is, moreover, direct evidence for local production of IgG antibodies to plaque components in inflamed gingiva (12, 31, 32) and to commensal gut bacteria in IBD lesions (33, 34).

The composition of the immune-cell populations present in inflamed intestinal mucosa and gingiva is quite similar to that usually seen in reactive lymph nodes, with a predominance of memory/effector B cells and CD4+ T helper (Th1) cells showing a high level of interferon-γ (IFN-γ) production (14, 17, 34). The protective effects of B- and T-cell responses in organized lymphoid tissue are obvious, and lymph nodes usually survive a reactive process with well-preserved function. However, similar immune responses in connective tissues such as the intestinal lamina propria, gingiva, skin, and synovial membranes often result in a state of hypersensitivity that clinically appears destructive. In lymphoid tissue the various immunologically active cells are organized in a setting adequate for elimination of antigens and immune complexes without the induction of excessive tissue damage. The follicular dendritic cells, for example, which retain immune complexes in germinal centers, are protected against the cytolytic effect of in situ terminal complement activation by concomitant binding of S-protein or vitronectin (35). So what is mainly protective for the host in one tissue might appear quite damaging in an other, although a local immune reaction defined clinically as hypersensitivity could be quite important for the protection of the host. This is probably true in terms of the control of endogenous infection both in the gut and in the gingiva.

An additional important point is that lymphoid organs are chiefly engaged in defense against exogenous pathogens, whereas IBD and PD are caused by commensal bacteria and therefore depend on significant preceding

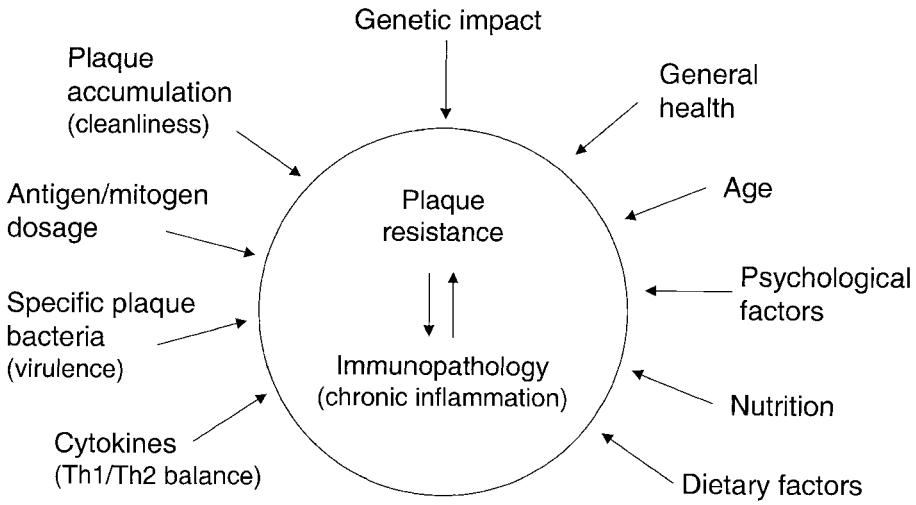

Fig. 3. The outcome of immune responses/immune reactions going on in the gingival area in terms of tissue repair or periodontal disease depends on numerous more or less well-defined variables related to the potential pathogenicity (virulence) of the indigenous microbiota accumulating in dental plaque, immunological factors such as cytokines (for example, Th1/Th2 cell balance), and the general health and nutritional status of the host. A similar scheme would be relevant for the relationship of microbial defense in the gut and the development of inflammatory bowel disease.

circumstances in addition to the causative microorganisms. Some of these predisposing factors are undoubtedly determined by a variable host response orchestrated by genetics and systemic health (Fig. 3); but in relation to PD the most obvious predisposing factor is the teeth, with their hard surfaces enabling prolonged retention and accumulation of indigenous bacteria. A nonpathogenic dental plaque, in the sense of not causing gingivitis, has never been observed (36).

Immunopathogenesis of ulcerative colitis and Crohn disease

Studies of IBD pathogenesis must be related to current knowledge of the immunophysiology of the normal intestinal mucosa. The prevailing adaptive immune effector mechanism throughout the gut is the immunoglobulin A (IgA)-producing B-cell system (5) that exhibits noninflammatory defense properties within the lamina propria and gives rise to secretory IgA (SIgA) antibodies that perform immune exclusion at the epithelial surface (Fig. 4). Moreover, in the normal situation the mucosal T cells show no signs of hyperactivation; despite being mainly primed (memory) cells in the lamina propria (the $CD4^+CD45R0^+$ phenotype dominating) and in the epithelium (the $CD8^+CD45RB^+/R0^+$ phenotypes dominating), they show little evidence of recent stimulation because CD25 (p55) or the interleukin-2 (IL-2) receptor is expressed at a remarkably low level (37).

This seemingly well-balanced immunological homeostasis in the intestinal mucosa is abrogated in IBD, and the local immune system features signs suggestive of unsuccessful immune elimination. The adhesion properties of the mucosal microvascular endothelium are critically altered, thereby lacking the restriction normally exerted for extravasation of B and T cells mainly primed in various parts of the organized gut-associated lymphoid tissue such as the Peyer patches (5, 38). In active IBD lesions the endothelium, instead, shows adhesion properties more similar to those found on the high endothelial venules in peripheral lymph nodes, thus enabling extravasation of B and T cells reflecting systemic immunity. This produces accumulation of a disproportionately large number of potentially proinflammatory IgG-producing plasma cells and recruitment of monocyte-like macrophages with aggressive properties as well as T cells showing various antimicrobial specificities directed against the commensal microbiota (6, 17, 33, 34).

Immunopathological features of the IBD lesions

Local production of dimeric IgA with J chain and the resulting generation SIgA antibodies are disfavored in IBD. This adverse development is shown by decreased J-chain expression and strikingly increased IgG production by local plasma cells in both UC and CD (6, 34). Moreover, a significant shift from IgA2 to the less resistant IgA1 subclass takes place in IBD (6, 34), again highlighting the similarity to a progressive PD lesion (39). Preferential overproduction of the IgG1 subclass compared with IgG2 is seen in UC; apical deposits of the former isotype together with activated complement on the surface epithelium (6, 34) are suggestive of a cytotoxic auto-

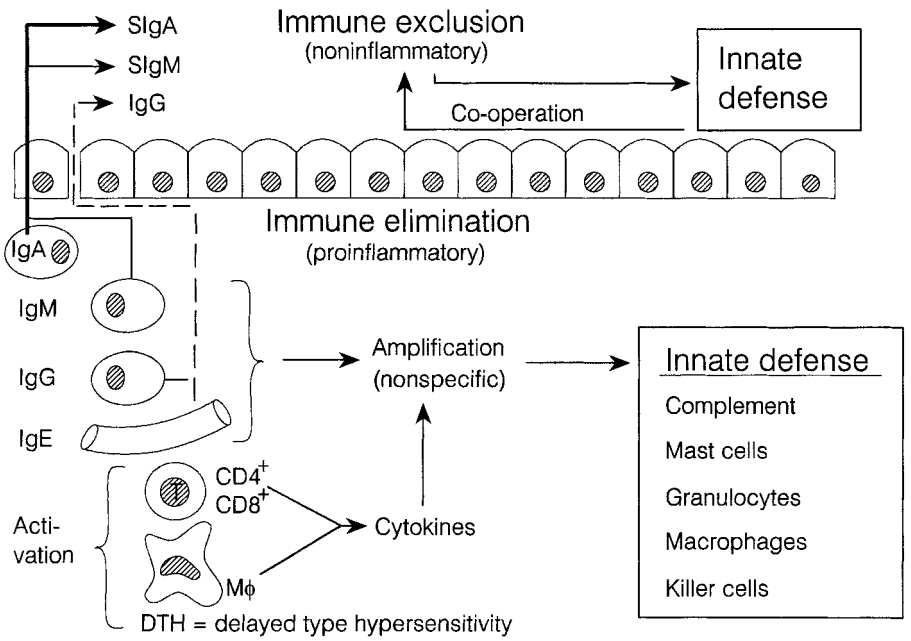

Fig. 4. Schematic representation of the first and second level of mucosal immune defense. 1) Immune exclusion limits epithelial colonization of microorganisms and inhibits penetration of foreign substances. This principally noninflammatory mechanism is mediated by specific antibodies in cooperation with various innate mucosal protective factors such as mucin, lysozyme, peroxidase, gastric acid, and intestinal peristalsis. Antibody activities in external secretions are mainly carried by actively transported (*unbroken, graded arrows*) secretory immunoglobulins (SIgA and SIgM) and, to a variable extent, by smaller amounts of locally produced or serum-derived IgG antibodies that leak through the surface epithelium (*broken arrow*). 2) Immune elimination aims at neutralization and removal of foreign material that has gained access to the lamina propria. This mechanism is principally proinflammatory because it can amplify nonspecific defense systems by complement-activating IgG antibodies and by cytokines released from activated T cells (T) and macrophages (Mø) in a type-IV hypersensitive reaction (or DTH).

immune attack directed against brush border antigen(s). Comparison of identical twins, discordant with regard to clinical expression of UC (17), suggests a genetic impact on this IgG1 response, which might contribute to the diffuse and superficial presentation of UC (6, 17, 40). In addition, IBD lesions contain many recently recruited and activated T cells as well as monocyte-like macrophages ($CD14^+$) and neutrophils with increased capacity for production of proinflammatory cytokines, particularly IL-1 and tumor necrosis factor (TNF), as well as reactive metabolites of oxygen and nitrogen (17). All these cellular changes signify less restricted extravasation of precursor cells because of altered expression of adhesion molecules on the microvasculature.

Mucosal microvascular endothelial cells (ECs) function as 'gatekeepers' that regulate local tissue homeostasis via their adhesion molecules and by expression of proinflammatory cytokines and chemokines. The microvasculature is therefore central in the pathogenesis of IBD. Extensive in situ modulation of ECs is known to occur in IBD. Possible therapeutic blocking of the extravasation of selected inflammatory cell subsets in the future will require detailed knowledge of the underlying molecular mechanisms. To better analyze such functional variables, primary monolayer cultures of human intestinal microvascular endothelial cells (HIMECs) have been established in our laboratory (17). When subjected to proinflammatory cytokines in vitro, HIMECs show enhanced ICAM-1 expression and induction of functional E-selectin and VCAM-1 as well as MHC class-II molecules with antigen-presenting and T-cell stimulatory properties (17). Furthermore, the in situ-activated ECs express an array of cytokines and release rapidly prestored IL-8, a potent neutrophil chemoattractant (17).

Collectively, such alterations constitute severe derangement of mucosal homeostasis, apparently involving break of tolerance against the indigenous microbial gut flora followed by nonspecific amplification of proinflammatory innate defense mechanisms (Fig. 4). In addition, the immunopathology of IBD includes various autoimmune phenomena, particularly in UC (40). The origin of abrogated immunological tolerance at the mucosal level may be alterations both in leukocyte extravasation and in antigen-presenting mechanisms induced by aberrant expression of endothelial and epithelial MHC class-II molecules as well as a changed profile of costimulatory molecules such as CD40 and B7 on macrophages and lack of a putative immune-modulating ligand (gp 180) on the

epithelium (17, 41). A shift from B7.2 (CD86) on resident antigen-presenting cells to B7.1 (CD80) on recently recruited $CD14^+$ macrophages may particularly disfavor mucosal Th2 responses and their associated down-regulatory cytokines. Stimulation by the gram-negative indigenous microbiota via the lipopolysaccharide receptor CD14 and the Toll-like receptor TLR4 probably skews the local immune response towards a Th1 profile (42). The activated Th1 cells appear to be particularly long-lived because IL-12, as well as complexes of IL-6 and soluble IL-6 receptor, induces antiapoptotic mechanisms (43). A strong and persistent Th1 response may thus override regulatory intestinal $CD4^+$ T cells that normally perform active suppression by secreting IL-10 (Tr1) or transforming growth factor (TGF)-β (Th3) as part of mucosal tolerance maintenance (44). Thus, perturbation of a tightly controlled cytokine network, with abnormal crosstalk between several mucosal cell types, appears to be the first step of a progressive immunopathological cascade reaction in IBD.

Although the initiation of this undue series of mucosal immune events remains undefined, several potential targets for new IBD therapy can tentatively be identified in the aberrant cellular crosstalk (17). The successful clinical application of humanized monoclonal antibody (mAb) to TNF suggests that overactivated mucosal macrophages are of central pathogenic importance (45). Blockade of this cytokine probably reduces its stimulatory effect on stromal cells producing both tissue-destructive metalloproteinases and keratinocyte growth factor that induces excessive epithelial cell proliferation (17). Also, the increased vascular adhesive properties induced by TNF are most likely reduced by this treatment. Animal experiments have shown that deregulation of the transcription factor NF-κB by anti-sense molecular strategy represents an efficient anti-inflammatory treatment, and this effect may collectively be ascribed to activation control of macrophages, neutrophils, and endothelial cells. Vascular adhesiveness may further be controlled by mAbs or adhesion antagonists blocking selected endothelial leukocyte receptors, thereby restoring the gatekeeper function of the microvasculature. Finally, treatment with recombinant IL-10 may cause not only macrophage and neutrophil inhibition but also stimulation of regulatory Tr1 cells that inhibit a proinflammatory Th1 cytokine profile (44).

How does immunopathology develop in IBD?

Lessons from mice with immunological dysfunction

The importance of a finely tuned immune regulation for mucosal homeostasis is emphasized by the general appearance of intestinal pathology in knockout mice whose immunoregulatory capacity has been genetically manipulated (16, 45, 46). These disease models lend strong support to the notion that the intestinal immune system by oral tolerance normally is hyporesponsive to soluble dietary constituents and the noninvasive indigenous gut microflora despite being able to elicit protective immunity against overt pathogens. These two functions are potentially conflicting, and when the mucosal immune system is out of control, as in mutant mice, the mere presence of commensal bacteria is sufficient to cause chronic mucosal inflammation, apparently because unsuccessful antigen elimination maintains 'frustrated' nonspecific amplification mechanisms induced by local immunity.

The experimental IBD models occurring spontaneously in knockout mice have some features of CD or UC depending on whether a defect is introduced in the T-cell receptor, MHC class II, signal transduction (G protein α_{i2}), or a particular cytokine (IL-2 or IL-10) gene (46). The pathogenic mechanisms are unclear, but the disease development apparently has its basis in altered functions of $CD4^+$ T cells, although B-cell dysregulation might modulate the pathogenic process. A primary role of uncontrolled gut-seeking T cells has been highlighted by transplanting congenic T cells into mice with severe combined immunodeficiency (SCID); the $CD4^+$ subset entering the SCID gut mucosa are apparently hyperreactive against some luminal antigen(s), as shown by a Th1 cytokine profile, epithelial invasion, and induction of B-cell accumulation in the lamina propria. Similar observations have been made in transgenic (Tgε26) mice with aberrant thymic T-cell selection (46). Moreover, cadherin mutation, which causes lack of epithelial integrity in genetically manipulated mice, results in enteritis that resembles CD (46). Recently, a pathogenic role of mast cells has been suggested by aggravation of experimental colitis in transgenic mice overexpressing the human high-affinity receptor for IgE (18).

IBD apparently reflects break of tolerance against the intestinal microbiota

Although the initial lesion(s) has as yet not been clearly defined, it seems at present justified to consider IBD as clinical presentations of nonspecific biological amplification systems resulting from overactivation of innate and adaptive immune mechanisms (Fig. 4) operating on a polygenic background. No fundamental differences have been identified in the immunopathology of the two disease entities except for a more intensive Th1 response in CD and autoimmunity in UC (perhaps causing diffuse damage to the epithelium). Various IBD models developed in knockout mice clearly show that the major trigger of local immunological effector mechanisms is the indigenous microbial gut flora (16, 44). Confounding cotriggers of human IBD may be variables such as smoking, which appears to increase the risk of acquiring CD but to protect against UC (16).

Altogether, two prevalent immunological theories exist to explain the development and perpetuation of IBD: a) some unknown (probably bacterial) antigen(s) is unsuccessfully eliminated from the mucosa and therefore triggers persisting ('frustrated') immune responses with resulting

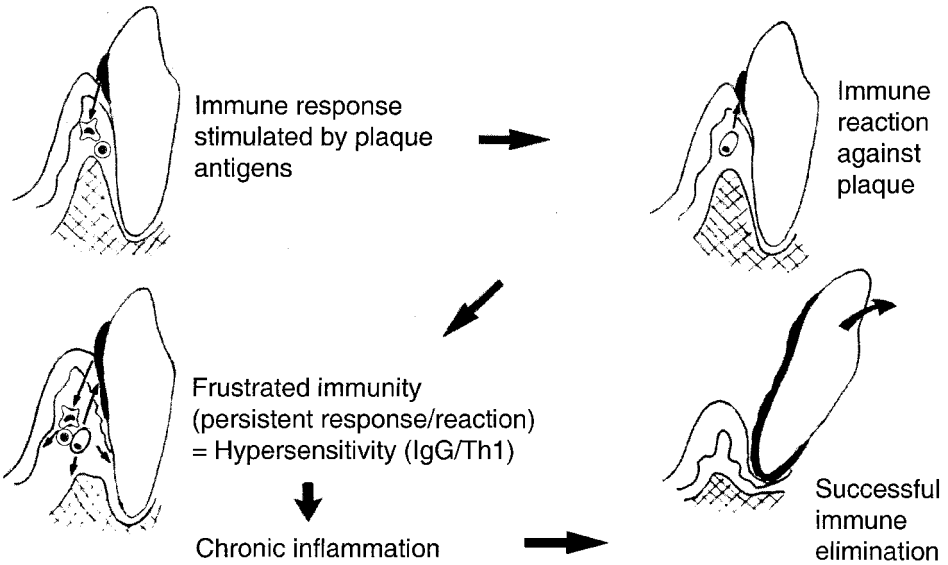

Fig. 5. A simplistic immunopathological notion of the pathogenesis of progressive periodontal disease. Adapted from Brandtzaeg (48). For details, see text.

immunopathology; and b) an inherent immunoregulatory defect gives rise to overreaction, or break of mucosal tolerance, against constituents of commensal gut bacteria. These two possibilities are difficult, if not impossible, to distinguish and could in fact be part of the same scenario because of the high concentration of luminal bacterial antigens in the distal gut.

Epilogue

The initiating event(s) causing abrogation of mucosal homeostasis remains elusive both in IBD and PD, but its origin appears to be alterations both in leukocyte extravasation and in antigen-presenting mechanisms induced by aberrant expression of MHC class-II molecules, as well as a changed local profile of costimulatory molecules. Excessive exposure to antigens from the indigenous microbiota is clearly involved, causing maintenance of 'frustrated' immune elimination mechanisms. Persistent local stimulation of protective immunity may thus result in immunopathology generated by humoral (antibody-mediated) or delayed-type (cell-mediated) hypersensitivity, also called type-IV hypersensitivity (Fig. 4), against commensal bacterial components. This development will be influenced by various genes involved in the immune system, the dosage and potential virulence of indigenous bacteria, the general health and nutritional state of the host, smoking, and psychological factors (Fig. 3).

A simplistic notion of progressive PD

Observations in both AIDS patients (47) and experimental animals (13) have indicated that an intact immune system has an important protective role in the periodontium. Thus, not unexpectedly, it has been suggested that the humoral antimicrobial response has a protective role in the pathogenesis of PD by promoting tissue repair (26, 27). However, when bacterial plaque is allowed to accumulate persistently on the teeth, the gingival area becomes a site of immunological conflict. Although immune mechanisms most likely contribute significantly to the prevention of microbial spread to deeper and distant tissues, antigen elimination (the ultimate goal of the immune system) cannot be achieved as long as plaque persists. Such 'frustrated immunity' may be settled either by mechanical (and antibiotic) plaque removal or by tooth loss—which, in fact, may be viewed as successful immune elimination (Fig. 5). Superimposed on this simplistic, although attempted holistic, immunopathological concept of PD (48) come the individual patterns of disease progression, which may be explained both by microbial and immunological variables and by more or less well-defined confounding factors (Fig. 3).

Conclusions

Perturbation of a tightly controlled cytokine network, with abnormal crosstalk between several mucosal cell types, may be the first step in a progressive immunopathological drive of chronic inflammatory mucosal diseases in general. Although the initiation of this series of adverse immune events often remains undefined, several potential targets for new therapy have tentatively been identified in an attempt to block undue biological interactions in IBD (17, 45). Thus, inhibition of TNF has been documented to

have a striking beneficial clinical effect in many (but not all) patients with CD. A similar approach has successfully been used in rheumatoid arthritis, supporting a central pathogenic role of TNF in chronic inflammatory diseases. Although such new therapeutic principles may be available for PD in the future, removal of dental plaque remains the only practical means to ease ongoing immunopathological mechanisms in the gingiva. Without such treatment the immune system will in the end usually eliminate subgingival bacterial plaque along with the tooth (Fig. 5). In a similar manner, the immunopathology will be persistently maintained by the indigenous microbiota in IBD. Notably, commensal bacteria should not be eliminated from the gut lumen because they maintain an important pressure against colonization of overt pathogens and are essential for many intestinal functions (49). Interestingly, however, of all available IBD therapies, only removal of the large bowel with its content (total colectomy) is a curative approach for UC (50).

Altogether, the current immunopathological notion of both IBD and PD fits with Sobin's (51) elegant description of inflammatory reactions in general:

Inflammation is meant to be good
That's the way it would be if it would
Remain in proportion
Avoid all distortion
Resolve at the time that is should.
Inflammation may last and turn chronic
Situation that is most ironic
Instead of defending
Result is offending
Protractive destructive demonic.

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