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What can we learn about biofilm/host interactions from the study of inflammatory bowel disease

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Abstract

Objectives: The aim of this review was to evaluate possible common pathogenic pathways and risk factors in inflammatory bowel disease (IBD) and periodontitis.

Materials and Methods: A MEDLINE–PubMed research was conducted.

Results: The pathogenesis of both diseases is multi-factorial leading to a substantial defect of the mucosal barrier, deregulation of the immune response and chronic inflammation of the mucosa. Environmental factors, particularly bacteria, are key factors in the pathogenesis of both diseases. Genetic predisposition is a key factor in the IBD pathogenesis, while a clear role of genetics in the pathogenesis of periodontitis is still unclear. The immune response in IBD is mediated by T lymphocytes as a consequence of a genetic trait associated with T-cell deregulation. On the other hand, in periodontitis plasma cells and lymphocytes are the predominant cells in the chronic inflammatory lesion, with the presence of B cells being proportionally larger than T cells.

Conclusion: IBD and periodontitis share several factors in their aetiology and pathogenesis, although they also have distinct characteristics.

Key words: inflammatory bowel disease; pathogenesis; periodontitis

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Inflammatory bowel disease (IBD) is a complex chronic inflammatory intestinal disease with a prevalence of up to 43.6 per 100,000 in western countries and 5 per 100,000 in developing countries (Best et al. 1976). This prevalence has been constantly increasing globally during the recent years, suggesting that environmental and lifestyle factors play an important role in its pathogenesis. IBD preferentially manifests in the second and third decade of life. Crohn's disease (CD) and ulcerative colitis (UC) are the main clinical manifestations of IBD.

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UC is a chronic non-transmural intestinal inflammatory disease characterized by the mucosal inflammations, usually confined within the colon (with the rare exception of the so-called backwash ileitis). Its typical clinical presentation consists of bloody diarrhoea, mucorrhea, pus, and abdominal pain. In severe manifestations (15–20% the cases), the patient shows fever, fatigue, weight loss, hydro-electrolytic imbalance, anaemia, toxic megacolon, and septic state. This is a grave clinical condition requiring total proctocolectomy in many instances. The natural history of the disease is characterized by alternating periods of reactivation and long remission. Overall, life expectancy of patients with UC is normal, but the severe chronic symptoms may have a significant impact on their quality of life.

CD is an idiopathic IBD that may affect any part of the alimentary tract, from the mouth to the anal–rectum. CD is characterized by a chronic transmural granulomatous inflammation of the gastrointestinal tract. At the time of the initial diagnosis, the most frequent localizations are terminal ileum (up to 50%), colon (28%), combined ileo-colon (21%), and upper gastrointestinal tract (3%). The disease is generally classified in structuring, penetrating (fistulas, abscesses), or the combination of both. The clinical presentation is widely dependent on the disease localization. Common features include mucus and bloody diarrhoea and abdominal pain. In the severe manifestations of CD (30%), the patient presents symptoms of fever, anaemia, fatigue, and weight loss, together with signs of intestinal stenosis and abdominal obstruction, such as abdominal and pelvic abscesses. This is a grave clinical condition requiring surgery with intestinal resection in

many cases. Patient's life expectancy is slightly reduced and the severe chronic symptoms generally have a significant impact on the quality of life.

The clinical expression of IBD is characterized by the co-existence of extra-intestinal manifestations, which may precede or follow the intestinal symptoms even for years. These may include affection of the joints, eyes, skin, mouth, liver and pancreas (Bevenius 1988, Veloso et al. 1996, Jiang et al. 2006) (Table 1). The prevalence of oral lesions in patients with CD ranges between 6% and 20% (Basu 1976, Greenstein et al. 1976, Rankin 1990, Plauth et al. 1991). Oral manifestations can also be caused by IBD-induced malabsorption. Common oral signs and symptoms in patients with CD include pyostomatis vegetans, gingival hyperplasia, papillomatosis of the oral mucosa, vesicular eruptions such as in pemphigus vegetans, periodontitis, and caries (Sundh & Emilson 1989, Mergulhao et al. 2005, Ruiz-Roca et al. 2005, Brito et al. 2008). Different gingival and mucosal lesions have been reported in association with IBD including hypertrophy and swelling of lips, gingival hyperplasia, resembling epulis fissuratum, cobblestone appearance of the oral mucosa and palate, presence of vesicles, erosions, ulcers, aphthous-like ulcerations, polypoid ''taglike'' lesions, and areas of necrosis (''snail-track'' lesions) (Ojha 2007).

The differential diagnosis is usually clinical after excluding other granulomatous chronic inflammatory diseases, such as tuberculosis and sarcoidosis. Clinicians can confirm this clinical diagnosis with serological test, including assays for anti-neutrophil cytoplasmic antibody (Williams & Greenberg 1991, Lloyd et al. 1994, Sciubba & Said-Al-Naief 2003).

The aim of the review was to evaluate the possible pathogenic pathways and common risk factors in IBD and periodontitis by describing the current knowledge on the pathogenesis of IBD and periodontitis.

Table 1. Extra-intestinal manifestations of IBD

Eyes: uveitis, episcleritis, iritis
Skin: erythema nodosun, pyoderma gangrenosum
Joints: ankylosing spondilytis, sacroileitis, arthritis, tendinitis
Major organs: pleuritis, myocarditis, primary sclerosing cholangitis or overlap syndrome, nephrolithiasis, pancreatitis, sensoneural hearing loss

Pathogenesis of IBD and periodontitis

The pathophysiology of IBD is multifactorial and results from a complex interaction among genetic, immunological, and environmental factors leading to a substantial defect of the intestinal mucosa barrier (Fig. 1). Its pathogenesis is the result of an aberrant immune response in a susceptible host and it is clearly influenced by environmental factors (MacDonald et al. 2000, Bouma & Strober 2003, Schreiber et al. 2005, Eckburg & Relman 2007).

Until recently, IBD was included in a group of diseases with uncertain aetiology and with a pathogenesis somehow autoimmune related or due to a non-specific inflammatory response. At present, there is a general agreement that IBD is the result of the interplay of at least four factors: genetic predisposition, an altered immune response, the microbial flora of the gut, and environmental factors that may act as a trigger of the disease manifestations (MacDonald et al. 2000, Bouma 2003, Kinane & Mark Bartold 2007).

Similar to IBD, a combination of genetic predisposition, presence environmental factors, mainly a pathogenic microflora and an excessive host response, are main factors involved in the pathogenesis of periodontitis (D'Aiuto et al. 2004b, Kornman 2008, Salvi et al. 2008) (Fig. 2). This excessive host response is complex and involve several interactions mechanisms (Lindhe et al. 1980, Shapira et al. 2005).

Genetic factors in IBD and periodontitis

Familial aggregation of IBD has been classically documented. In fact, the risk for IBD is higher in the presence of a positive family history. There is a 22% chance of developing UC or CD when CD is diagnosed in a first-degree relative and a 15% chance of developing UC in case of a first-degree relative with UC. Another strong evidence of genetic predisposition comes from concordance in twin studies. A 40–60% concordance has been reported in mono-zygotic twins and 7–10% in di-zygotic twins.

The search for the responsible key genetic factor in IBD pathogenesis has advanced in the last years with the implementation of DNA analysis and sequencing techniques, such as genome-wide associations in multi-centre databases and the identification in 2001

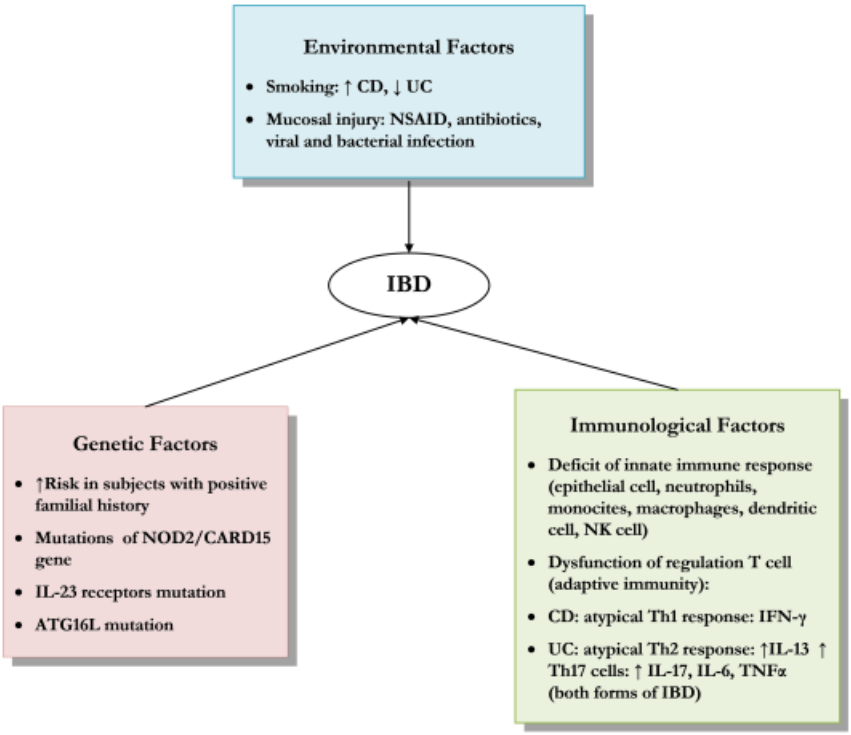

Fig. 1. Multifactorial pathogenesis of IBD.

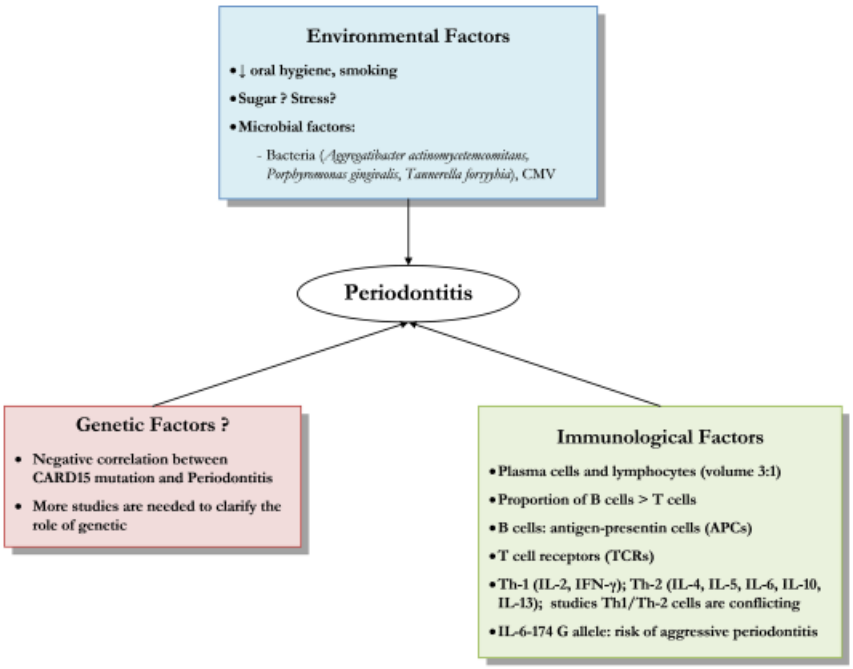

Fig. 2. Multifactorial pathogenesis of periodontitis.

of a specific mutation in the nucleotide-binding oligomerization domain 2/caspase recruitment domain 15 (NOD2/CARD15) gene. The NOD2 is a protein localized within the cytosol that holds the capability of recognizing bacterial muramyl-dipeptide, a component of the bacterial cell wall. This mutation of the NOD2/CARD15 gene impairs the ability to recognize bacterial components of the commensal intestinal microbiota and triggers an inadequate immune response (Hugot et al. 2001, Ogura et al. 2001). A strong association with the CARD15 variant has been demonstrated in patients with CD, with carrier frequencies of one or more variant CARD15 alleles [single nucleotide polymorphisms (SNPs)] between 22% and 60% (Hampe et al. 2001, Hugot et al. 2001, Tukel et al. 2004). A mutation associated with an increased production of pro-inflammatory cytokines by monocytes and macrophages and a reduced activation of antimicrobial proteins by epithelial cells has been demonstrated in about 20% of patients with IBD (particularly, CD) (Esters et al. 2004). This pathogenic pathway has been studied in experimental murine models. Other gene mutations that have been recently studied involve the IL-23 receptor mutation, which plays a role in the IL-12/23 pathway of pro-inflammatory cytokines and the ATG16L mutation, where a failure in cell apoptosis triggers a local inflammatory response (Rioux et al. 2007) but their role needs further confirmation.

In a similar manner, different authors have investigated the genetic influence in the pathogenesis of chronic periodontitis. It is very clear that in spite of the cause–effect relationship between lack of oral hygiene and development of gingival inflammation, this condition only evolves to destructive periodontitis in a minority of patients (Loe et al. 1965, Neely et al. 2001), hence suggestion a genetic, predisposing factor for chronic periodontitis. In recent years, the focus of research has mainly aimed to associate different susceptibility genes (SNPs) with destructive periodontal conditions in population-based studies. Although cytokine gene polymorphisms have demonstrated positive associations in some studies, the evidence on its pathogenic role is still inconclusive (Huynh-Ba et al. 2007, Nikolopoulos et al. 2008).

An attractive new concept has been recently introduced, infectogenomics, as the relationship between host genetic factors and the composition of the subgingival microbiota (Nibali et al. 2009). In fact, these authors have demonstrated a significant association between IL-6 gene and Fc-γ gene receptor variants and the subgingival detection of *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis* in periodontitis patients (Nibali et al. 2007, 2008). More studies are needed, however, to clarify the role of genetics in the pathogenesis of periodontitis (Stein et al. 2010).

Microbial and environmental factors in IBD and periodontitis

The environmental factors play a pivotal role in the development of both diseases. In IBD, a clear north south gradient in the prevalence has been reported in epidemiological studies. These differences can be explained by differences in both access to and quality of health care and hygiene standards. This is supported by the observation of increased prevalence of IBD in immigrants from underdeveloped to developed countries (Leong et al. 2004, Zheng et al. 2005). Moreover, several north European and north American epidemiological studies have documented a higher prevalence in urban compared with rural areas. It is conceivable that excessive sanitation might reduce the exposure to a wide array of environmental agents, what could impair the natural process of evolution and maturation of the intestinal mucosa immune system, resulting in a sort of immune tolerance that can be the basis for an unregulated immune-inflammatory response when re-exposed to the same agents later in life (Mawdsley & Rampton 2005). Several potential triggers have been investigated and there is no evidence that a single agent or bacteria is responsible for the development of IBD. Breaks in the integrity of the mucosal barrier, such as secondary to the use of NSAID, antibiotics, and viral and bacterial infections have been clinically identified as common triggers for the disease.

Intestinal commensal bacteria clearly play a role in IBD. There is evidence that the gut flora is necessary to develop IBD in animal models, and treatment with a specific antibiotic, such as metronidazole, is effective in treating fistulizing CD. Moreover, patients with IBD fail to mount tolerance to their own gut flora and there is also evidence that gut flora can modulate the expression of genes involved in different intestinal activities such as adsorption, secretion, mucosal natural barrier regulation, xenobiotic metabolism, and angiogenesis (Bibiloni et al. 2006). There is no evidence, however, that a specific infectious agent (e.g. *Mycobacterium paratubercolosis* as it was initially

hypotesized) is the causative agent for the disease.

Smoking is a well-recognized risk factor for CD development. Particularly, tobacco smoking is associated with increased incidence and clinical severity of CD (Calkins 1989, Johnson et al. 2005, Thomas et al. 2005) but it is associated with a lower incidence of pouchitis (Merrett et al.1996, Thomas et al. 2005) and UC (Thomas et al. 2005). The reasons for these differences are not fully elucidated. The potential beneficial effects of nicotine in UC appear to be due to increased mucus production secondary to the release of both inflammatory cytokines and nitric oxide. On the other hand, nicotine appears to increase the presence of neutrophils in gut mucosa, enhancing the chronic inflammatory condition (smoking cessation has been proven to be effective in ameliorating the clinical picture in CD) (Cosnes 2004, McGrath et al. 2004).

Important interactions between the nervous system and the inflammatory response based on interactions between acetylcholine and α7-nicotin acetylcholine receptor (α7nAChR) have been reported. Studies have attempted to use the α7nAChR agonist, nicotine, for the treatment of mucosal inflammation. The efficacy of nicotine as a treatment for IBDs, however, remains questionable and requires further research (Scott & Martin 2006).

Diet and stress do not have a proven relationship in IBD pathogenesis. They can, however, alter gut flora and different diet components (e.g. iron, aluminium) can modify the functional properties of the flora. Breastfeeding has been associated as a protective factor against IBD in the offspring (Klement et al. 2004), although these data are still controversial.

It is well known that subgingival bacteria are the main causative factor in the initiation and progression of periodontitis. Periodontal destruction, however, is not caused directly by the pathogens, but rather through an excessive host response against the microbial challenge. Although several specific bacteria have been identified as periodontopathogens, mainly due to possessing virulence factors that evade the host responses and perpetuate the chronic inflammatory response, their number is imprecise (American Academy of Periodontology 2005). Recent estimates of the number of bacterial species (assessed by means of massive parallel DNA sequencing) have suggested that the oral cavity may contain as many as 19,000 bacterial phylotypes (Keijser et al. 2008) and most of these bacteria are still uncultivable. An in depth review of the role of bacteria in periodontitis is published in this special issue (Wade et al. 2011).

The role of tobacco smoking in the pathogenesis of periodontitis is also clearly established. Tobacco smoke and smoke components influence both the epithelial barriers and the host immune and inflammatory response (Borovikova et al. 2000, Wang et al. 2003, Kherani et al. 2004, de Jonge et al. 2005, Ulloa 2005, Brito et al. 2008). In fact, smoking is the stronger environmental risk factor associated with periodontitis.

The role of both stress and psychosomatic factors has also been associated with periodontitis; however, the confirmation from well-designed prospective studies is still lacking (Miller 1950, Hilgert et al. 2006).

Immunological factors in IBD and periodontitis

The basis for the development of IBD is an inappropriate response of the gut immune system to both the intestinal flora and other luminal agents.

Several pathways have been associated in this process. In IBD, the presence of a leaky mucosal barrier that allows luminal agents to reach the underlying mucosal tissue has been demonstrated, usually preceding the clinical onset of the disease (Soderholm et al. 2002). The natural mechanism of antigen presentation, recognition, and processing by antigen-presenting cells has been shown to be altered in subject with IBD (Franchimont et al. 2004). A dysregulation of the innate gut immune system has also been demonstrated, through a different expression of Toll-like receptors (TLR) (Cario & Podolsky 2000). Finally, the activity of effector T cells and natural killer (NK) cells is also altered, with delayed apoptosis and over reaction of these cells (Ina et al. 1999, Van den Brande et al. 2003). The alterations at different level demonstrate that the delicate balance of the intestinal system is disrupted with gut immune cells (myeloid dendritic cells) improperly recognizing commensals as pathogens and thus allowing the commensal flora to trigger and maintain an inflammatory response (Malmstrom et al. 2001, Hart et al. 2005). This change in functional status from tolerogenic to activating T cells promotes the differentiation of naïve T cells into NK and effector T cells, which induces gut mucosal aggression and damage.

The two different clinical expressions of IBD represent distinct mechanisms of gut inflammation. UC is characterized by an atypical T helper 2 (Th2) response, with elevated production of IL-13, while CD demonstrates a characteristic Th1 type of immune response, dominated by overproduction of IFN-γ (Cobrin & Abreu 2005, Targan & Karp 2005).

In the pathogenesis of IBD, both the innate and the adaptive immunity are affected. The innate immunity is activated within minutes or hours towards a variety of antigens and is mediated by several different effectors such as epithelial cells, neutrophils, monocytes, macrophages, denditric cells, and NK cells (Medzhitov & Janeway 2000). It is a widely non-specific reaction, primarily directed towards luminal microbial antigens. The recognition process is mainly mediated by TLRs localized on the gut cell surface and NOD proteins of the cytoplasm (Inohara & Nunez 2003, Abreu et al. 2005). The role of innate immunity in the gut mucosa appears to be crucial, because defects of the innate immune response trigger changes in the Th1 and Th2 cell responses and this disruption of the regulatory T cells contribute to alter the mucosal immunity. Adaptive immunity needs longer time to activate (from few to several days) and strongly depends on type, number, and functionality of T cells. Even though many different T cell types are involved in the process, mainly T regulatory and the recently described Th17 cells appear critical in the process. There is evidence that regulatory T cells are reduced in the gut of IBD patients (Brimnes et al. 2005). Th1-mediated immune response is typically triggered in response to intra-cellular pathogens (e.g. virus, mycobacteria, hystoplasma), aimed at localizing the infectious agent (typical granuloma) and producing factors that either directly execute the intra-cellular killing (IFN-γ and TFN-α) or induce the differentiation of cells that mediate the killing (citotoxic T lymphocytes). Recently, a novel Th subset has been identified, Th17 cells that secrete IL-17 and IL-22, known pro-inflammatory cytokines resulting in tissue destruction

(Weaver et al. 2007). Th1 and Th17 have been associated in autoimmune and inflammatory conditions linked to infections and tissue damage, but their specific involvement in IBD is still under investigation. It is still unclear whether single alterations in the innate immunity with or without disruption of the adaptive immunity are needed to trigger IBD.

The periodontitis lesion is characterized by large proportions of inflammatory cells and vascular proliferations, with a clear predominance of plasma cells and lymphocytes in the inflammatory infiltrate (Charon et al. 1981, Joachim et al. 1990, Afar et al. 1992, Celenligil et al. 1993, Lappin et al. 1999, Hillmann et al. 2001, Berglundh et al. 2002a, Berglundh & Donati 2005). Alterations and disregulations of the inflammatory and immune response in response to subgingival bacteria have been identified at different levels, from the function of leucocytes in the innate response to antigen recognition by antigen presenting cells and T-cell receptors (TCRs), the type of lymphocyte activation (T and B cells), and the different cytokine profiles of Th cells and autoimmune reactions. A thorough review of these studies is published elsewhere in this special issue (Budunelli et al. 2011).

The role of auto-antibodies in the regulation of host response in periodontitis as in other chronic infectious diseases needs to be clarified. A particular group of cells involved in autoimmune reactions are $CD5^{+}B$ cells, termed B-1a cells. This group of B cells is found in large numbers in the peripheral blood of patients with autoimmune diseases, e.g. rheumatoid arthritis and Sjogren's syndrome. Unlike conventional B (B-2) cells developed from bone marrow precursors, B-1a cells derive from peritoneal precursor cells. Further, B-1a cells may transform into plasma cells and produce immunoglobulins of other classes than IgM. B-1a cells are represented in a larger proportion in subjects with chronic and aggressive forms of periodontitis compared with healthy controls (Berglundh et al. 2002a, Kishimoto 2006).

Common and discordant elements in the pathogenesis of IBD and periodontitis

The pathogenesis of IBD and periodontitis have both common and discordant elements. The pathophysiology of both diseases is multi-factorial and based upon a complex interaction of genetic, immunological, and environmental factors, leading to a substantial defect of the mucosal barrier and the interaction of exogenous antigens, such as bacteria that evoke an exuberant response leading to chronic inflammation and tissue distruction.

Breaks in the integrity of the mucosal barrier have been identified in both the intestinal disease (the gut intestinal mucosa) as well as in the pocket epithelium of the periodontal pocket. This disruption allows the direct exposure of bacteria and other microorganisms with the underlying immuno-competent tissues. Although the gut flora is necessary to develop IBD in animal models, there no evidence that a specific infectious agent is the causative agent, but rather it is the commensal gut flora that is responsible for the aberrant host response. Moreover, this commensal gut flora can modulate the expression of genes involved in a number of peculiar intestinal activities such as adsorption, secretion, mucosal natural barrier regulation, xenobiotic metabolism, and angiogenesis. In contrast, specific periodontal pathogens seem to play a key role in the pathogenesis of destructive periodontitis by possessing virulence factors that evade both innate and adaptative immune responses and allow the exuberant chronic inflammatory reaction characteristic of the periodontitis lesion.

Smoking is recognized as a risk factor for both periodontitis and CD. It is, however, unclear its role in UC, with some research reports even ascribing smoking a protective role in this condition.

The role of diet and stress has not been proven as clear risk factors in the development of IBD. Their role in periodontitis is more likely, because there are some published positive significant associations, such as with deficient vitamin C intake with the inability to cope with stress. These observations, however, require further confirmation.

Genetic predisposition is a key factor in the pathogenesis of IBD. Mutations in the NOD2/CARD15 gene have been identified in patients with CD. Moreover, mutation of the IL-23 receptor and ATG16L genes have also been recently associated with IBD. In the pathogenesis of periodontitis, there is insufficient evidence to associate specific gene polymorphisms with the initiation or progression of periodonitis. This disease seems to be more the result from complex interaction between multiple bacteria and genes. More studies are needed to clarify the role of genetic factors in the pathogenesis of periodontitis.

Immunological factors play a key role in the pathogenesis of both diseases. An inappropriate response of the defective gut immune system to both intestinal flora and other luminal agents is characteristic of patients with IBD. The two different clinical expressions of IBD represent distinct mechanisms of gut chronic inflammation. UC is characterized by an atypical Th2 response, with elevated production of IL-13, while in CD predominates a Th1 type of immune response, dominated by overproduction of IFN-γ. The gut mucosa Th1 and Th2 type of response may be the consequence of defects of the innate immune response and by disrupting the regulatory T cells, the mucosal immunity demonstrates an abnormal response against normal antigens, such as the commensal gut bacteria. The alterations in the immune responses in IBD, therefore, include both changes in the innate and adaptive immunity. Even though many different T cell types are involved in the process, the T regulatory and Th 17 cells seem to play the most important pathogenic role.

In the pathogenesis of periodontitis, alterations of the host response have been identified at different levels, from the innate response to the antigen recognition by TCRs, the nature of the lymphocyte type (T and B cells), the expression of different cytokine profiles by the Th cells and autoimmune reactions. These different reactions may be the consequence of the expression of different virulence factors by the periodontopathic bacteria present in the periodontal pocket and invading the periodontal tissues by the disruption of the pocket epithelium. Unlike IBD, the proportion of B cells is larger than that of all T cells and Th cells that occur in larger number than T cytotoxic cells. Both T and B cells express co-stimulatory molecules and contribute to antigen recognition and cell activation. Host response to antigenic challenges in peridontitis includes specific immune reactions in which the TCRs interact with the processed antigen of APCs. Activation of Th cells results in the productions of various cytokines and it is likely that an alteration of the balance between Th1 and Th2 responses modulates the disease expression in periodontitis.

Thus, while immune-mediated mechanisms are strongly dependent on T lymphocytes in the pathogenesis of IBD, the B lymphocytes have a key role in the pathogenesis of periodontitis.

Conclusions

The pathogenesis of both diseases is multi-factorial and based upon a complex interaction of genetic, environmental, and immunological factors, leading to a substantial defect of the mucosal barrier, dysregulation of immune response, and chronic inflammation of the mucosa.

The pathogenesis of IBD and periodontitis have common and discordant elements, particularly with regard to the role of the bacteria and the specific host response. The immune response in IBD is T lymphocyte mediated, and may be the consequence of genetic defects associated with the regulation of T cells resulting in inflammation of the mucosa. The immune response in periodontitis is more B cell dependent, although further studies are required to clarify the role of T lymphocytes and cytokines in the pathogenesis of periodontitis.

Environmental factors are of key significance in the pathogenesis of both diseases. Particularly, periodontal bacteria seem to play a key role in the pathogenesis of periodontitis. Genetics is a key factor in IBD pathogenesis, while current studies do not confirm a clear role of genetics in the pathogenesis of periodontitis.

On the basis of common pathogenetic mechanisms shared between IBD and periodontitis, the treatment of periodontitis can benefit from the same drugs used for IBD, such as antibiotics, steroids, azathioprine, cyclosporine, thalidomide, and anti-tumour necrosis factor (Wiesenfelfd 1985, van der Wall et al. 2002, Hegarty et al. 2003, Groselj et al. 2008, Van Assche et al. 2006). In fact, it is clinically relevant that most of the therapy utilized for IBD could improve periodontitis.

Patients with persistent gingival and/or other oral lesions and symptoms, including gingival ulcerations, oedema, burning, erythema, swelling and pustules, as well as abdominal pain, diarrhoea, arthralgia, and skin lesions, should be evaluated by an interdisciplinary specialized team for a possible diagnosis of IBD and, on the other hand, patients with IBD presenting with oral symptoms should undergo a careful periodontal evaluation (Fig. 3).

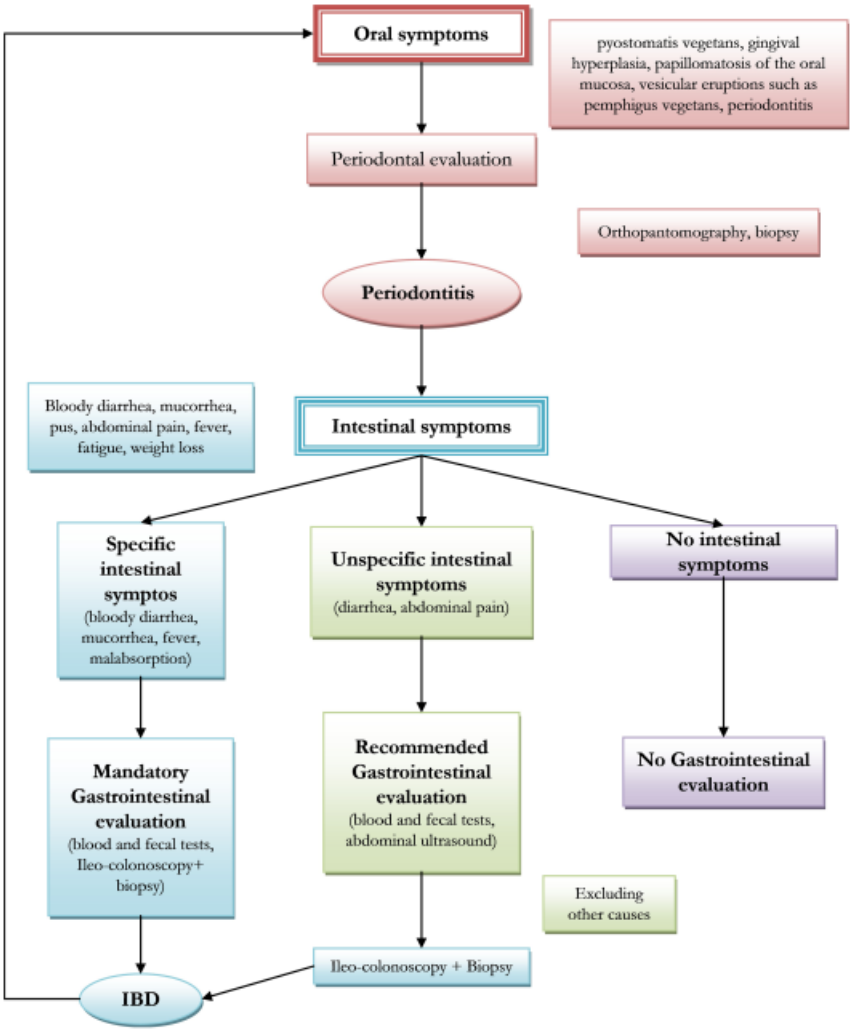

Fig. 3. Diagnostic algorithm of oral and intestinal symptoms in patients with periodontitis and IBD.

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Clinical Relevance

Scientific rationale for the study: To our knowledge, this paper is the first review evaluating the possible common pathogenic pathways between periodontits and IBD.

Principal findings: The pathogenesis of both diseases is multi-factorial leading to a substantial defect of mucosal barrier, deregulation of the immune response and chronic inflammation of the mucosa. Subgingival bacteria are the main causative factor in the initiation and progression of periodontitis. Genetic predisposition is a key factor in the IBD pathogenesis, while a clear role of genetics in the pathogenesis of periodontits is still unclear. The immune response in IBD is mediated by T lynphocytes as a consequence of a genetic trait associated with T-cell deregulation. In periodontitis plasma cells and lynphocites are the predominant cells in the chronic inflammatory lesions, with the presence of B cells being proportionally larger than T cells.

Practical implications: The two diseases may be associated through sharing relevant pathogenic mechanisms and when both diseases coexist, their progression could be accentuated and on the contrary, their treatment could improve both conditions. A practical consideration is that patients with periodontitis and intestinal symptoms should be referred for gastrointestinal evaluation; similarly patients with IBD and oral symptoms should be referred for an extensive periodontal evaluation.