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ROLE OF PLASMA MATRIX METALLOPROTEINASES 3& 9 IN DETERMINING DISEASE ACTIVITY IN PATIENTS WITH ULCERATIVE COLITIS

Essay
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دور الإنزيمات المحلله للبروتين المعدني ٣ و ٩ فى البلازما فى مرضى التهاب القولون التقرحي وعلاقتها بنشاط المرض

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Summary and Conclusion

Ulcerative colitis is a chronic inflammatory disease of the rectum and colon . Results from many studies in people and animals of intestinal inflammation suggest that ulcerative colitis results from environmental factors triggering a loss of tolerance for normal intestinal flora in genetically susceptible individuals.

The timely breakdown of extracellular matrix (ECM) is essential for embryonic development, morphogenesis, reproduction, and tissue resorption and remodeling. The matrix metalloproteinases (MMPs) also called matrixins are thought to play a central role in these processes. The expression of most matrixins is transcriptionally regulated by growth factors, hormones, cytokines, and cellular transformation.

The proteolytic activities of MMPs are precisely controlled during activation from their precursors and inhibition by endogenous inhibitors, α-macroglobulins , and tissue inhibitors of metalloproteinases (timps).

Degradation and remodelling of the extra cellular matrix (ECM) is increasingly implicated in the pathogenesis of many inflammatory diseases such as inflammatory bowel disease, MMPs play a key role in these events.

MMPs can cleave all components of the ECM and in health act in harmony as part of normal tissue turn over. During inflammation their dysregulation leads to excess degradation of the matrix components and

loss of tissue integrity. MMPs are released from almost all connective tissue cells in response to inflammatory stimuli such as cytokines

The plasma mean concentration of MMP3 & MMP9 in ulcerative colitis is increasing according to disease activity so can be used as a bio marker of disease activity

In conclusion, our informations confirm the role of both MMP-3 and MMP-9 in the pathogenesis of ulcerative colitis. However may be useful as a biomarker of the disease activity.

CONTENTS

INTRODUCTION

Although UC and CD are the two most common types of inflammatory bowel disease, there is a spectrum of inflammatory bowel diseases encompassing various types and degrees of intestinal inflammation that must be distinguished from inflammation caused by infections, drugs, ischemia, and radiation. This chapter covers the epidemiology, etiology, and pathogenesis of inflammatory bowel diseases and reviews the diagnostic workup of ulcerative colitis. The key distinguishing features of these two conditions are mentioned separately. A treatment overview section includes coverage of medical therapy, nutritional therapy, supportive therapy, and surgical therapy. Ulcerative Colitis and Crohn's disease are treated separately. Complications of inflammatory bowel disease include extra intestinal complications, intestinal complications, and adenocarcinoma. **(Stephen, 2010).**

Epidemiology:-

UC and CD share most epidemiologic characteristics. These diseases are relatively common in developed nations and infrequent in undeveloped countries. In North America and Europe, the incidence is approximately five cases per 100,000 populations for each disease, with a combined prevalence of approximately 100 per100,000 populations. The diseases can affect persons of any age, but onset most commonly occurs in the second and third decades of life. Much smaller, secondary peaks in incidence occur in the sixth and seventh decades. Males and females are affected equally. Risk of disease is higher in some ethnic groups than in others. Ashkenazi Jews have a higher risk of IBD than Africans, African Americans, and Asians; the incidence of IBD increases in these lower-risk groups, however, when they emigrate to developed nations adopt Western culture and diet. (Stephen, 2010).

Etiology and Pathogenesis:-

- **Genetic Factors.**
- **Autoimmune**.
- **Environmental Tigers.**
- **Bacterial Factor.**

(A) Genetic Factors:

In contrast to Crohn's disease, for which the *NOD2/CARD15* gene has been established as a genetic susceptibility factor with a phenotypic correlate with this disease.**(Bonen, 2003).**

No specific gene has yet been linked to ulcerative colitis. Nevertheless, there is compelling evidence that genetic factors do contribute to the susceptibility to develop ulcerative colitis. **(Ahmad,2003).**

Epidemiologic studies demonstrate familial concordance for disease type, extent and extra-intestinal manifestations for siblings with ulcerative colitis, but the concordance rates are smaller than for Crohn's disease. **(Satsangi, 2003).**

Several potential genetic susceptibility factors/regions have been described for ulcerative colitis. The region of the MHC locus on chromosome 6p that contains the genes encoding the HLA Class I and II histocompatibility molecules has been implicated in susceptibility to ulcerative colitis by both association and linkage studies; however, the linkage studies do not discriminate between risk for ulcerative colitis and Crohn's disease. More specifically, ulcerative colitis has been most consistently associated with HLA Class II alleles. **(Bonen, 2003).**

Another potential 'functional candidate gene' is the multidrug resistance gene (*MDR1*) that is located in an area of linkage on chromosome 7. **(Ahmad, 2003).**

A weak association of multidrug resistance gene (*MDR1*) with ulcerative colitis has been identified,but that requires additional confirmation and replication.**(Schwab M *et al.* (2003).**

In addition to the probable contribution of genetics to the susceptibility of developing ulcerative colitis, there is a strong likelihood that genetics also impact on the incidence of extra- intestinal complications of

ulcerative colitis. **(Orchard, 2003).**

In particular, the association between HLAB27 and the development of ankylosing spondylitis and sacroiliitis in patients with ulcerative colitis has been reproduced and approaches 100%. Peripheral arthropathies accompanying ulcerative colitis are also associated with HLA polymorphisms that associate with erythema nodosum and uveitis (type I [large-joint involvement] and type II [small-joint involvement]).
(Orchard, 2002).

(B) Autoimmune:

A destructive inflammatory response directed toward a self-antigen such as mucin, goblet cells, colonocytes, or other cells has been proposed as the underlying basis of IBD, particularly in regards to UC. **(MacDonald, 2000).**

As noted above, antibodies against neutrophils have been found in many but not all UC patients. **(MacDonald, 2000).**

However, the titers of antineutrophil antibodies do not seem to correlate with disease activity in UC and their biological significance in UC patients is unclear. **(Roozendaal, 1999).**

Levels of antibodies against a human intestinal tropomyosin isoform also have been reported to be increased in UC patients in some studies. **(Onuma, 2000).**

In addition, activated complement factors have been noted to colocalize with anticolon antibodies on the luminal surface of the epithelium. **(Merger, 1998).**

Exposure to microbial peptides that share immunogenic determinants with self-antigens has been suggested as the trigger for the disruption in immune tolerance to endogenous gut antigens.
(Merger, 1998).

Less information is available regarding the pathogenesis of UC. However, several studies suggest that UC differs from CD in the profile of cytokines in the intestinal mucosa **(Papadakis, 2000).**

For example, Th2 cells rather than Th1 cells have been hypothesized to play a prominent role in UC, but only limited data are available

to confirm this idea. In support of this notion, though, IL-12 transcripts have been found in the intestinal mucosa of CD patients but not generally in UC. **(MacDonald, 2000).**

In the UC intestine has many immunoglobulin G (IgG) secreting plasma cells and IgG1 colocalizing with the complement component C3b on the surface of epithelial cells. **(MacDonald,2000).**

Nonetheless, although lamina propria T cells from UC patients have been reported to secrete greater amounts of IL-5 than do those from controls, the production of IL-4 does not appear to be increased in UC, which would be expected with a Th2-cell response.

(Matsumoto,1998).

Table 1: Characteristics of T-cell Subsets

Designation	Origin	Antigen	Marker	Mechanisms of action
T_{REG}	Thymus	Self antigen (possibly)	FoxP3, $CD25^+$	Cell–cell contact, membrane- bound TGF-ß
T_R1	Intestine	Luminal bactieria	None	Secretion of IL-10 > TGF-ß
T_H3	Intestine	Oral protein	None	Secretion of TGF-ß> IL- 10

CD, cluster designation; FoxP3, forkhead box P3; IL, interleukin; TGF, transforming growth factor; TH3, type 3 T-helper lymphocyte; TREG, regulatory T cell; TR1,type1 regulatory T cell. With permission© **American Gastroenterological Association Institute, Bethesda, MD.(2006).**

IMMUNE MEDIATORS OF EXTRAINTESTINAL MANIFESTATIONS:

As outlined above, a number of extraintestinal manifestations of CD and UC have been described. Although the occurrence of extra intestinal symptoms often coincides with intestinal disease activity, the pathogenesis of these manifestations of IBD is not well understood. In the case of arthritis, studies of HLA-B27 transgenic rats suggest that recirculation of memory T cells between the intestine and synovium occurs. **(DeVos, 1998).**

In support of this idea, adherence of lamina propria lymphocytes to synovial high endothelial venules has been demonstrated. A role for mucosal macrophages transporting antigens from the intestine to the

joints also has been postulated. In addition, in the HLA-B27 transgenic rat, intestinal bacteria appear to play a significant role in the pathogenesis of the arthritis **(Sartor, 1997).**

(C) Environmental Triggers:

Studies have implicated several environmental factors in the pathogenesis of IBD. These factor include smoking, which is protective in ulcerative colitis but detrimental in Crohn's disease, diet, the use of antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs), stress and infection. Unfortunately, the mechanisms by which these factors initiate the onset of disease or reactivate quiescent IBD are not well understood. From a broad perspective, these triggering factors alter mucosal barrier integrity, immune responses, or the luminal microenvironment, each of which have an impact on susceptibility inflammation. **(Loftus,2004)**.

Infection&**NSAIDs** can transiently initiate nonspecific inflamation, break the mucosal barrier and activate innate immune responses. These events could then lead to enhanced uptake of commensal bacterial antigens and adjuvants that stimulate protracted T-cell-mediated intestinal inflammation in the genetically susceptible host. An example of this is induction of chronic colitis in ***IL-10*** mice, by exposure to the NSAID piroxicam for 2 weeks. **(Berg, 2002).**

Dietary components can alter the composition and virulence of enteric commensal bacteria, providing one potential explanation for the marked increase in the incidence of IBD in Western countries in the second half of the twentieth century, and more recently in Eastern countries, as they adopt Western dietary practices.

(Loftus, 2004).

Nonabsorbed carbohydrates (prebiotics) such as inulin and fructose oligosaccharides enhance the growth of *Bifidobacterium* and *Lactobacillus* species, and provide a substrate for the production of short-chain fatty acids by these bacterial species. Short-chain fatty acids, especially butyrate, are the preferred metabolic substrates of colonocytes, and can stimulate various mucosal barrier functions. **(Sartor, 2004).**

Both iron and aluminum are usually food additives in Western diets and are processed identically by mammalian and bacterial acquisition and storage proteins. Dietary iron and aluminum can potentate experimental colitis. **(Lerner, 2006).**

Stress can alter mucosal permeability, mucosal blood flow, epithelial electrolyte and water secretion and expression of cytokines and neuropeptides. **(Erichsen, 2005).**

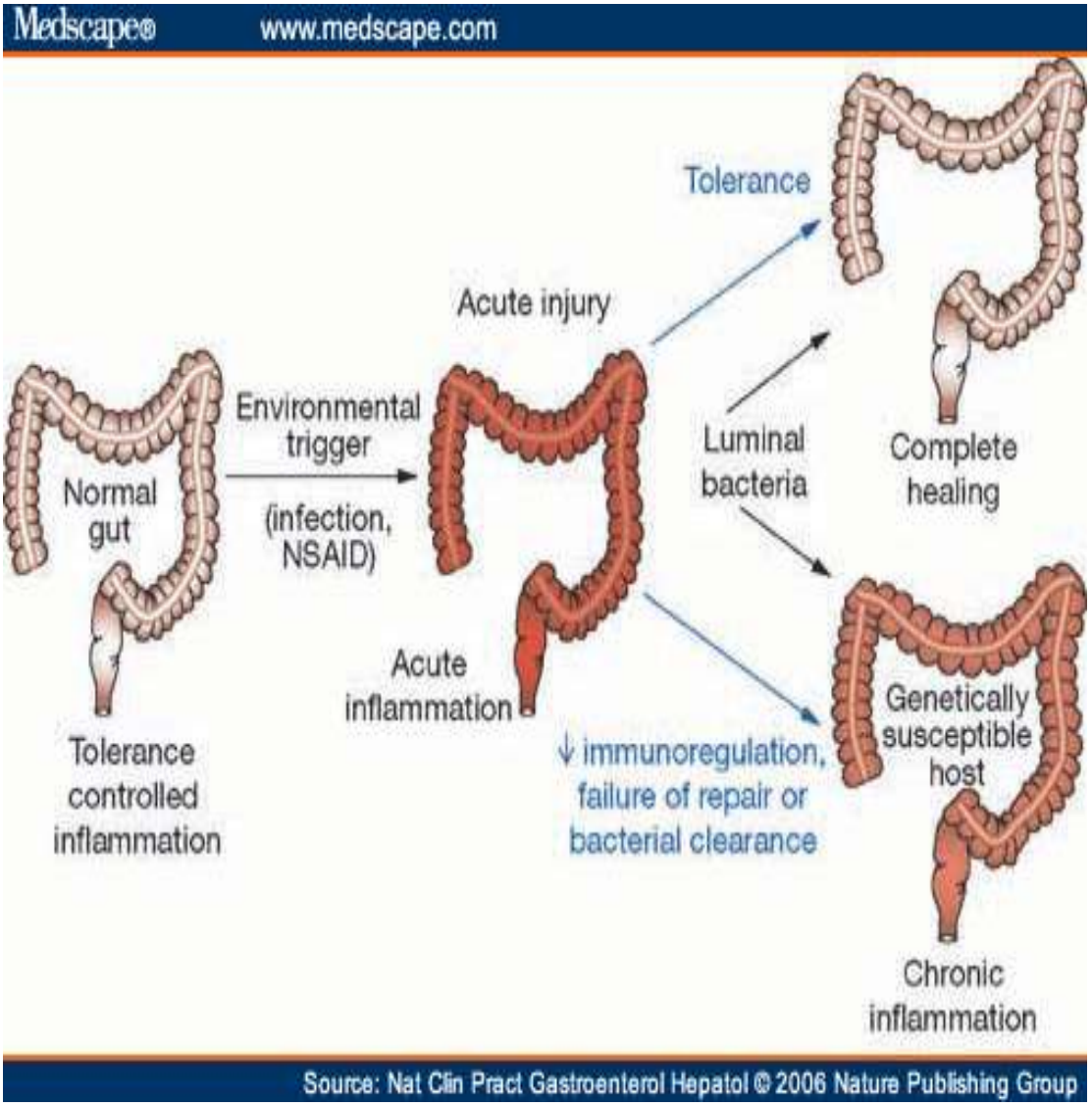

Fig.1 Different responses to transient intestinal injury in genetically susceptible versus genetically resistant hosts. After nonspecific injury from an environmental trigger, such as an infection or exposure to a nonsteroidal anti-inflammatory drug (NSAID), normal hosts rapidly repair the mucosal defect and downregulate innate and T-cell immune responses with no residual tissue damage. By contrast, individuals inwhom immunoregulation, epithelial barrier function or bacterial killing is defective, develop chronic inflammation that is mediated by aggressive T-cell responses to commensal bacterial antigens. Chronic inflammation is perpetuated by continued uptake of luminal antigens. With permission ©**American Gastroenterological Association Institute, Bethesda, MD.(2006)**

Smoking is perhaps the most thoroughly documented environmental contributor to IBD, but its opposite effect on Crohn's disease and ulcerative colitis, respectively, is difficult to understand. Nicotine, carbon monoxide and hypoxia have all been suggested to b mediators of the effects of smoking on IBD.**(Birrenbach, 2004).**

The long-standing finding that cigarette smoking protects against the development of ulcerative colitis has withstood the test of time. Indeed, case series continue to demonstrate a protective effect of smoking on both the development and course of ulcerative colitis. **(Abraham, 2003).**

Smoking accounts for much of the discordance between ulcerative colitis and Crohn's disease within families or siblings -- in families with siblings affected by either ulcerative colitis or Crohn's disease, cigarette smoking continues to demonstrate a protective role against ulcerative colitis. **(Halme, 2002).**

Although smokers are less likely to develop ulcerative colitis, however, ex-smokers are more likely to develop extensive or severe colitis. Others believe that ex-smokers account for the preponderance of the second age peak for ulcerative colitis in patients over the age of 40 years. **(Mitchell, 2002).**

The protective effect of smoking also extends to the extra-intestinal manifestations and post-surgical complications of ulcerative colitis. **(Mitchell, 2002).**

Appendectomy. Another consistent epidemiologic clue to the pathogenesis of ulcerative colitis is the observation that appendectomy, particularly at a younger age both reduces the likelihood of developing ulcerative colitis and is associated with a less severe disease course. The impact of appendectomy seems to be an additive protective factor to cigarette smoking against the development of ulcerative colitis. **(Radford, 2002).**

(D) Bacterial Factors:-

One ubiquitous factor in animal models of colitis and in the human disease is the relationship with bacteria. In experimental models of IBD, colitis does not develop in animals that are raised in germ- free environments. Commensal bacteria, not pathogens, are sufficient to induce colitis, but this is determined by both host and bacterial specificities. **(Sartor, 2004).**

In addition, different phenotypic patterns of colitis are seen in specific animal models and with specific bacterial species. Commensal bacteria can also induce a protective effect that can be transmitted by bacteria-responsive regulatory CD4+T cells. **(Cong, 2002).**

Although it has not been possible to identify bacterial strains that are specific to ulcerative colitis,there are increased numbers of mucosa-associated (adherent) *Bacteroides* and *Enterobacteriaceae* species in patients with inflamed segments. **(Swidsinski, 2002).**

The concept that early childhood exposure to bacteria or helminthes may prevent the onset of IBD has been proponsed by Weinstocks and colleagues and has led to clinical trials with nonpathogenic worms (*Trichuris suis*)totry to ameliorate intestinal inflammation.

(Summers,2003).

The recognized heterogeneity of IBD may be accounted for by differing immunologic responses (or tolerance),as measured by the serologic response to various distinct bacterial antigens.

(Landers, 2002).

Alternatively, functional activity of microbial strains may also lead to 'DYSBIOSIS' (early death of cells) and affect the metabolic activity of colonocytes or enterocytes, leading to the development of ulcerative colitis.**(Sartor, 2004).**

The potential inductive or protective role of bacteria has also led to considerable interest in prebiotic or probiotic therapies for ulcerative colitis and its complications. **(Sartor, 2004).**

An altered balance of beneficial versus aggressive microbial species could lead to a proinflammatory luminal milieu that drives chronic intestinal inflammation in a susceptible host. Numerous studies have implicated several commensal organisms, such as *E. coli*, *Bacteroides*, *Enterococcus* and *Klebsiella* species,in the pathogenesis of experimental intestinal inflammation and human IBD. **(Sartor, 2004).**

By contrast,various *Lactobacillus* and *Bifidobacterium* species have predominantly protective effects and have been used therapeutically as probiotics. Several groups have documented alterations in luminal or adherent microbial commensal flora in patients with Crohn's disease, ulcerative colitis and pouchitis. **(Sartor, 2004).**

An alternative means of changing the microenvironment in such a way as to stimulate aggressive immune responses is the acquisition of virulence factors by commensal bacteria.As discussed above, entero-adherent and invasive *E. coli* have been found in the neoterminal ileum of patients with postoperative recurrence of Crohn's disease**. (Darfeuille, 2002).**

Adjuvants:

Numerous bacterial adjuvants, most notably lipopolysaccharide, peptidoglycan, flagellin and nonmethylated DNA (CpG motif),can bind selectively to various TLRs on innate immune cells, intestinal epithelial cells and mesenchymal cells (Figure 2). **(Cario, 2005).**

Ligation of these TLRs activates NFB and the mitogen-activated protein kinases, which stimulate the transcription of a host of proinfla-mmatory and regulatory genes. (**Haller, 2002**).

Activation of macrophages from susceptible individuals, by enteric lipopolysaccharide, peptidoglycan, flagellin or CpG, stimulates the production of IL-1ß, TNF, IL-6, IL-8 and other chemokines, IL-12 p40 (and thus IL-12 and IL-23), adhesion molecules, IL-18, reactive oxygen species, nitric oxide and leukotrienes, which can all participate in the inflammatory response.**(Haller, 2002).**

Lipopolysaccharide can stimulate IL-12 p40 production by bone-marrow-derived dendritic cells in IL-10-deficient mice, and colonization of previously germ-free rodents with various commensal bacterial species can induce ICAM1 and IL-6 expression by intestinal epithelial cells.

(Ruiz, 2005).

In addition to their proinflammatory properties, bacterial adjuvants can induce protective anti-inflammatory responses. For example, lip polysaccharide stimulates IL-10 production in dendritic cells from normal mice,and certain CpG preparations can prevent the onset of experimental colitis by inducing the production of type 1IFN (IFN-a /ß) in plasmacytoid dendritic cells, via TLR9 ligation. **(Katakura, 2005).**