Kallikrein – Kinin System and Coagulation System in Inflammatory Bowel Diseases

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1. Introduction

Inflammatory bowel diseases (IBD), including Crohn's disease and ulcerative colitis (UC), are complex disorders characterized by chronic, local and systemic inflammation and spontaneously relapsing course. The causes of these diseases are unknown, however they display genetic and environmental components and appear to be immunologically mediated in part by enteric microbiota (Baumgart & Carding, 2007).

There are convincing evidences that IBD are diseases of immunological hyperresponsiveness within the mucosa. Immunological reactions may be directed against luminal bacteria and their products normally present in the intestine (Sartor, 2006). Alternatively, mucosal inflammation in IBD might represent an immune response against unusual antigens such as environmental factors and/or epithelial HLA halotypes. The initiating events may be nonspecific and induce transient injury. The normal response is suppression of inflammation, but genetically susceptible host amplifies the inflammatory response. The activation of intestinal T helper cells (TH1, TH2 and TH17) play a pivotal role in experimental and human IBD because they modulate of the response to enteric microbiota and autoimmunity which is probably critical to IBD chronicity. Crohn's disease is TH1 and TH17 related disorder with local over-production of interleukin – 2 (IL-2), interpheron γ (INFγ), IL - 12, and IL-23, whereas in UC it is apparent activation of TH2 lymphocyte cytokine profile, mostly IL-4 and IL-10 as well as IL-13 by natural killer T cells. Interaction of activated T cells with effector cells (macrophages and neutrophils) leads to release of cytokines, eicosanoids and activation of complement cascade and coagulation and kallikrein - kinin systems which cause tissue injury. Many cytokines including interleukin 1 (IL-1), tumor necrosis factor (TNF) and IL-8 are increased in both active UC and Crohn's disease. The tissue levels of arachidonic acid metabolities; prostaglandins,leukotrienes and thromboxanes correlate with gross and histological evidence of intestinal inflammation in IBD. The activation of coagulation has been recognized as important component of the inflammatory response in both Crohn's disease and UC, and also is significant in progression and possibly pathogenesis of these entities (Danese et al., 2007). A significance the kallikrein – kinin system in human IBD is still uncertain although in animal IBD models kallikreins and kinins have been documented in part to mediate intestinal and systemic inflammation. There are two types of kallikreins, plasma and tissue; both serine protease

enzymes may cleave kininogens to release kinins, a potent inflammatory mediators (Bhoola et al., 1992).

2. Plasma kallikrein-kininogen system

A single gene codes for plasma kallikrein, which is synthetized in the liver. The plasma kallikrein-kinin system is comprised of factor XII (Hageman factor) factor XI (initiator of intrinsic coagulation pathway), plasma prekallikrein, and high molecular weight kininogen (HK). Activation of the plasma kallikrein – kinin system (known also as the contact system) is initiated by autoactivation of factor XII yielding factor XIIa, which, in turn, activates prekallikrein to kallikrein. Kallikrein can cleave its own heavy chain (56 kDa) at Lys140-Ala141 to form two fragments of 28kDa and 18 kDa. Kallikrein can also react with C1-inhibitor (C1-INH) to form an inactive complex (Mr 190 kDa) (Campbell, 2001; Colman, 2006 c). Plasma kallikrein cleaves HK to release bradykinin, and enhances plasmin formation by activating prourokinase to urokinase (Ichinose et al., 1986). The major regulator of activation of the contact system is the plasma protease inhibitor, C1-INH, which inhibits activated factor XIIa, kallikrein, and factor XIa. In addition, alfa- 2 macroglobulin is an important inhibitor of kallikrein and a 1-antitrypsin for factor XIa. Plasma kallikrein exists as a zymogen, prekalliktein, 75% of which circulates in the blood in a noncovalent complex with HK. HK is multifunctional protein, β-globulin, with a plasma concentration about 80 μg/ml. HK is consisted of 6 domains divided into heavy chain (HK domains 1-3), and light chain (HK domains 5-6), linked by domain 4 which contains the sequence of bradykinin. Low molecular weight kininogen (LK) is present in plasma and various tissues. LK is β-globulin with a plasma concentration of 220 μg/ml, it has identical domain 1 through domain 4 of HK. However LK domain 5 is completely different from HK and domain 6 is lacking (Colman, 2006). Cleavage of HK by plasma kallikrein generates proinflammatory and proangiogenic bradykinin, and forming biologically active kininogen fragment HKa. Products of this pathway induce a variety of inflammatory events. Kallikrein is also implicated in neutrophil activation with release of lysosomal enzymes, such as elastase (Wachtfogelet al., 1983), as well as potentiation of superoxide formation (Schapira et al., 1982). In addition, plasma kallikrein and factor XII fragments may activate the alternative and classical complement pathways, respectively. Recent studies shown that HKa may stimulate in vitro secretion of cytokines; IL-1 β, IL-6, and TNF and chemokines from monocytes through signaling pathways by urokinase –type plasminogen receptor, integrin α-1 β2 (MAC-1) receptor, and complement protein C1q receptor (Khan et al., 2006). IL1- β release is localized to domain – 3 and domain -5 of HK. In addition HK and HKa have an-adhesive properties and HKa and domain 5 of HK inhibit angiogenesis (Colman 2006 b).

3. Tissue kallikreins and kinins

Tissue and plasma kallikreins differ in their molecular weight, isoelectric point, immunological properties, and substrate preference. Tissue kallikreins is a member of a multigene family that shows different patterns of tissue specific gene expression ((Clements et al., 1992). Under physiological conditions, tissue kallikrein is present in the highest concentration in exocrine glands, mostly in salivary glands and pancreas (Wolf et al., 1998). In salivary glands tissue kallikrein occurs in active form, while in pancreas is present as proenzym.Both active and precursor forms are present in excretory product such as urine

and sweat. Kallikrein purified from both rat and human colon was found to be biochemically similar, if not identical, to tissue kallikrein for salivary gland and pancreas (Chen et al., 1995). Although HK is a better substrate for plasma kallikrein to release bradykinin and low molecular weight kininogen (LK) is better substrate for tissue kallikrein liberates kallidyn (Lys – bradykin), both are substrate for both plasma and tissue kallikreins. Kallistatin present in tissues and plasma is a main inhibitor of tissue kallikrein (Chao et al., 1996). Plasma kallikrein releases nonapeptide, bradykinin from HK, while tissue and glandular kallikreins liberates decapeptide, kallidyn (Lys–bradykinin) from LK. Kallidyn is rapidly converted to bradykinin by aminopeptidase. Bradykinin has short half life – 30 second in circulation. Kinins are rapidly destroyed by kininases, which are present in blood and in tissues. Removal of its C-terminal arginine by kininase I (carboxypeptidase N) forms an active metabolite des-Arg ^{9} bradykinin, which has a half life approximately 2 hours. Kininase II, known also as angiotensin converting enzyme (ACE) to remove the COOH – terminal peptides metabolizes kinins to their inactive forms (Bhoola et al., 1992). The final metabolite of bradyninin and des-Arg^9-bradykinin is bradykinin 1-5. T-kinins forming by
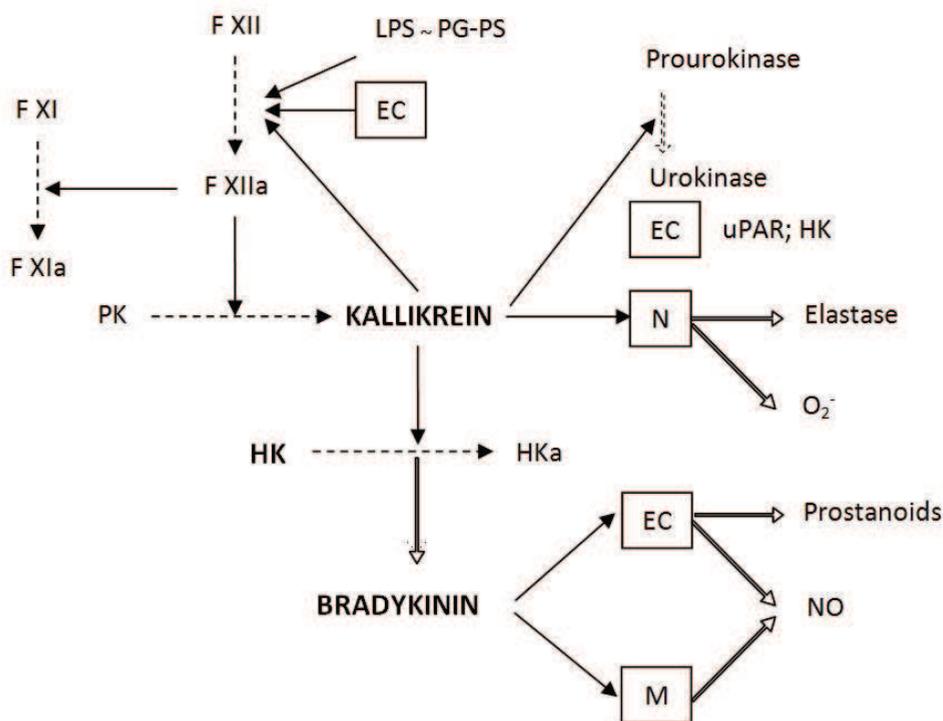

Fig. 1. Potential significance of plasma kallikrein- kinin system in inflammation.
PG-PS: peptidoglycan – polysaccharide; LPS: lipopolysaccharide; EC: endothelial cell; M: monocyte; N: neutrophil, HK: high molecular weight kininogen; TF: tissue factor; NO: nitric oxide, uPAR: urokinase plasminogen activated receptor. Solid arrows designate activation or cofactor amplification, dashed arrows designate conversion, and open arrows indicate release, expression, or synergistic properties

cleavage T – kininogen were exclusively identified in rats (Okamoto et al., 1993). Bradykinin and kallidin and theirs active metabolite, des-Arg^9-bradykinin and Lys - des-Arg^9-bradykinin respectively bind to two transmembran G protein - coupled receptors designated as bradykinin receptor - 2 (B2R) and bradykinin receptor – 1 (B1R). BR2 are constitutive mainly expressed in endothelial cells, stimulated by bradykinin to release nitric oxide and other negative regulators of smooth muscle tone and platelet function. However BR2 might also be upregulated in the acute phase of inflammation (Calixto et al., 2003; Moreau et al., 2005). B1R are inducible following tissue injury or after treatment with bacterial endotoxins or inflammatory cytokines such as interleukin -1 β (IL1- β) or tumor necrosis factor – α (TNF- α). Cytokine-induced B1R expression is mediated by nuclear factor – κ β (NF- κ β) and specific MAP – kinase pathways (mainly p38 and JNK) (Ni et al., 1998).
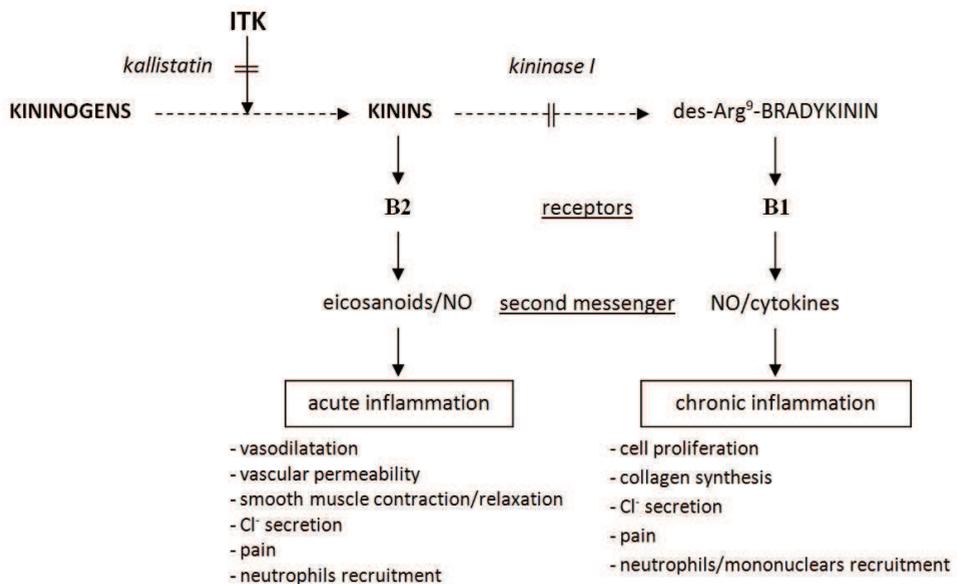

Fig. 2. Potential role of intestinal tissue kallikrein – kinin system in inflammatory bowel disease. Solid arrows designate activation, dashed arrows designate conversion, open arrows indicate induction, and interrupted lines indicate blockade. B2 and B1: kinin receptors; NO: nitric oxide; ITK: intestinal tissue kallikrein

4. Plasma kallikrein – kinin system in IBD

In the past two decades, the role of plasma kallikrein- kinin system in experimental and human sepsis (Pixley et al., 1995), and other acute inflammatory states including Rocky Mountains spotted fever (Rao et al., 1988), human experimental endotoxemia (DeLa Cadena et al., 1998), and acute pancreatitis has been well delineated . In 1990s we have developed experimental model of enterocolitis induced by bacterial cell wall polymer peptidoglycan – polysaccharide from group A streptococci (PG – APS) (Sartor at al., 1996). Female Lewis rats, the highest responders injected intramurally by PG-APS developed acute intestinal

inflammation that peaks 1-2 days after PG – APS injection, gradually decreases over the next 10 days and spontaneously reactivates beginning on day 14, accompanied by peripheral erosive arthritis, granulomatous hepatitis, normochromic anemia and leukocytosis, with histological findings of intestinal fibrosis and granulomas. Acute intestinal inflammation developed in all rat strains investigated, but chronic, transmural, granulomatous reactivation only in genetically susceptible Lewis rats, but not in Buffalo or Fisher rats. This model has unique features resembling Crohn's disease. Inflammation induced by APG – PS, similar to human IBD is mediated by large number of inflammatory cascades and liberation of soluble mediators including cytokines, prostanoids and activation of the kallikrein-kinin system. We have developed a specific plasma kallikrein inhibitor (P8720) to evaluate a direct relationship between the plasma kallikrien- kinin activation and inflammatory changes. Treatment with the specific, oral plasma kallikrein inhibitor, P8720, in the acute and chronic granulomatous phase of enterocolitis in Lewis rat decreased the increase of gut gross and histological score and systemic inflammation, and prevented the decrease of plasma FXI and HK. (Stadnicki et al., 1996; Stadnicki et al., 1998 b). This activation is not specific for PG-APS since it has been demonstrated that it can also be induced in Lewis rats chronic enrerocolitis model- induced by indomethacin (Stadnicki et al., 1998 c). Looking for a functional mechanism involved in selective activation of the kallikrein- kinin system in genetically susceptible Lewis rats, we found that HK cleavage and yielding bradykinin by plasma kallikren was faster in Lewis rat plasma than in Buffalo rat plasma and Fisher rat plasma (Sartor at al., 1996). It has been found that   a single point mutation at nucleotide 1586 translating from Ser511 (Buffalo and Fisher) to Asn511 (Lewis) is associated with N-glycolization indicating that this molecular alteration may be one contributing factor resulting in chronic reactive colitis in Lewis rats (Isordia Salas et al., 2003). Administration of PG – APS causes a similar biological response as triggered by endotoxins (LPS) which is detectable in plasma in most IBD patients during relapse (Gardiner et al 1995) indicating that both bacterial products act through similar the innate immunity activation, cytokines and mediators. Later it has been demonstrated that in patients with UC in active disease phase (but not in inactive UC) there was moderate activation of this system as significant decrease of plasma prekallikrein, HK and functional levels of C1 – inhibitor, and in some patients formation of kallikrein – inhibitor complexes on Western blot (Stadnicki et al., 1997). However in Crohn's disease study it not been found these chances in plasma of patients probably due the high plasma levels of C1 – inhibitor (Devani et al., 2002).

5. Intestinal tissue kallikrein – kinin system in IBD

5.1 Intestinal tissue kallikrein

The presence of kallikrein in gastrointestinal tract has been observed since 1960s (Schachter et al., 1986; Werle, 1960) but little has been done to evaluate its role in IBD. Long time ago only one study (Zeitlin & Smith, 1973) reported the presence of tissue kallikrein in normal human colon and a higher concentration in the inflamed colon of patients with UC. In rat model of PG – APS stimulated chronic inflammation we have shown that the normal location of ITK was the goblet cells and substantial amounts of ITK were present in the macrophages of the granulomas found in the submucosa indicating that ITK is present at the site of inflammation (Stadnicki et al., 1998 a). ITK concentrations were markedly reduced in the inflamed cecum as compared with the normal, but ITK protein concentration was associated with unchanged ITK mRNA levels, which indicated that its reduction was not

due to suppression of its gene expression. Further evidence that inflamed intestinal tissue cells had secreted ITK to a greater extend that normal it has got from in vitro culture study showing marked IIK decrease in supernatant from in vitro cultures of inflamed intestine. In addition a potent tissue kallikrein inhibitor, kallikrein binding protein in the rat (whose human homolog is kallistatin) was decreased in rat plasma during inflammation suggesting release ITK into plasma. In human studies we have demonstrated that ITK was in goblet cells in normal and inflamed human colon which was in agreement with previous findings in rats (Stadnicki et al., 2003). Again ITK levels were significantly decreased in inflamed intestinal tissue from patients with IBD compared to normal controls consistent with its secretion in vivo. The kallistatin, a specific inhibitor, naturally occurring serine protein inhibitor (serpin) of human tissue kallikrein, was localized to epithelial cells. Kallistatin apparently colocalizes within ITK in the macrophages within the granulomas. It has been shown also decreased plasma levels of kallistatin in IBD patients similarly like kallikrein binding protein in rat enterocolitis which indicated that the secretion of ITK results in active form since kallistatin only steichometrically combines with enzymatically active tissue kallikrein (Xiong et al., 1992). Other study indicated that the goblet cells may have a more active role in the regulation of intestinal homeostasis and immunologic processes by interaction this other cells such as macrophages and lymphocytes (Lichtenstein, 2000). The factors which determine ITK secretion and activation are still not defined. It is known that inactive tissue prokallikrein can be activated by trypsin, plasmin, or even plasma kallikrein (Bhoola et al., 1992). Such enzymes could enter the intestinal space through several routes: by transudation of plasma or release from inflammatory cells. Interestingly a proinflammatory effect of ITK in the intestine are due to macrophage production and secretion. It has been demonstrated tissue kallikrein on human blood neutrophils, but did not detect the enzyme in monocytes (Figueroa et al., 1989). It is possible that tissue kallikrein is only expressed in stimulated monocytes or macrophages, as is the case for tissue factor (Gregory & Edgington, 1985). However, luminal ITK may enter the inflamed mucosa due to enhanced permeability, where it could hydrolyze growth factors and peptides which could act on the epithelial mucosa cells. In fact it has been demonstrated that ITK immunoreactivity was significantly weaker in gobled cells in both Crohn's disease and ulcerative colitis patients, but with strong reactivity in intestinal interstitium of IBD patients (Devani et al., 2005). ITK can cleave low kininogen which is present in intestine as well as both LK and HK, which are present in plasma and likely to be present in the protein – rich exudates of the inflamed intestine. Apart from its kininogenase activity, tissue kallikrein has been implicated in the processing of grow factors and peptide hormones. Tissue kallikrein hydrolyze vasoactive intestinal peptide and procollagenase in vitro (Techesche et al., 1983). If these reactions take place in IBD, ITK may influence intestinal motility, secretion and connective tissue metabolism. Moreover in experimental and human IBD the number of mast cells and mast cells tryptase expression are increased in the colonic mucosa and submucosa (He, 2004). In addition, activated basophils and mast cells contain and can release kallikrein as an additional local intestinal source of tissue kallikrein (Min & Paul, 2008).

5.2 Kinins and kinin receptors in IBD

Almost fifty years ago it has been demonstrated that bradykinin was able to evoke cardinal signs of inflammation (Lewis, 1964). In addition in chronic inflammation B1R seems to be important in neutrophil accumulation in inflamed tissue (McLean et al., 2000). Both B1R and B2R are involved in onset and maintenance of nociceptive alterations and inflammatory

pain perceptions (Drey, 1997; Rupniak et al., 1997). Research on involvement of B2Rs in inflammatory states has progressed more quickly than that on B1Rs, and it was favored by the systematic development of selective peptidic B2R antagonists by the pharmaceutical companies, at this time. Thus we described B2Rs distribution in PG – APS induced model of granulomatous enterocolitis in intestinal layer showing B2R in epithelial cells, smooth muscle cells, and in serosa (Stadnicki et al., 1998 c). In this model a specific bradykinin BR2 antagonist (HOE – 140) attenuated arthritis but exhibited only minimal preventive effect on enterocolitis suggesting that kinin stimulation via B2R was a more important in arthritis than of enterocolitis (Stadnicki et al., 1999). In dextran sulfate (DDS) - induced colitis model in mice a selective B2R antagonist suppressed shortening of the large intestine (Arai et al., 1999), which was in agreement with future results indicated that intestinal contraction was regulated by B2R (Hara et al., 2007), however demonstrated only limited effect in intestinal inflammatory lesions. Later in human studies we demonstrated the increase in the ratio of B1R to B2R gene expression in relation to the degree of intestinal inflammation, and visualized both B1R and B2R in normal as well as inflammatory human colon and ileum (Stadnicki et al., 2005). B2R protein was normally present in the apices of enterocytes in the basal area and intracellularly in inflammatory tissue. In contrast, B1R protein was found in the basal area of enterocytes in normal intestine, but in the apical portion of enterocytes in inflamed tissue. B1R protein was significantly increased in both active UC and Crohn's disease intestines compared to controls. In addition B1R was observed in the nerve of the colonic submucosa. Importantly B1R but not B2 was present in macrophages inside granulomas of Crohn's intestine. The total level of B1R was significantly higher in enterocytes of patients with active phase of UC as well as in Crohn's disease as compared with controls. Recent studies have demonstrated that the B2R receptor may be recycled several times in the same enterocytes after internalization (Bachvarov et al., 2001; Souza et al., 2007). This process was supported by the appearance of B2R intracellularly in some enterocytes in UC intestine. In contrast B1R normally do not internalize following agonist stimulation, but they seem to translocate and aggregate after agonist binding, probably to facilitate the amplification of B1 receptor mediated responses (Sabourin et al., 2002). Taken together the results strongly indicated that the B1R receptor is a major structural background for kinins function in human IBD. Kinins are involved in intestinal glucose and electrolyte transport and local blood flow under normal conditions. However in intestine, kinins may be more important as pathophysiological mediators. It has been shown that bradykinin produces 2 – 4 – fold greater concentration of prostanoids in animals with experimental colitis than in normal controls, which may contribute to the increased intestinal secretion of chloride (Zipser et al. 1985). Bradykinin – induced chloride secretion by the guinea pig ileum occurs by direct binding of the ligand to its receptor (Maning et al., 1982). It has been shown that both inducible B1R and constitutive B2R mediate the ion transport in intestinal epithelium (Cuthbert, 2001). The secretion of chloride into the lumen is accompanied with natrium secretion and in turn water, thus leading to secretory diarrhea, and this effect of kinins is much prostaglandin-independent. In relation to IBD kinins may act on endothelial cells, smooth muscle cells, epithelial cells, and fibroblasts, which stimulate cell response through G proteins - coupled kinin receptors. By opening the tight junctions between endothelial cells, kinins can increase capillary permeability (Gaginella & Kachur, 1989). Kinins may stimulate though B2R inflammatory cell adhesion molecules, and white blood cells migration. Subsequently B1R stimulation promote more cell adhesion molecules, and cells influx mainly neutrophils into extravascular comparment(McLean et al., 2003;

Ulbrich et al., 2000). Kinins may act as mitogens to increase DNA synthesis, thereby promoting cell proliferation. The ability of kinins to stimulate fibroblast proliferation may contribute to fibrosis in chronic intestinal inflammation (Marceau et al., 1986). Kinins may stimulate macrophage release of IL-1 and TNF – α (Tiffany & Burch, 1989). This effect is probably mediated by stimulation of the RB1, since a specific RB1 antagonist block kinin-induced cytokine release. In human study it has been demonstrated a positive staining for TK, kallistatin and the B1R (but not the B2R) in macrophages forming granuloma and for B1R in plasmocytes in the border of granulomas which emphasizes the close relationship between the immune responses important in IBD and the inflammatory mediators including the ITK – kinins. Kinins may also evoke pain by stimulating sensory nerves to mechanical stimuli and other chemical mediators and, in turn, causes hyperalgesia (Drey, 1997). The role of B1R and its agonists in inflammatory pain has been shown in animals (Rupniak et al., 1997). In addition, bradykinin accelerates mucin discharge from goblet cells (Stanley & Philips, 1994). Although it is not know if ITK is co – secreted with mucin after bradykinin action, it raises the possibility of positive feedback loop between local ITK release and bradykinin generation. In addition, it has been demonstrated a B1R polymorphism in human IBD, but its clinical significance remains unknown (Bachvarov at al., 1998). The recent experimental study investigated the role of BR1s in TNBS - induced mouse model of colitis showing that that selective, orally active, non - peptide B1R antagonist SSR240612 markedly reduced TNBS – induced colitis e.g. intestinal tissue damage and neutrophil influx (Hara et al., 2008). Importantly this study clarified evidence that TNF – α may upregulate B1R expression in TNBS colitis model suggesting that anti- TNF- α monoclonal antibodies may in part modulate IBD by regulation of BR1 expression. It should be noted that kinins are implicated in the regulation of blood pressure, sodium homeostasis and the cardioprotective effect of preconditioning (Chao et al., 2004). Angiotensin- converting enzyme (kininase II) inhibition increase blood levels of bradykinin and kallidin peptides (Colman et al., 2006 c). Thus, the potentially salutary role of kinins in the circulation not encourage systemic administration of B1R antagonist. In fact commonly used ACE inhibitors are cardioprotective in part by elevating bradykinin, and thus increasing nitric oxide as well as decreasing angiotensin II formation (Colman et al., 2006c). Kinins have been demonstrated to stimulate synthesis of eicosanoids, nitric oxide and cytokines by white blood cells, endothelial cells and epithelial cells, and promote adhesion molecule – neutrophil cascade known to be important in IBD. A selective B1R receptor antagonist may have potential in therapeutic trial. It has been postulated that topical drug delivery to intestine as for 5 – ASA compounds to avoid side effect may be appropriate for the management of IBD (Marceau & Regoli, 2008). In fact the levels of kinin peptides in tissue were higher than in blood suggesting the primary tissue localization of the kallikrein – kinin system (Campbell, 2001). Nevertheless it seems that the contact system plays an important role in many inflammatory cascades by activation of the complement system, enhances liberation of prostanoids and cytokines, and specifically interacts with coagulation, fibrinolytic components and platelets.

6. Hemostatic alterations in IBD

The current model of coagulation in vivo emphasizes tissue factor as initiator of coagulation activation, underlines main role of thrombin in amplification of coagulation, and the interaction of coagulation factors with blood cells and endothelial cells (Hoffman & Monroe,

2007). Activated cells, especially platelets are critical in amplification and propagation phases providing a negatively – charged phosfolipid surface on which clotting reactions may take place. In IBD the coagulation system may be activated following cellular injury mainly through the extrinsic pathway. Tissue factor, a potent trigger of coagulation, functions as a monocyte and endothelia cell receptor which binds factor VII and facilitates activation of both factor IX and factor X. Activated factor X (FXa), Ca ++ , activated factor V (FVa), and platelet phospholipid form the prothrombinase complex that cleaves prothrombin, producing thrombin and liberating a prothrombin fragment, F1 + 2. Thrombin hydrolyzes fibrinogen forming fibrin, which is cross-linked by activated factor XIII. Cross-linked fibrin is then degraded by plasmin with the liberation of D-dimer and other degradation products. Factor XII converts the zymogen, factor XI, to an active enzyme, factor XIa, which, in turn, converts factor IX to factor IXa, thereby activating the intrinsic pathway of coagulation. (Clolman, 2006 a).
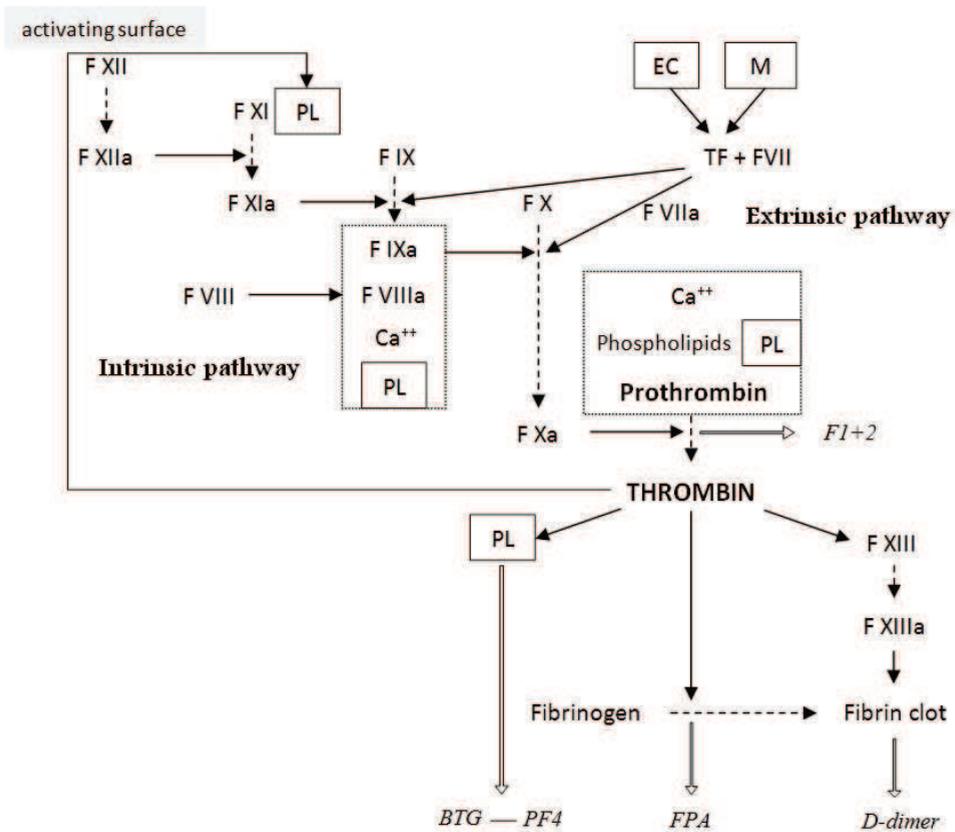

Fig. 3. Diagram of main pathways of coagulation. EC is endothelial cell, M is monocyte, PL is platelet, F1+2 is prothrombin fragment, FPA is fibrinopeptide A, βTG is β-thromboglobulin, TF is tissue factor. Solid arrows designate activation or cleavage, dashed arrows conversion, and open arrows indicate release, expression, or synergistic properties

6.1 Systemic coagulation changes

Early reports have presented hemostatic changes in IBD patients; elevation of plasma factor V, factor VIII, fibrinogen and thrombocytosis observed in the active IBD phase (Lam et al., 1975; Morowitz et al., 1968). Later reports have shown an acquired plasma antithrombin deficiency in active IBD patients, a feature which implies a real risk of thrombosis (Knot et al., 1985). Subsequent studies have shown the presence of increased markers of activate coagulation in both active and quiescent IBD (van Bodegraven et al., 2002; Hudson et al., 1992; Souto et al., 1995). In contrast other investigators did not found a significant increase of coagulation intermediates in IBD patients with an inactive stage (Edwards et al., 1987; Novacek et al., 1997; Stadnicki et al., 1997). It is assumed that the reaction with thrombin during the clotting activation causes consumption of plasma FXIIIa and, therefore, a fall in FXIII may be sign of clotting activation (Ichinose, 2001). In fact it has been found a decrease of FXIII subunit A, but not FXIII subunit B in both active UC (Stadnicki et al., 1991) and Crohn's disease (Hudson at al., 1993). Later other investigators shown reduced level of FXIII active subunit A (but not carries subunit B) in active IBD patients, but generally not in patients with quiescent disease suggesting its consumption as result of active coagulation and increased turnover during active inflammation (van Bodegraven et al., 1995; Hayat et al., 2002). In addition, elevated D-dimer was found almost exclusively in active IBD patients which provides evidence of fibrin formation and reactive fibrinolysis (Chiarantini et. al., 1996, Hudson et al.,1992, Stadnicki et al., 1997). Natural coagulation inhibitor, protein C plasma level has been shown to be unchanged or decreased in IBD (Larsen et al., 2002)), while decreased its cofactor, protein S plasma level was demonstrated in most studies (Aadland et al., 1994; Saibeni et al., 2001). In addition, an inhibitor of tissue factor, tissue factor protease – inhibitor (TFPI) plasma levels have been reported to be lower in IBD (Souto et al., 1995). Differences between ulcerative colitis and Crohn's diseases including disease location, histology, clinical course and complications although it is likely that both entities share similar immunoregulatory abnormalities and common pathways. The lower levels of coagulation intermediates or fragments in UC patients, as compared with Crohn's disease, may be simply due to more superficial distribution of intestinal inflammation always found in UC. In addition patients with Cronh's disease have higher tissue IL-1 β and plasma IL-6 levels (Mazlam & Hodgson, 1994). A role of intrinsic coagulation activation pathway, associated with the contact system, in IBD is unclear. FXI (an initiator of intrinsic pathway) is activated by thrombin (Olivier et al., 1999), or by the contact pathway initiated by autoactivation of FXII. Surprisingly in two large studies plasma factor XI functional level remained unchanged in active UC (Stadnicki et al., 1997) and Crohn's disease (Devani et al., 2002). In contrast other authors observed increased active plasma level of FXII and FXI among other signs of thrombin generation in active UC patients suggesting both extrinsic and intrinsic coagulation pathways activation in active UC stage (Kume et al., 2007; Kyriakou et al., 2002). However whether the plasma contact system is activated in intestinal circulation and if so, what is the role of HKa to maintain inflammation remains to be investigated.

6.2 Systemic fibrinolytic capacity

Disturbed fibrinolysis, which has been reported in general circulation and in colonic mucosa, has also been postulated to play a role in procoagulant potential in systemic circulation, however also in intestinal bleeding of IBD. It have been demonstrated the decrease of plasma t-PA with concomitant increase of its inhibitor, plasma PAI-1 indicated

hypofibrinolytic capacity in general circulation of IBD patients (de Jong et al., 1989). T- PA is mainly released by vascular endothelium, thus its plasma decrease in IBD suggests endotheliopathy. This phenomenon is supported by data (Gris et al., 1991) indicating impaired fibrinolytic response to the venous occlusion test in patients with colitis. Systemic endothelial cell dysfunction has been reported in both UC and Crohn's disease. A serum von Willebrand factor concentration and thrombomodulin level, the markers of vascular injury have been shown to be increased in serum of IBD patients in relation with disease activity (Boehme MW et al., 1997; Wan der Wouwer et al., 2004). Recently discovered thrombin activatable fibrinolysis inhibitor (TAFI) provides link between coagulation and fibrinolysis (Bouma, 2004), and primarily its levels have been linked with thrombophilia in IBD. However TAFI plasma level in IBD is equivocal thus its significance is unclear (Koutroubakis et al., 2008; Saibeni et al., 2004). In addition, Italian group (Saibeni et al., 2006) has been demonstrated a prevalence of anti – t- PA antibodies in IBD patients which may reduce systemic fibrinolysis.

6.3 Intestinal coagulation and fibrinolytic disturbances

Nevertheless, those alterations occur in systemic circulation and, while reflecting the systemic inflammatory response, does not portray the actual events within the inflamed intestine. It has been indicated that regional vasculopathy leading to activation of coagulation cascade and local fibrin formation are pathogenic factors in Crohn's disease (Wakefield et al., 1989, 1991). Platelets thrombi linked with fibrin, and expression of tissue factor were also observed in Crohn's intestinal lesions (More et al., 1993; Wakefield et al., 1989). Similarly mucosal capillary thrombi have been identified in UC, but similar changes were also found in self – limited colitis, thus their pathogenic significance in UC is less appreciated (Dhillon et al., 1992). However a higher platelets aggregation has been found in mesenteric circulation in IBD, hence circulating platelets aggregates may contribute to ischemic damage, and platelets aggregates have been identified histologically in rectal biopsies from patients with UC (Collins et al., 1997). Latter data demonstrated that CD40L positive platelets adhere to mucosal endothelium in IBD, hence trigger proinflammatory reactions (Danese et al., 2003 a). Importantly, platelets may mediate leukocyte recruitment to the inflamed colon via CD40 – CD40L (Danese et al., 2003 a), and independently platelets taken from IBD patients release RANTES, a chemokine recruiting monocyte and T – memory cells (Fagerstam et al., 2000). In addition interaction of plaletets expressed CD40 with CD40 expressed vascular component may increase influx of white blood cells to extravascular compartment. Activated protein C (APC) exert anti- inflammatory effect and directly maintain vascular barrier integrity. However protein C anticoagulant pathway has been found to be impaired in IBD, hence it may enhance thrombin generation. A reduced expression of endothelial protein C receptor (EPCR) in microvasculature endothelium has been shown in IBD patients (Faioni et al., 2004). It is still uncertain if the intestinal vascular alterations in IBD is the primum movens of the disease (Wakefield et al., 1989), or the consequence of inflammation (Binion et al., 1998). In the inflamed mucosa of IBD patients it has been presented a decrease of t-PA and increase of u-PA (de Bruin et al., 1988; de Jong et al., 1989). U-PA, in contrast to t-PA, is less fibrin dependent; thus plasmin generated due to u-PA may act as proinflammatory protease as well as enhance intestinal bleeding which is typical feature especially in UC. Interestingly u-PA is secreted as prourokinase which can be activated to urokinase by plasmin itself or in the cells surface by plasma kallikrein in the presence of high kininogen (Ichinose et al., 1986). Urokinase binds to its receptor, uPAR, on

the endothelial – cell surface (Colman, 2006). Prekallikrein binds to HK, which associates with the same receptor hence the conversion of plasminogen to plasmin is efficient. Thus prekallikrein may be anti- thrombotic by virtue of its role in the fibrinolytic system. Although a moderate amount of FXIII has proved sufficient to secure hemostasis, its low level in the presence of other coagulation abnormalities may contribute to intestinal bleeding, but its relationship to intestinal bleeding during IBD is controversial Other investigations have shown enhanced local fibrinolytic activity in IBD patients which led to use tranaxemic acid, an antifibrinolytic agent, in the context of an increased intestinal bleeding tendency (Kondo et al., 1981)). This drug acts mainly preventing the interaction of tissue t - PA with fibrin which is required for its catalytic activity. However local fibrinolysis in IBD is related to u-PA, which is fibrin independent.

7. Serine proteases act via PARs

Four protease – activated receptors (PARs) 1-4 have been identified as mediators of cellular responses. It has been shown that coagulation activation may mediate inflammatory response, which support the concept of mutual activation of inflammatory and coagulation cascades in IBD. Thrombin is a key player of PARs activation as this enzyme can activate PAR1, 3 and 4, and in turn activates platelet and endothelial cells, whereas tissue factor can act due to PAR1 or 2 (Steinhoff et al., 2005). Recent study demonstrated that active factor X (FXa) may induce PAR -2 activation, and in turn may mediate inflammation and fibrosis, a features of IBD (Borensztajn et al., 2009). Interestingly, investigation revealed that PAR1 and PAR2 are present on intestinal epithelium, and PAR1 has been shown to mediate intestinal secretion (Oikonomopoulou et al., 2006). In addition tissue kallikrein may activate directly B2R independently of bradykinin release. Thus in addition to thrombin and trypsin which can affect tissues by activating a novel family of protease activated receptors (PARs 1-4), tissue kallikreins represent PAR regulator, and consequently B2R may belong to a new group of PARs. In animal studies a decreased plasma protein C activation was shown in DDS – induced colitis in mice (Yoshida et al., 2008), and APC administered to mouse colitis model also provided protection against thrombosis and accompanied colonic inflammation. In addition via thrombin generation platelets may by activated by PARs (Biloduane & Hamm, 2007). PARs activated coagulation cascade might participate in the progression of IBD suggesting that PARs blockade might provide a novel therapeutic target for the management of IBD.

8. Platelet as inflammatory cell in IBD

IBD patients have an increase of platelet numbers which correlate with both UC and Crohn's activity (Morowitz et al., 1968). In early 1990s it has been documented abnormal platelet aggregation in vitro, and activation in vivo expressed by elevation of tromboxane B2, tromboxane A2, and specific chemokines as platelet factor – 4 and β – tromboglobulin as well as higher expression of P– selectin and GP53 on platelets surface in both active and inactive IBD phases (Collins et al., 1994, Webberley et al., 1993). Thus platelet activation is a feature of IBD. During inflammation an increased endothelial exposure of adhesion glycoproteines may enhance binding of platelets and leukocyte. Later it has been (Danese et al., 2003 b) observed increased platelet expression of activation - dependent of CD40 – ligand (CD40L) as well as increased plasma level of soluble CD40 in both UC and Cronh's

disease compared to normal controls. The increased of platelet-leukocyte aggregated (PLA) in systemic circulation account for platelet activation and platelet- leukocyte interaction in IBD patients (Irving et al., 2004). Taken together it seems that in IBD platelets show not only prothrombotic but also proinflammatory properties. Suppression of the adverse effect of thromboxane A2 can be achieved either by inhibiting its synthesis and/or antagonizing the receptor through which it acts. Selective antithromboxane agents have been shown to ameliorate experimental colitis (Vilaseca et al., 1990) however ridogrel not shown enough therapeutic effect (Tytgat et al., 2002). Unfortunately, ridogrel is a weaker thromboxane receptor antagonist than synthetase inhibitor, so that activation of the former by endoperoxides such as PGH-2 (accumulating after inhibition of thromboxane synthetase) activate thromboxane recepotors. New generation of antiplatelet compounds which selectively inhibit platelet activation rather than platelet aggregation merit future studies in IBD.

9. Thromboembolic complications in IBD

9.1 Risk factors for thromboembolism
Coagulation activation in IBD is one of significant feature to enhance prothrombotic potential, increased risk of thromboembolism is related to extension of intestinal inflammation, but coagulation system abnormalities found in IBD may also be caused by other acquired factors. Nutritional deficiencies of vitamins B6 and B12, and folic acid in Cronh's disease patients may be caused by ileitis, while sulfasalazine or methotrexate – induced folate deficiency may have similar effect in both Crohn' s disease and UC. Those deficiencies may lead to hyperhomocysteinemia which has been found in IBD patients (Bjerregaard et al., 2002). Increased level of lipoprotein (a) an independent risk factor for TE has been shown to account for tendency to thromboembolism in some Crohn'n disease patients (van Bodegraven & Meuwissen, 2001). Other ways that may predispose to thromboembolism in IBD include immobility, the need to undergo surgery, fluid depletion diarrhea – induced, and use central venous catheter for parenteral nutrition. At present no interaction between IBD and inherited factors of thrombophilia e.g. factor V gene (FV Leiden) mutation, prothrombin G20210A mutation, and methylenetetrahydrofolate reductase (MTHRF) gene mutation (related to hyperhomocysteinemia) were found (Guedon et al., 2001; Papa et al., 2001) .

9.2 Thrombotic manifestations
The thromboembolic complications are common extraintestinal manifestations in both Crohn's disease and UC, appear to have a 3-4 fold increased risk of developing compared to control patients), and also exist in quiescent disease (Bernstein et al., 2001). Importantly thromboembolic complications increased risk was found to be specific for IBD because neither in patient with rheumatoid arthritis, nor in patients with celiac disease had an increased thromboembolic risk compared with their controls (Miehsler et al., 2004). Deep venous thrombosis and pulmonary embolism are most common thrombotic complications in IBD, but there were also described in unusual sites *e.g.* portal vein, mesenteric vein, retinal vein, and cerebral sinus veins. In addition arterial thromboembolic events and ischemic heart disease risk is increased in IBD patients, (Bernstein et al., 2008). Systemic thrombotic events are life – threatening since mortality related to thromboembolism in IBD is described in high ranges between 8% - 25 % during acute thromboembolic episodes

(Quera & Shanahan, 2004). As unconventional IBD treatment heparin have paid attention because its anti- inflammatory effect, hence heparin interferes with anti-inflammatory cascade by influencing cell migration into tissue and modulates a release of proinflammatory cytokine. Early study indicated a beneficial effect of heparin in refractory ulcerative colitis (Gaffyney et al., 1995). In general better therapeutic efficacy of unfractionated heparin (UH) than low molecular weigh heparin (LMWH) in UC is probably related to more beneficial immunomodulatory effect of UH (Panes et al., 2000). In fact an efficacy of heparin treatment in UC is still controversial and not established. However a recent small open study demonstrated a reduction of inflammation using oral, slow- release LMWH (parnaparin) capsules in left- sided UC patients (Pastorelli et al., 2008). It appears that IBD is a thrombophilic syndrome, a risk of thromboembolic events in IBD is multifactoral including active intestinal inflammation and malnutrition, (Quera & Shanahan, 2004). Prophylactic anticoagulation against thromboembolism is currently not fully defined, and intestinal bleeding worsening may occur. In high – risk patients e.g. active IBD patients confined to bad, subjects with familial thrombosis, and patients with myocardial infraction, or stroke before age 50 in first degree relatives should be considered for using moderate dose of heparin (Zitomersky et al., 2011).

10. Coagulation, intestinal barrier and healing

The epithelium of the intestine creates a barrier to potentially immunogenic and noxious factors, including microorganisms and dietary components within the intestinal lumen. Healing of the intestinal surface is regulated by a complex mechanism that involves growth factors, cytokines, as well as intracellular matrix proteins and blood clotting factors to preserve homeostasis and integrity of the intestinal mucosa (Dignass & Podolsky, 2004). Once the intestinal epithelial barrier is damaged, luminal highly immunogenic bacterial antigens can enter the normally sterile submucosal layers and thus may play a role in the pathogenesis of IBD. The antibiotics, mainly tobramycin and metronidazole, have been found to be effective as adjunctive therapy not only in Crohn's disease but also in UC patients (Rahimi et al. 2007). Among the regulatory peptides that are expressed within the intestinal mucosa, transforming growth factor-β (TGF-β) and epidermal growth factor family peptides (EGFs) play especially important role. EGFs, potent stimulators of intestinal epithelial cells proliferation, and may increase the concentration of bioactive TGF-β, whereas TGF-β is capable of regulating growth, differentiation, and function of immune cells (Stadnicki et al., 2009). Interestingly, EGF enemas have been proved to be beneficial in UC patients (Dieckgraefe et al. 2007). Importantly, TGF-β1 that counteracts TNF-α and acts as negative regulator of mucosal inflammation is essential for wound healing (Blobe et al., 2000). The role of TNF-α, that occupies central position to generate the inflammatory cascade, has been well defined in Crohn's disease and recently in UC (Blonski et al., 2011). Infliximab administered with steroids, has been found to be effective in inducing responses and maintaining remissions in patients with moderate and severe stage of IBD. Interestingly treatment with infliximab, a chimeric antibody against TNF-α, has been reported not only induced clinical remission but also decreased thrombin generation in IBD patients (Hommes et al. 1997). Intestinal epithelial wound healing and tissue repair may also act trough growth factors independent pathway involved in cells interactions and blood coagulation factors. Besides fibrin, FXIIIa also cross-links actin, collagen, and fibronectin., thus it is as much connective tissue factor as a clotting factor. FXIII and other transglutaminases may be

important in the maintenance of normal intestinal integrity and intestinal repair mechanism (D'Argenio et al. 1995). Our and others data suggested that interaction of factor XIII subunit A a with its natural plasmatic substrates e. g. fibronectin and α–2 plasmin inhibitor, plays a role in healing of UC lesions (Stadnicki et al., 1992). Consequently, factor XIIIa infusion has been shown to promote intestinal wound healing in both UC and Crohn's disease patients (Lorenz et al., 1991; Oshitani et al., 1996). In contrast vascular endothelial growth factor (VEGF) increases vascular permeability to activate metaloproteinases which participate in degradation of extracellular matrix, hence may have detrimental effect on intestinal barrier (Ferrara, 2004).

11. Kinins and angiogenesis in IBD

Recently it has been provided the direct evidences that angiogenesis has a role in the pathogenesis of both UC and Crohn's disease showing a higher density of microvessels within intestinal mucosa and sub-mucosa and increased expression of αvβ3 - integrin in endothelium with simultaneous increase of intestinal VEGF expression (Danese et al., 2006) . Most recent data demonstrated the increase of genes expression as well as protein levels for VEGF and its Flt-1 receptor in active inflammatory colonic tissue and increased VEGF levels in serum and plasma in active UC patients (Frysz – Naglak et al., 2011). TGF-β1 may directly stimulate angiogenesis in vivo; the stimulation can be blocked by TGF-β1 antibodies (Pepper, 1997). The influence of kinins in angiogenesis has recently been appreciated. Kinin promotes angiogenesis by upregulation of basic fibroblast growth factor through bradykinin - B1 receptor and by stimulation of VEGF formation by bradykinin both B1 and B2 receptors (Colman, 2006 b), and kinins may act synergistically with TGF-β1. Monoclonal antibody C11C1 which prevents binding HK to endothelial cells also limits its conversion to bradykinin thus downregulating angiogenesis (Colman et al. 2000). Thus, it is possible that kinins as proangiogenic may promote angiogenesis in IBD although the interaction between kinins and growth factors is highly complex, and requires future investigation. In contrast HKa or its domain 5 inhibit endothelial cells migration and proliferation needed for angiogenesis (Colman et al, 2003).

12. Conclusions

IBD appear to be immunologically mediated by activation of immune system cells and plasma proteolytic cascades. Products of activated cells such as cytokines, eicosanoids, lysosomal enzymes as well as kallikrein – kinin and coagulation system are reported to be increased in intestinal lesions and in the systemic circulation of IBD. The activation of coagulation has been recognized as important component of the inflammatory response in both Crohn's disease and UC, and also is significant in progression and possibly pathogenesis of these entities. A significance of coagulation in IBD was underestimated, now it appears that IBD is a thrombophilic syndrome in both active and quiescent phases. A risk of thromboembolic events in IBD is multifactoral including coagulation activation. Prophylactic anticoagulation against thromboembolic complications is currently not fully defined, however high – risk patients should be considered for using moderate dose of heparin. Kinins exert their biological effect by activating constitutive bradykinin receptor -2 (BR2), which are rapidly desensitized, and inducible by inflammatory cytokines bradykinin receptor -1 (BR1), resistant to densensitization. Intestinal tissue kallikrein (ITK) may

hydrolyze growth factors and peptides whereas kinins increase capillary permeability, evoke pain, stimulate synthesis of nitric oxide and cytokines, and promote adhesion molecule – neutrophil cascade. Thus activation of intestinal kallikrein – kinin system may have relevance to idiopathic inflammatory bowel disease (IBD). These results promise to yield new insight in the pathogenesis of IBD. Currently it seems that upregulation of bradykinin B1 recepror (B1R) in human and animal intestinal inflammation provides a structural basis for the kinins function, and selective B1R antagonist may have potential in therapeutic trial of IBD patients.

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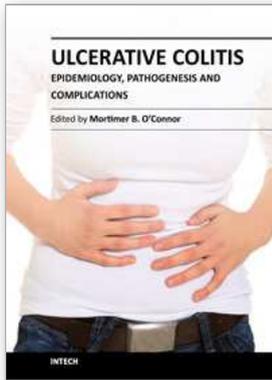
Ulcerative Colitis - Epidemiology, Pathogenesis and Complications
Edited by Dr Mortimer O'Connor

This book is intended to act as an up-to-date reference point and knowledge developer for all readers interested in the area of gastroenterology and in particular, Ulcerative Colitis. All authors of the chapters are experts in their fields of publication, and deserve individual credit and praise for their contributions to the world of Ulcerative Colitis. We hope that you will find this publication informative, stimulating, and a reference point for the area of Ulcerative colitis as we move forward in our understanding of the field of medicine.

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