



MMPs, ADAMs and Their Natural Inhibitors in Inflammatory Bowel Disease: Involvement of Oxidative Stress

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Abstract

Matrix metalloproteinases (MMPs) are enzymes involved in the degradation of extracellular matrix proteins and in several functions such as wound repair. The regulation of MMPs occurs at various levels including expression and inhibition by tissue specific inhibitors of MMPs (TIMPs). An alteration of intracellular redox state can modulate the activation and/or expression of MMPs. The increased expression and activity of MMPs are related to inflammatory state and pathogenesis of inflammatory bowel disease (IBD). In particular, an imbalance between MMPs and TIMPs is present at intestinal level in IBD, and this can be responsible of alterations of different processes such as repair of damaged mucosa, function and migration of immune cells and mucosal ulceration. A disintegrin and metalloproteinase 17 (ADAM17), belonging to ADAM family, plays an important role in the intestinal inflammation and increases in human colonic mucosa of IBD patients. In this review we report the effects of MMP, ADAM17 and TIMP altered levels on damage amplification caused by inflammation and oxidative stress in IBD. Moreover, the review evidences the role of the intracellular redox state and antioxidants on regulation of expression and activity of some MMPs in condition of oxidative stress in IBD.

Keywords

MMPs, ADAM17, IBD, Oxidative stress, Antioxidants

Introduction

The inflammatory bowel disease (IBD) includes two major forms of chronic intestinal disorders, Crohn's disease (CD) and ulcerative colitis (UC). The exact aetiology of IBD is not well known. There are several factors involved in development of this group of diseases, which include changes in the immune system, bacterial infection and genetic variations [1]. CD is characterized by discontinuous transmural inflammation that, although can occur in any region of gastrointestinal tract, strikes mostly the ileum and the colon. On the contrary, in UC the inflammatory state, typically limited to the mucosa, involves the rectum and may affect a part or the entire colon in a continuous pattern [2,3]. Table 1 shows the highest incidence and prevalence of IBD in principal areas of the world. It is evident

that these parameters are more prevalent in highly industrialized nations than in less developed countries [4,5]. The lifestyle and dietary factors affect the development of IBD. In fact, the cigarette smoke enhances the risk for CD and influences negatively the life quality of patients [6,7]. The excessive consumption of milk, animal proteins, carbohydrates and polyunsaturated fatty acids (PUFAs) can enhance the risk for IBD. In particular, starch, generally present in human diet, can promote development of microbic species involved in the induction of autoimmunological reaction in IBD [8]. It has been observed that the imbalance in the consumption of Omega 6 PUFAs and Omega 3 PUFAs is very important in the development of IBD. In fact, Omega 3 PUFAs, differently from Omega 6 PUFAs, do not alter parameters, such as intestinal microbic flora and intestinal permeability, which contribute to IBD pathogenesis [9]. In the development of IBD, an important role is attributed to oxidative stress, due to altered balance between reactive oxygen species (ROS) and antioxidant activity [10]. In particular, the increased oxidative state in intestinal mucosa of CD patients is involved in the chronicization of this pathology [11,12]. Recently, it has been demonstrated that the compounds with antioxidant capacity, associated or not to the traditional therapy for IBD, such as sulfasalazine, azatriopine, corticosteroids, 5-aminosalicylic acid and infliximab, can be beneficial for IBD treatment [13,14]. The

Table 1: Highest annual percent of incidence and prevalence of ulcerative colitis (UC) and Crohn's disease (CD) in the principal areas of the world.

Continent	Incidence	Prevalence
Europe ¹	0.243 (UC)	5.05 (UC)
	0.127 (CD)	3.22 (CD)
North America ¹	0.192 (UC)	2.486 (UC)
	0.202 (CD)	3.18 (CD)
Asia and Middle East ¹	0.063 (UC)	1.683 (UC)
	0.05 (CD)	0.679 (CD)
Australia	0.174 (UC) ¹	0.16 (UC) ²
	0.293 (CD) ¹	0.14 (CD) ²

¹Ref. 5; ²Data from the final IBD report of Australian crohn's and colitis association (ACCA) 2007.

compounds used in the antioxidant therapy are polyphenols, such as curcumin, resveratrol, quercetin, catechin, present in plants and in food originating from plants [15]. Also food rich in micronutrients with antioxidant properties, such as vitamin E and C, can ameliorate ROS-induced symptoms [16]. Proteinases, such as matrix metalloproteinases (MMPs), and A disintegrin and metalloproteinase 17 (ADAM17), belonging to ADAM metalloproteinases, affect the intestinal tissue damages and the inflammatory processes which characterize IBD [17-19]. In fact, the oxidative stress can play a crucial role in the modulation of MMPs activity and expression [20]. MMPs are involved principally in the turnover of extracellular matrix, while ADAM17, a membrane-bound enzyme, cleaves cell surface proteins such as cytokines and cytokine receptors [21]. Deregulated activity and expression of MMPs affect cell adhesion, immune cell migration, cytokine production and impairs wound healing [22]. The activities of MMPs are closely regulated at various levels such as transcription, activation of zymogens and inhibition by endogenous inhibitors named tissue inhibitors of MMPs (TIMPs) [23,24]. TIMPs reduce MMPs activity, by forming non covalent 1:1 stoichiometric complex, [25] but they also affect, through their specific receptor, cell growth, apoptosis, differentiation and angiogenesis [26]. The balance between MMPs and TIMPs is very important in the inflammatory response and in the outcome of tissue injury. In fact, an increased MMPs/TIMPs ratio has been found in inflamed colon of IBD [27], and an enhanced activity of MMPs may amplify intestinal immune response by recruiting the inflammatory cells [28]. Given that, it has been suggested the potential use of inhibitors of MMPs in IBD treatment as demonstrated in IBD animal models in which the administration of several MMP inhibitors reduces the inflammatory state [29,30]. Moreover, some data indicate that the antioxidant compounds may have a therapeutic effect by reducing the altered levels of MMPs detected in intestinal subepithelial myofibroblasts (ISEMFs) isolated from colonic mucosa of CD patients (CD-ISEMFs) [31,32]. An increase of ADAM17 has been also found in human colonic mucosa of IBD patients [33] and this suggests that ADAM17 inhibition may be an alternative strategy to block signalling pathway of tumor necrosis factor (TNF- α), a cytokine involved in intestinal inflammation.

Metalloproteinases

MMPs, collectively called matrixins, participate in the modulation of homeostasis of extracellular matrix (ECM) by cleaving ECM proteins such as collagen, fibronectin, elastin and laminin [34]. However, even if MMPs are involved in the normal tissue remodelling, they also act on substrates different from ECM proteins, regulating many physiological functions such as cell proliferation, adhesion, migration, growth factor bioavailability, chemotaxis and signalling [34]. Under normal physiological conditions, MMPs are present in the latent form and at low concentration. They generally present a prodomain, a catalytic domain, a hinge region and a hemopexin domain [34]. To date 23 MMPs have been found and identified in humans. On the basis of substrate specificity, sequence similarity and domain organization, MMPs can be divided into: Collagenases, Gelatinases, Stromelysins, Matrilysins, Membrane-Type MMPs. These last MMPs distinguish in transmembrane or glycosylphosphatidylinositol- (GPI)-anchored MMPs (Table 2). Seven MMPs are not classified in the above categories and have been indicated as other MMPs. In particular, MMP-12 (metalloelastase), mainly expressed in macrophages, is essential for their migration and digests, besides elastin, a number of other proteins [35,36]. MMP-19 is identified as T-cell-derived autoantigen from patients with rheumatoid arthritis [37]. MMP-20, located within newly formed tooth enamel, is also called enamelysin and digests primarily amelogenin [38]. MMP-21 has been detected in neuronal tissues [39], in cancer and fetal tissue [40], indicating a role in human embryogenesis and tumor progression. MMP-22 function is still not known, but its substrates “*in vitro*” are gelatin and casein [41]. The characterization of MMP-21 and MMP-22 genes showed almost identical sequences [42]. MMP-23, mainly expressed in reproductive tissues, is a membrane-anchored protein with four domains. Differently to other MMPs, it lacks the cysteine switch motif in the prodomain and also the hemopexin domain. Instead, it has a cysteine-rich domain followed by an immunoglobulin-like domain [43]. The latest member added to MMP family is MMP-28, epilysin, initially found in keratinocytes. It is expressed in a number

Table 2: Classification of different MMPs on substrate specificity.

MMPs		Substrates	
Collagenases	MMP-1 (Collagenase 1)	Collagens type I, II, III, VII, VIII, X and XI, gelatin, fibronectin, vitronectin, laminin, entactin, tenascin, aggrecan, link protein, myelin basic protein, versican	
	MMP-8 (Collagenase 2)	Collagens type I, II and III, aggrecan	
	MMP-13 (Collagenase 3)	Collagens type I, II, III, IV, VI, IX, X and XIV, collagen telopeptides, gelatin, fibronectin, SPARC, aggrecan, perlecan, large tenascin-C	
	MMP-18 (Collagenase 4)	Collagen type I (rat)	
Gelatinases	MMP-2 (Gelatinase A)	Collagens type I, II, III, IV, V, VII, X and XI, gelatin, elastin, fibronectin, vitronectin, laminin, entactin, tenascin, SPARC, aggrecan, link protein, galectin-3, versican, decorin, myelin basic protein	
	MMP-9 (Gelatinase B)	Collagens type IV, V, X and XIV, gelatin, elastin, vitronectin, laminin, entactin, tenascin, SPARC, aggrecan, link protein, galectin-3, versican, decorin, myelin basic protein	
Stromelysins	MMP-3 (Stromelysin 1)	Collagens type III, IV, IX, X and XI, collagen telopeptides, gelatin, elastin, fibronectin, vitronectin, laminin, entactin, tenascin, SPARC, aggrecan, link protein, decorin, myelin basic protein, perlecan, versican, fibulin	
	MMP-10 (Stromelysin 2)	Collagens type III, IV and V, gelatin, elastin, fibronectin, aggrecan, link protein	
	MMP-11 (Stromelysin 3)	Collagens type IV, gelatin, fibronectin, laminin	
Matrilysins	MMP-7 (Matrilysin 1)	Collagens type I and IV, gelatin, elastin, fibronectin, vitronectin, laminin, entactin, tenascin, SPARC, aggrecan, link protein, decorin, myelin basic protein, fibulin, versican	
	MMP-26 (Matrilysin 2)	Collagens type IV, gelatin, fibronectin, vitronectin	
Membrane-type MMPs	Trans-membrane	MMP-14 (MT1-MMP)	Collagens type I, II and III, gelatin, fibronectin, tenascin, vitronectin, laminin, entactin, aggrecan, perlecan
		MMP-15 (MT2-MMP)	Fibronectin, tenascin, entactin, laminin
		MMP-16 (MT3-MMP)	Collagens type III, gelatin, fibronectin, vitronectin, laminin
		MMP-24 (MT4-MMP)	Fibronectin, gelatin, chondroitin sulphate proteoglycan, dermatan sulphate proteoglycan
	GPI-anchored	MMP-14 (MT1-MMP)	Gelatin
		MMP-15 (MT2-MMP)	Collagens type IV fibronectin, gelatin, chondroitin sulphate proteoglycan, dermatan sulphate proteoglycan

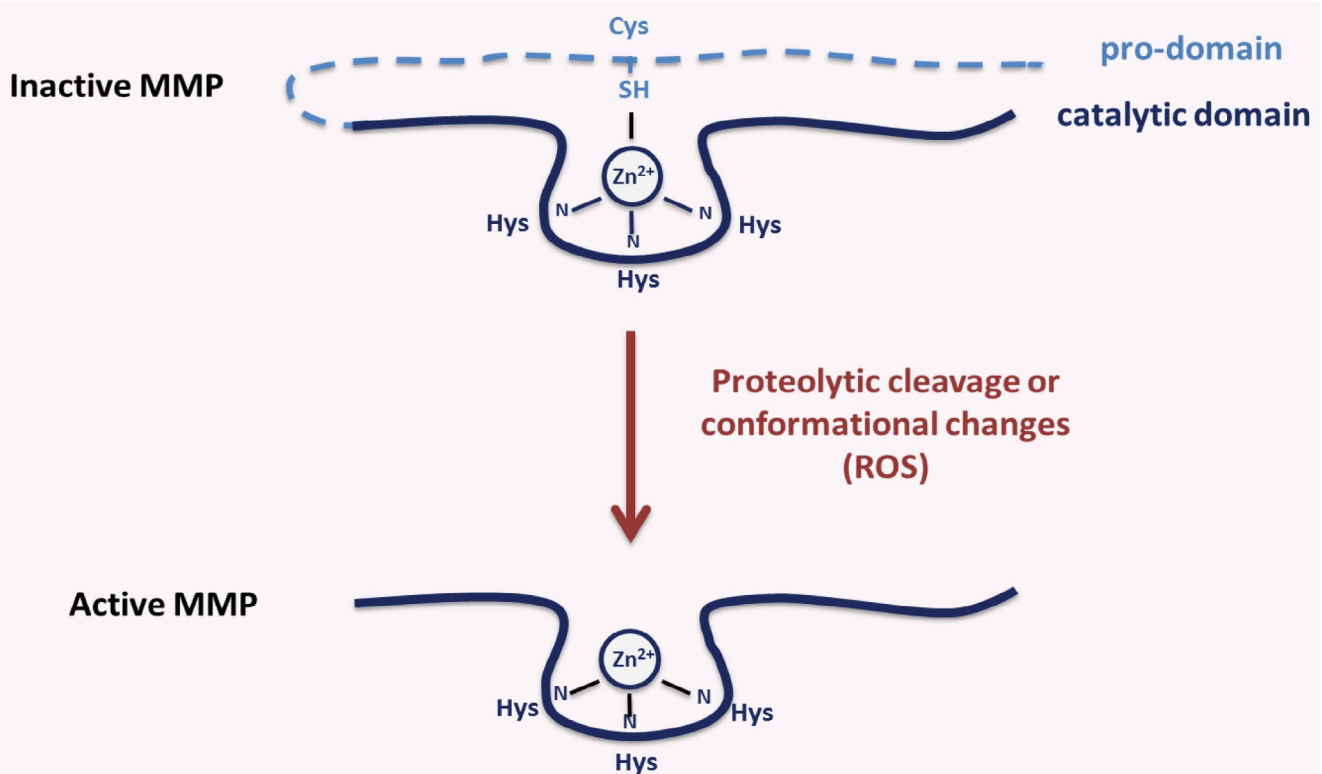


Figure 1: MMP activation: involvement of “cysteine-switch” mechanism.

MMPs are activated through pro-domain proteolytic cleavage or conformational changes. Reactive oxygen species (ROS) break thiol-Zn²⁺ interaction and induce conformational changes which favor MMP activation.

of normal tissues, suggesting that it regulates tissue homeostasis [44]. Enhanced expression of epilysin has been observed in basal keratinocytes during wound healing; in fact, expression patterns in intact and damaged skin suggest that MMP-28 might function both in tissue homeostasis and wound repair [45].

Regulation of MMPs

Catalytic activity of MMPs is regulated at four levels: gene expression, compartmentalization, proenzyme activation, enzyme inactivation. Moreover, it is further controlled by substrate availability and affinity. Some MMP members, such as MMP-2, MMP-19, MMP-28 and several MT-MMPs, are expressed in normal tissue, being involved in tissue homeostasis. However, most MMPs are induced in tissue repair or remodelling subsequently to diseases or inflammatory processes. For the most part, the production of MMPs is regulated at transcription level by specific signals that are temporally limited and spatially confined [34]. MMPs are secreted as proenzymes and are activated in the pericellular and extracellular space. One-third of MMPs contains or RRKR sequence between the pro and catalytic domain, which serves as a target sequence for proprotein convertases (PPCs), a family of proteins that activate other proteins. One of the most well-known PPCs is Furin, a subtilisin-like serine protease present in trans-Golgi network [46], which cleaves protein precursors on motifs such as Arg-X-X-Arg and Lys/Arg-Arg. In fact, MMPs with a furin cleavage site are processed intracellularly before secretion [47,48].

In MMP prodomain is present a conserved cysteine that interacts by its thiol group with the zinc ion of the catalytic site. In this way, ProMMPs are kept in the inactive state and become catalytically active after disruption of the thiol-Zn²⁺ interaction [34]. This process, named the “cysteine-switch”, represents a general and required step in the activation of all proMMPs [49]. The break of thiol-Zn²⁺ interaction can be due to the proteolytic activity of other proteinases that directly remove the prodomain. ROS, SH-reactive agents, or detergents can also induce conformational changes of the proenzyme, thus favouring conversion to an activated state by autolytic cleavage of the prodomain [50] (Figure 1). However, allosteric perturbation,

due to binding of proMMPs to macromolecules, such as integrins, gelatin, collagen, can activate MMPs in their intact or partially cleaved form [51]. In fact, in the cysteine-switch mechanism, the removal of prodomain is not necessary for the activation of proMMPs; differently, the elimination of zinc-thiol interaction is required. Oxidants firstly activate, by oxidating the thiol prodomain, and subsequently inactivate MMPs, by modifying amino acids crucial for their catalytic activity. In particular, ROS, by modifying cysteine SH-group, activate proMMPs via autolytic cleavage “*in vitro*” [52]. However, this ROS effect occurs at low concentrations; in fact, high concentrations of ROS induce the inactivation of MMPs [53]. Also S-glutathionylation of the cysteine in the conserved domain of propeptide that occurs in the presence of peroxynitrite and glutathione (GSH), activates MMPs without cleavage of prodomain [54]. On the contrary, other studies show that MMPs activation, due to peroxynitrite alone or with GSH, is followed by the cutting of prodomain [55], indicating that both mechanisms are possible.

The local tissue activities of MMPs are also modulated by TIMPs, specific inhibitors of matrixins [56,57]. Four TIMPs (TIMP-1, TIMP-2, TIMP-3 and TIMP-4) have been identified in vertebrates [58], and their expression is regulated during development and tissue remodelling. Under pathological conditions, changes in TIMP levels are very important considering that they directly affect and unbalance MMP activity. TIMPs have an N- and C- terminal domain of about 125 and 65 amino acids respectively, each containing three conserved disulfide bonds [59,60]. The N-terminal domain folds as a separate unit and is able to inhibit MMPs [59]. TIMP-1 structure and its inhibition mechanism were determined by X-ray crystallographic studies of the TIMP-1-MMP-3 complex [61]. TIMPs inhibit all MMPs tested so far, except for TIMP-1 that failed to inhibit MT1-MMP [62].

MMPs in IBD

Collagenases (MMP-1, MMP-13)

An increased expression of MMP-1, related to degree of inflammation, has been detected in biopsies from colonic mucosa of

patients with active IBD [27,63]. In particular, MMP-1 expression increases by 230-fold in ulcerated colonic mucosa of IBD patients as compared to normal controls. Moreover, the increase of MMP-1 is attributed principally to macrophages present within the inflamed mucosa [27]. The enhanced expression of MMP-1 potentiates the inflammatory response in IBD intestinal ulcers [64] and in CD granulation tissue [65,66], suggesting that MMP-1 plays an important role in the increase of inflammatory state. The increased expression of MMP-1 in the colonic mucosa of UC patients, related to the enhancement of MMP-1 plasma levels [67], induced acute tissue injury and initial steps of ulceration due to an excessive cleavage of ECM proteins [68]. Indeed, the expression of MMP-1 is greatly increased in ulcerated and inflamed colon areas and in serum of UC patients [67,69-71]. All together, these results suggest that MMP-1 expression and release correlate with UC severity and mucosal damage. Analysis of the relationship between MMP-1 expression and the severity of the disease shows that the expression of MMP-1 in patients with moderate UC is significantly higher than that in patients with mild UC, demonstrating that MMP-1 can be used as biomarker to judge the severity of clinical symptoms in patients. An enhanced expression of MMP-1 up-regulates TIMP-1 in ulcerated mucosa of UC patients, but this leads to an imbalance between MMP-1 mRNA and TIMP-1 mRNA levels. In reality, TIMP-1 mRNA levels do not counteract those of MMP-1 mRNA with consequent overdegradation of ECM in UC [68].

MMP-13 is another collagenase that has as substrate also pro-MMP-9, and is considered important in IBD being strongly expressed in fibrotic areas of chronic cutaneous ulcers in IBD patients. In particular, it is detected only in fibroblasts of the ulcer bed, for this it could be involved in remodelling of the submucosal matrix [72]. The pro-inflammatory role of MMP-13 is due to its ability to release TNF- α from membranes [73]. In fact, it has been demonstrated that both the administration of dextran sulphate sodium (DSS) in rats, in order to mimic colitis clinical conditions, and lipopolysaccharide (LPS)-induced sepsis up-regulate MMP-13 levels involved in the TNF- α cleavage [74]. The formation of bioactive TNF- α causes alterations of intestinal epithelial barrier integrity by increasing intestinal permeability and destabilizing tight junctions [74]. To our knowledge there are no data about the role of oxidative stress on collagenase activity in IBD. However, some data in literature show that an increase of MMP-1 expression and activity, related to ROS production, occur in a variety of cell lines and tissues [75]. Also buthionine sulfoximine (BSO), inhibitor of GSH synthesis, and aminotriazol, catalase inhibitor, increase MMP-1 expression [76]. MMP-13 is overexpressed in osteoarthritic chondrocytes when an increase of ROS production occurs [77]. On the contrary, antioxidants such as the polyphenol epigallocatechin-3-gallate, present in green tea, GSH, Vitamin A and E decrease MMP-1 expression in liver fibrosis, in transformed human heart fibroblasts and in a porcine model of atherosclerosis [78-80]. Moreover, resveratrol, polyphenolic compound present in red wine with anti-inflammatory and antioxidant properties [81], inhibits production of MMP-1 and stromelysin MMP-3 in human chondrocytes [82], and MMP-13 expression in osteoarthritic rats [83].

Gelatinases (MMP-2, MMP-9)

MMP-2 is expressed in normal colon, mainly in the epithelial cells and in lamina propria. An increase of MMP-2 activity was detected in IBD [17,63] and in particular in CD intestinal fistulae [84]. In fact, the increased proteolytic activity of MMP-2 can have an important role in fistulae formation by degrading the basement membrane that supports endothelial and epithelial cells in the gut [84]. The epithelial barrier dysfunction characterizes the pathogenesis of intestinal inflammation and MMP-2 represents a key factor for intestinal barrier functionality [85,86]. However, the role of MMP-2 in the development of colitis is still unclear. Some authors demonstrated that MMP-2 plays an important protective role in maintenance of the integrity of intestinal epithelial barrier [87]. They show that in experimental animal models of colitis, induced by chemicals or bacteria, MMP-2-

-/- mice develop the acute colitis much more intensely than WT mice [87]. Myofibroblasts are an important source of MMP-2 in intestine during the inflammatory state [84]. An increase of MMP-2 secretion and activation, related to decrease glutathione/oxidized glutathione ratio (GSH/GSSG) and inflammatory state, is detected in CD-ISEMFs [31]. In these cells, N-acetylcysteine (NAC), a precursor of GSH synthesis, down-regulates MMP-2 secretion through the increase of GSH/GSSG ratio and exhibits a direct inhibitory action on MMP-2 activity. Moreover, NAC is also able to reduce MMP-2 activation induced by TNF- α thus restoring the physiological activity of enzyme in CD-ISEMFs [31]. Redox regulation of MMP-2 secretion involves c-jun N-terminal kinase (JNK) pathway [31] that phosphorylates transcriptional factors present in most MMP promoters [88]. All data on MMP-2 indicate the importance of correct regulation of production and activity of this MMP. In fact, the lack of MMP-2 can be responsible for deregulation of intestinal barrier function; on the contrary, the excess of MMP-2 can induce fistulae formation. The role of oxidative stress on secretion and activation of MMP-2 has been confirmed in CCD-18Co cells (18Co), a myofibroblast cell line derived from human colonic mucosa, in which the intracellular redox state was modulated through BSO or NAC [31].

High levels of MMP-9 are also present in several animal models of colitis and in human IBD [63,89]. Experimental DSS-induced colitis in rats increases pro-MMP-9 activity [29]. The synthetic inhibitor of MMPs, CGS-27023, administered to these rats for 14 days, increases mucosal repair process and reduces inflammation, indicating a close relationship between pro-MMP-9 activity and injury in inflamed colonic tissue [29]. MMP-9 is the most abundantly expressed protease that correlates with disease activity in IBD [17,90], and it is associated with fistulae in acute CD [17,91]. It has been demonstrated, by immunohistochemical analysis, that MMP-9 is expressed abundantly in fistulae of patients with CD, but only in those with prominent acute inflammation [84]. In the fistulae formation, MMP-9 could have a similar role to that of MMP-2; however, MMP-9 may promote tissue injury by inducing extravasation of neutrophils in areas with acute inflammation and by accelerating the proteolysis of matrix proteins partly degraded by other MMPs [91]. These tissue damages play a pivotal role in IBD; in fact, differently to that occurs for MMP-2, MMP-9-/- mice do not develop colitis due to bacteria or chemicals [86] and are resistant to inflammatory processes [29,92,93]. MMP-9 is involved in the inflammatory response by delaying re-epithelialization processes [94], impairing wound healing [95], increasing endothelial permeability [96,97], and activating several proteins including fibrinogen, interleukin (IL)-1 β , IL-8, and transforming growth factor- β (TGF- β) [95,98-100]. It is shown that serum concentration of MMP-9 is higher in UC and CD patients than that measured in control serum, and MMP-9 levels correlate well with the disease activity [101]. These data were confirmed by the demonstration that a significant increase of MMP-9 occurs in active CD and UC as compared with MMP-9 levels detected in controls and in patients with inactive forms [102]. The correlation between MMP-9 serum levels and the clinical activity of disease was observed also in children affected by IBD [103,104]. Fecal MMP-9 levels increase in IBD patients but this increase is higher in UC than in CD [105]. These results suggest that serum and fecal MMP-9 levels can be considered as supportive markers for disease activity or for diagnosis of different types of IBD, respectively. An up-regulation of MMP-9 expression has been associated with the release of vascular endothelial growth factor (VEGF) in animal models of colitis [106]. In fact, a strong correlation between circulating VEGF-A and serum MMP-9 in CD patients was observed [102]. MMP-9 seems to be involved in angiogenesis by recruitment of pericytes to the new vessels [107]. In this process platelet-derived growth factor (PDGF), whose availability as well as biological functions are regulated by its binding to ECM, plays the major role. Given that a correlation between the concentration of this growth factor and MMP-9 levels in both CD and UC was found, it has been speculated that MMP-9 might participate in the angiogenesis through the release of PDGF from ECM or degradation of ECM elements involved in PDGF binding [102]. Recent data demonstrate that aerial part extracts of *Lavandula dentata* and *Lavandula stoechas* improve the redox state by increasing GSH levels

in 2,4,6-trinitrobenzene-sulfonic-acid (TNBS)-induced rat colitis model [108]. Moreover, this increase of redox state is associated to down-regulation of MMP-9 expression [108].

Stromelysins (MMP-3, MMP-10)

MMP-3 is induced consistently in several animal models [109] and in human IBD [63]. It is expressed during IBD in mononuclear macrophage-like cells and in lamina propria stromal cells below the ulcerated areas [38,72,110]. An up-regulation of MMP-3 is present in CD [65,110] and, similarly to gelatinase MMP-9, it is related to mucosal damage and fistulae formation through degradation of the matrix in areas with active inflammation [17,73,91]. MMP-3 and MMP-9 concentrations in sera of pediatric patients with IBD reflect various stages of disease activity. In fact, significantly higher concentrations of these MMPs are present in the sera of patients with the active form of disease as compared to those found in sera of patients with the mild form or in control group [103,104]. Therefore, the levels of MMP-3 and MMP-9 might be useful in the clinical evaluation of patients. A marked overexpression of MMP-3 was assessed by mRNA levels in inflamed mucosal samples from patients with UC as compared to controls [27]. These results are also supported by data that demonstrate an overexpression of MMP-3 in intestinal inflamed sites of children with IBD [111]. Functional experiments in an *ex vivo* human foetal small intestine explant model have clearly shown that MMP-3 also acts as a key mediator of T cells, and TNF- α mediates tissue injury in the gut [112-114]. The increase of oxidative state present in CD-ISEMFs is responsible for the increased MMP-3 production detected in these cells stimulated or not with TNF- α , as compared to the control ISEMFs [32]. In fact, NAC restores MMP-3 levels in CD-ISEMFs to those of control ISEMFs. Data obtained in 18Co treated with BSO and/or NAC or curcumin, antioxidant present in *Curcuma Longa* with anti-inflammatory effect [115], highlight the regulatory role of antioxidants on production of MMP-3. However, their effect is not closely related to changes of oxidative state, suggesting that antioxidants affect MMP-3 production also by their direct action on transcriptional factors [32]. Indeed, mitogen

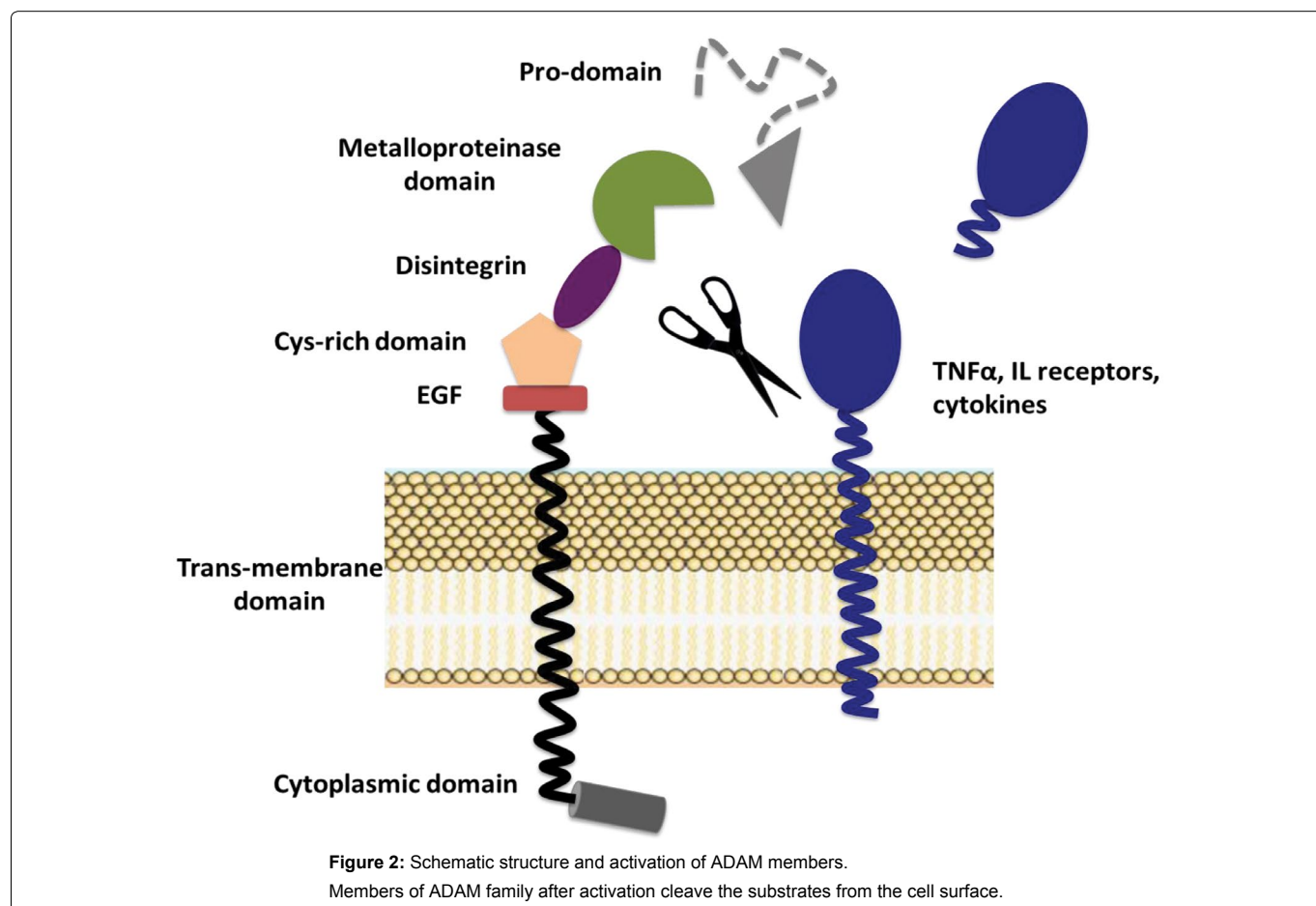
activated protein kinases (MAPKs), activated in the presence of oxidative stress, are involved in the modulation of MMP-3 levels [31,32]. Curcumin decreases MMP-3 expression both by increasing GSH levels and by inhibition of p38 mitogen activated protein kinase (p38 MAPK) signalling pathway and transcriptional factors, such as nuclear factor-kB (NF-kB) and activator protein-1 (AP-1) [116]. Moreover, curcumin reduces MMP-3 in biopsies and ISEMFs of adult and children affected by IBD [117] indicating the role of oxidative stress in the increased activity of MMPs in these patients.

MMP-10 together with matrilysin MMP-7 plays a role in intestinal wound healing [118], and MMP-10 is actively expressed in epithelial cells at the ulcer margin. This location and the finding that the same cells produce laminin-5 suggest an important role for MMP-10 in epithelial cell migration [72]. In addition, MMP-10 is also expressed in macrophage and lymphocyte-like cells in areas of inflammation but not in T lymphocytes. In fact, T lymphocytes do not express MMP-10 in the intestine but stimulate other cells of lamina propria to express it, participating in formation of early lesions in IBD [72,112].

Matrilysin (MMP-7, MMP-26)

MMP-7, expressed in many adult tissues, is implicated in innate intestinal defence [119]. Cytokines and growth factors, such as IL-1, epidermal growth factor (EGF) and TNF- α , at elevated concentrations at inflammatory sites, may induce the synthesis of MMP-7 [120]. The expression of this MMP is an important hallmark of surface epithelium at the edge of gastrointestinal ulcers. In fact, MMP-7 was not detected in intact tissue distant from the wound [65] and in normal gastric or colonic mucosa [121,122]. MMP-7 mRNA was detected in crypt abscesses associated with idiopathic IBD [65]. Its expression also increases in IBD and its levels correlate with disease activity in UC [123,124]. During IBD, MMP-7 has been detected in areas surrounding ulcers, suggesting a role in repair/wound healing. Recently, it has been demonstrated that the glandular epithelium MMP-7 correlates with the disease incidence in UC and with the lesion location in CD [125].

MMP-26, specifically expressed in epithelial carcinomas and



in normal adult kidney, decreases after anti-TNF- α treatments in intestinal neutrophils of CD patients [126]. This suggests the involvement of MMP-26 in tissue destruction or migration of neutrophils. MMP-26 is also expressed in migrating enterocytes localized next to the intestinal ulcer in IBD [127].

Other MMPs (MMP-12, MMP-19, MMP-28)

MMP-12 increases in the immune response in lamina propria macrophages [72,128], and this proteinase may have a role in macrophage migration and tissue inflammation in CD [128]. MMP-19, expressed in non-migrating enterocytes in IBD intestine [127], seems to be important for appropriate immune response in colitis. In fact, in DSS-induced colitis the lack of MMP-19 causes an increase of inflammatory state and mucosal damage in mice [129]. MMP-28, differently to previously described MMPs, decreases in inflamed mucosa in UC [130], suggesting that this MMP is not involved in IBD intestinal damage [127].

ADAM17 and its regulation

The differences between MMPs and ADAMs consist in domain structure and in particular in the sequence of catalytic domain. The ADAM structure contains a prodomain, a metalloproteinase catalytic domain, a disintegrin domain, an EGF-like (cysteine-rich) domain, a single transmembrane domain and a cytoplasmic portion [21] (Figure 2). Members of ADAM family have emerged as major ectodomain shedding proteinases, which release a large number of molecules in various physiological conditions. However, the uncontrolled release of some substrates is related to various pathological processes. ADAM17, also known as tumor necrosis factor- α converting enzyme (TACE), is a membrane-bound enzyme belonging to ADAM family that cleaves cell surface proteins such as cytokines (TNF- α) or cytokine receptors (IL-6-receptor and TNF-receptor). Considering the effect of ADAM17 on TNF- α or IL-6, it has been speculated that its inhibition could improve autoimmune diseases [131]. In fact, membrane-bound TNF- α acquires the pro-inflammatory activity after its cleavage by ADAM17 [132]. Moreover, the shedding of IL-6R from membrane induces IL-6 trans-signalling on cells expressing only IL-6 receptor chain gp130, thus increasing the inflammatory state with consequent cancer risk [133,134]. Phorbol ester, phorbol 12-myristate 13-acetate (PMA), is a potent activator of ADAM17 by protein kinase C (PKC) and extracellular signal-regulated kinase (ERK) activation. In fact, the inhibition of these kinases decreases ADAM17 activity [135]. ROS induce an increase of ADAM17 activity through direct modification of disulphide bonds that allows ADAM17 to assume an open active conformation [136] and also mediate up-regulation of ADAM17 expression [137,138]. The compartmentalization plays an important role in the regulation of ADAM17. In fact, it is stored in perinuclear region and its translocation on cell membrane occurs after phosphorylation of Thr 735 modulated by p38 MAPK activation [139]. Apoptosis also induces, probably by activation of p38 MAPK, an increase of ADAM17 activity and consequent translocation on cell surface [140]. ADAM17 activity is down-regulated by the natural tissue inhibitor TIMP-3 [141], and it has been demonstrated that also Tetraspanin CD9 negatively regulates ADAM17-mediated TNF- α shedding as well as intercellular adhesion molecule-1 on the cell surface [142].

Members of adam family in IBD (ADAM9, ADAM10, ADAM17, ADAM19)

ADAM17, normally expressed in the human colonic mucosa, increases in human IBD [33] and its expression is up-regulated by TNF- α in endothelial cells [143]. Transmigration of polymorphonuclear leukocytes (PMNL) across epithelia is the primary event of acute phase in CD, and it can be responsible for the TNF- α secretion by intestinal cells [144]. Moreover, in this phase of acute inflammation, an increase of the expression of ADAM17, but not of its inhibitor TIMP-3, occurs in intestinal endothelial cells (IEC) [145]. All these data demonstrate that the early upregulation of ADAM17 was linked to TNF- α production during PMNL transepithelial migration. Reduced levels of ADAM17 increase sensitivity to colitis in mice [146] and studies, performed

in DSS-induced colitis, demonstrate that epithelial ADAM17 is very important to provide colitis resistance in rats [147]. In fact, it is possible that ADAM17, through the activation of EGFR and its signalling pathways, promotes mucosa repair by inducing epithelial cells proliferation and goblet cell differentiation [147]. Some data show that the ADAM17 expression levels, detected in epithelial cells and in intestinal biopsies derived from intestinal mucosa of IBD patients, were not significantly different from ADAM17 values measured in control samples [148,149]. On the contrary, other data demonstrate that ADAM17 expression enhances in CD patients and promotes neutrophil migration and colitis [145]. It is possible that the differences highlighted in these studies may be due to different inflammatory state of intestinal mucosa and/or therapy used. In fact, ADAM17 levels can be related to oxidative stress considering that an increase of this protease occurs in intestinal myofibroblast cell line in which is present an increase of ROS due to BSO and/or TNF- α treatment [138]. The involvement of ADAM17 in IBD is also observed in mice with DSS-induced colitis, in which TACE significantly increases during the period of DSS treatment and returns to normal levels in the remission phase. Moreover, the treatment with a specific inhibitor of ADAM17, compound 11p, reduces clinical signs of DSS-induced colitis maintaining the integrity of colon mucosa and avoiding the infiltration of inflammatory cells [150]. Resveratrol ameliorates experimental colitis by reducing ADAM17 and increasing TIMP-3 expression through the activation of the deacetylase, silent information regulator-1 (SIRT-1) [150]. ADAM17 can be considered a target in therapies for chronic inflammatory diseases and compounds able to inhibit ADAM17 activity have already been developed [151].

Although ADAM17 is the member of ADAM family highly expressed in IBD, it has been demonstrated that ADAM19 is also up-regulated in mucosa of IBD patients [152]. The major increase of ADAM19 is detected in patients with UC and its expression is stimulated by TNF- α and various cytokines. Differently, no variation of ADAM9 and ADAM10 expression between IBD patients and control was observed [152].

TIMPs in IBD (TIMP-1, TIMP-2, TIMP-3, TIMP-4)

TIMP-1: Contradictory data are reported in literature about the production of TIMP-1 in intestinal inflamed mucosa. In IBD it has been demonstrated that TIMP-1, expressed by inflammatory cells, activated fibroblasts and vascular smooth muscle cells, increases predominantly in the areas of mucosa with active inflammation and, in particular, at ulcer bases [64]. This localization suggests that TIMP-1, along with the increase of MMP-1, plays a role in the tissue reorganization after mucosal damage. An increased expression of TIMP-1, related to disease severity, is observed in inflamed intestinal area of UC patients [69], as well as in inflamed and especially ulcerated colon mucosa of IBD patients [27]. In a study using cultures of biopsies isolated from intestinal mucosa of IBD patients, TIMP-1 levels were higher in inflamed mucosa of both CD and UC as compared with uninfamed mucosa [153]. Moreover, TIMP-1 showed a strong correlation with levels of proinflammatory cytokines such as IL-6, IL-1 β and IL-10 [153]. An enhancement of TIMP-1 has been observed both in inflamed intestinal mucosa and in serum of UC patients [71]. In particular, it has been observed that TIMP-1 plasma levels in UC patients correlate positively with scored endoscopic degree of mucosal injury, with indices of disease and clinical activity, and with C reactive protein concentration, a marker of inflammation levels. Therefore, TIMP-1 plasma concentration may be a possible biomarker of disease activity [71]. No increase of TIMP-1 production has been detected in CD-ISEMFs type cells stimulated or not with TNF- α as compared to C-ISEMFs [32]. Similar results were obtained in 18Co treated with BSO and/or NAC indicating that the intracellular redox state does not affect the production of this inhibitor [32]. Indeed, an increased secretion of TIMP-1 is measured only in fibrotic myofibroblasts and is associated with the presence of fibrotic structures in CD [154]. Moreover, it has also been observed that TIMP-1 production enhances in myofibroblasts of CD patients only after treatment with infliximab (chimeric monoclonal antihuman TNF- α antibody), and

Table 3: MMPs, ADAMs and TIMPs expression and role in inflammatory bowel disease (IBD).

MMPs/G3:I20, ADAMs and TIMPs	Expression in IBD	Role in IBD
MMP-1	↑	Potentiates the inflammatory response Ulceration (UC) Biomarker of disease stage (UC)
MMP-13	↑	TNF α cleavage Mucosal damage
MMP-2	↑	Maintenance of intestinal epithelial barrier integrity Fistulae formation (CD)
MMP-9	↑	Mucosal damage Fistulae formation (CD) Angiogenesis Supportive biomarker for diagnosis of UC and CD and the disease stage
MMP-3	↑	Mucosal damage (UC) Fistulae formation (CD) Biomarker of disease stage
MMP-10	↑	Intestinal wound healing
MMP-7	↑	Intestinal wound healing. Biomarker of disease stage in UC
MMP-26	↑	Mucosal damage and neutrophil migration
MMP-12	↑	Immune response
MMP-19	N.D.	Increase of inflammatory state and mucosal damage
MMP-28	↓	Not involved.
ADAM-17	↑	TNF α cleavage Mucosa repair Colitis resistance? Neutrophil migration and colitis?
TIMP-1	↑	Biomarker of disease stage
TIMP-2	?	Not involved
TIMP-3	↓	TNF α cleavage deregulation
TIMP-4	↓	Increase of MMP-2 activity Increase of platelet aggregation

↑: Increase; ↓: Decrease; ?: Contradictory data; **N.D.**: No data to our knowledge.

MMP: Matrix Metalloproteinase; ADAM: A Disintegrin and Metalloproteinase; TIMP: Tissue Inhibitors of MMPs; UC: Ulcerative Colitis; CD: Crohn's Disease.

this effect is not accompanied by significant induction of apoptotic process or alterations in MMP expression [155]. Considering these findings, it has been hypothesized that not myofibroblasts but other inflammatory cells, such as lymphocytes and macrophages, may be the responsible source for the increased levels of TIMP-1 in intestinal mucosa of CD patients [27,32].

TIMP-2: No statistical difference in TIMP-2 levels was found between IBD patients and healthy controls in serum [156]. Moreover, no remarkable expression of TIMP-2 is observed in inflamed mucosa of IBD patients [156]. TIMP-2 mRNA levels, measured by PCR in biopsies from IBD patients, remain unchanged in inflamed and uninfamed mucosa [27]. On the contrary, other studies demonstrated an increase of TIMP-2 serum levels in UC and CD patients, suggesting its use as a potential marker for IBD activity [157].

TIMP-3: TIMP-3, present in both uninfamed and inflamed gut mucosa and predominantly expressed in macrophage-like cells or fibroblastic-like cells in lamina propria and in endothelial cells [72], inhibits the inflammatory response as shown by studies based on *timp3*^{-/-} mice or gene transfer "in vitro". TIMP-3 is essential for innate immune function and has a pivotal role in the regulation of inflammatory response [158]. In fact, the loss of this TIMP causes deregulation of cleavage of TNF- α and its receptors by inactivation of ADAM17 in innate immunity [158]. Very severe colitis, associated with increased expression of inflammatory cytokines, has been determined in TIMP-3-deficient mice after treatment with TNBS [149]. In contrast, transgenic mice for TIMP-3 express less cytokines and are largely resistant against TNBS-induced colitis. In addition, it has been demonstrated that TIMP-3 regulates negatively not only ADAM17 but also functional activity of MMPs that are increased in IBD [149]. For this reason, given that MMP-9 derived from epithelium has a crucial role in the induction of intestinal damage, the severe intestinal damage seen in phenotype TIMP-3-KO mice after TNBS administration, may be due to the lack of inhibitory effect of TIMP-3 on MMP-9. However, there are no commercial compounds that can selectively inhibit MMP-9 and ADAMs in order to assess the exact contribution of these two different proteases in colitis

occurring in TIMP-3-KO mice. A decreased expression of TIMP-3 has been detected in DSS-induced colitis in rats [159] and in inflamed intestine of CD patients [149]. These data are in contrast with the up-regulation of TIMP-3 that occurs in condition of oxidative stress in macrophages and in chondrocytes [160,161]. In particular, the up-regulation of TIMP-3 expression, related to ROS production and suppressed by NAC treatment is mediated by small mother against decapentaplegic (Smad) 2 protein [161]. Considering that TGF- β 1 increases TIMP-3 expression also in normal gut, it is possible that the diminished TIMP-3 expression in CD patients is in part due to Smad7, an inhibitor of TGF- β 1 signalling, expressed at high levels in CD mucosa [149]. TIMP-3 decrease can be responsible of the increased paracellular permeability and tight junction protein alteration due to TNF- α [148]. Taken all, these findings suggest that TIMP-3-based therapies capable of blocking TNF- α may be considered in clinical use to control IBD in TGF-1-stimulated chondrocytes.

TIMP-4: It is shown that the levels of TIMP-4 decrease in serum of IBD patients with a consequent increase of MMP-2 activity. This may be very important, because MMP-2 is a key player in proper wound healing, angiogenesis and re-epithelization, as well as in the regulation of epithelial barrier function of the intestine [156]. TIMP-4 also inhibits platelet aggregation suggesting its involvement in the regulation of platelet recruitment and aggregation, processes enhanced in IBD patients and even in inactive disease [162,163].

Table 3 summarizes the principal roles of MMPs, ADAM17 and TIMPs in IBD

Conclusions

MMPs, ADAMs and TIMPs play an important role in wound healing and in numerous pathophysiological processes. Moreover, they are involved in the modulation of inflammatory response, by controlling migration of immune cells, matrix deposition and degradation as well as cytokine activity. However, an increase of MMPs and ADAM17, often linked to the disease severity and not accompanied by an up-regulation of TIMP, is present in intestinal mucosa of IBD patients. This can contribute to increase

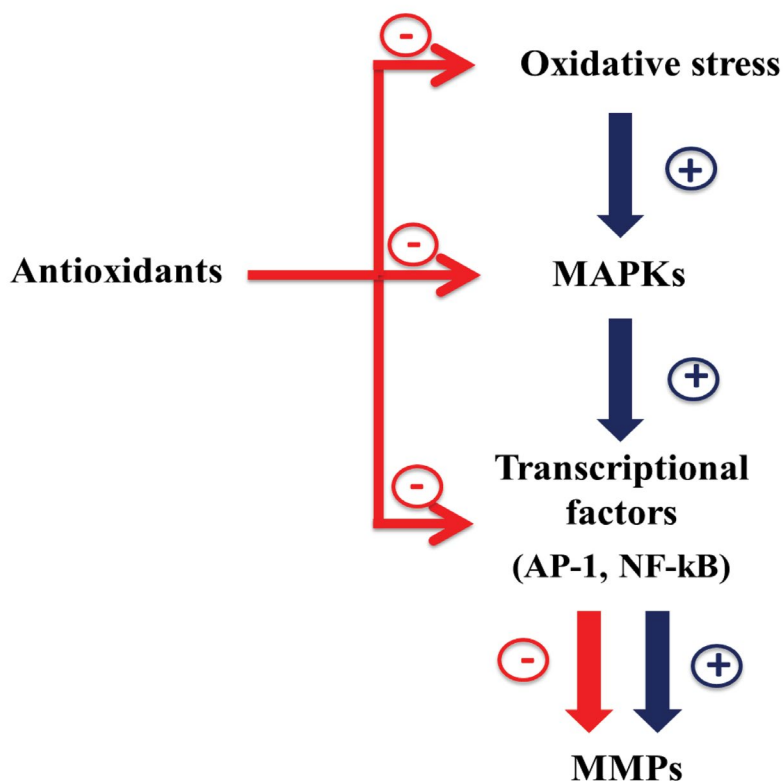


Figure 3: Down-regulation of MMPs expression by antioxidants: possible mechanisms.

the inflammatory state, cytokine production, and ulceration and fistulae formation. MMPs, differently to TIMPs, are also redox-regulated. This review highlights that the up-regulation of some MMPs production in IBD can be due to the oxidative stress present in intestinal mucosa of IBD patients. In fact, antioxidants are able to down-regulate MMPs production restoring their levels to those of control. Considering that an important role is attributed to oxidative stress in the pathogenesis of IBD, it is possible that the imbalance between oxidants and antioxidants can affect the expression of various MMPs in IBD. Moreover, antioxidants, in addition to restoring the intracellular redox state, act directly on the regulation of MAPKs and transcriptional factors (Figure 3). For this, in the development of MMP-targeting therapies, molecules with antioxidant property may be used to reduce dysfunction of epithelial barrier and prevent fistulae and ulceration in IBD.

Conflict of Interest

The authors have no conflict of interest.

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