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MINI REVIEW

Matrix metalloproteinases: key regulators in the pathogenesis of chemotherapy-induced mucositis?

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Abstract Chemotherapy is an effective anticancer treatment; however, it induces mucositis in a wide range of patients. Mucositis is the term used to describe the damage caused by radiation and chemotherapy to mucous membranes of the alimentary tract. This damage causes pain and ulceration, vomiting, bloating and diarrhoea, depending on the area of the alimentary tract affected. Although treatment is available for a small subset of patients suffering from mucositis, the majority rely on pain relief as their only treatment option. Much progress has been made in recent years into understanding the pathobiology underlying the development of mucositis. It is well established that chemotherapy causes prominent small intestinal and colonic damage as a result of up-regulation of stress response genes and pro-inflammatory cytokines. However, better understanding of the mediators of this damage is still required in order to target appropriate treatment strategies. Possible mediators of mucositis which have not been well researched are the matrix metalloproteinases (MMPs). MMPs have been shown to function in several of the pathways which are known to be up-regulated in mucositis and contribute to tissue injury and inflammation in many pathological conditions. This prompts the consideration of MMPs as possibly being key mediators in mucositis development.

Keywords Mucositis · Chemotherapy · Alimentary tract · Matrix metalloproteinases · Tissue inhibitors of metalloproteinases

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Introduction

Mucositis is a major oncological problem associated with the damage caused by anti-cancer therapy to mucous membranes of the alimentary tract (AT) [1–3]. AT mucositis has been reported to occur in 40% of patients receiving standard dose chemotherapy and 100% of patients receiving high dose chemotherapy [3–6]. This condition is manifest by a range of symptoms depending on the area of the AT that is most affected. Symptoms include ulceration, nausea and vomiting, diarrhoea, constipation and abdominal pain. Moreover, the effects of mucositis are not confined to AT symptoms but can also result in local and systemic

infections as well as fatigue as a consequence of bacterial colonisation and malnutrition, respectively [5, 7, 8].

The burden of mucositis is overwhelming to patients. Moreover, mucositis significantly affects clinical outcomes as a result of reductions in anti-cancer therapy doses and treatment breaks [5, 8]. A range of products are currently in development for mucositis and fall into four main categories; cell resistance modifiers, mechanism specific inhibitors, damage control agents and healing accelerators. However to date, most have proven to be ineffective for the treatment of mucositis. Better understanding of the pathobiology of mucositis is required in order for an effective therapy to be developed.

Over the last decade, significant progress has been made in understanding the underlying pathobiology for mucositis development. The mechanisms of mucositis are complex and include up-regulation of a range of stress response genes and subsequent activation of mitogen activated protein kinase (MAPK) signalling, nuclear factor κB (NFκB) signalling, Fos/Jun signalling and Wnt signalling [9, 10]. Furthermore, the downstream mediators of damage include cytokines, ceramide and cyclooxygenase-2 (COX-2) [3, 11]. Other possible mediators of mucositis which have not been well researched are the matrix metalloproteinases (MMPs). Through regulation of extracellular matrix (ECM) components in the gastrointestinal mucosa, MMPs affect numerous biological phenomena including cell growth, apoptosis, cell motility, immune responses and cytokine and chemokine bioactivity [12–14]. Although direct links between MMPs and mucositis development have yet to be established, MMPs have been shown to contribute to tissue injury and inflammation in many other gastrointestinal diseases [15–17]. This review will examine the mechanisms of mucositis and the role of MMPs in normal tissue, as well as in tissue injury and inflammation.

Chemotherapy and the gastrointestinal tract

A number of studies have been carried out to investigate the effect of chemotherapy on the histopathological features of the AT [11, 18, 19]. In the small intestine and colon, chemotherapy treatment has been shown to cause crypt hypoplasia, followed by rebound crypt hyperplasia and finally restoration of normal tissue [2, 18–20]. The historic paradigm for the development of mucositis proposed that chemotherapy has the ability to cause clonogenic cell death in normal cells of the AT thus leading to the observed epithelial atrophy, barrier degradation and ulceration [6, 21], resulting in AT symptoms. However, a study by Paris et al. found evidence of early damage to submucosal structures, including fibroblasts and endothelial cells, preceding epithelial tissue damage and manifestation of clinical signs [22]. This study prompted the revision of this 'historic paradigm' and the consideration of a range of signalling systems and events as underlying causes for the development of mucositis. Sonis et al. conducted studies to investigate the gene expression differences associated with the development of mucositis in an animal model by using microarray profiling. The findings of these studies demonstrated acute and delayed alteration to multiple gene expression profiles following anti-cancer treatment [10, 23]. They were able to conclude that the biological events underlying mucositis occur in an interdependent sequence and that the tissue and cellular sources of the up-regulated genes are associated with the endothelium, muscle, inflammatory infiltrate and epithelial cells [10, 23].

Signalling systems in mucositis

The 5-phase model for the development of mucositis

The current hypothesis for the development of mucositis was first introduced in 2004 [1, 4, 21]. Briefly, this hypothesis proposes that there are five biological phases of mucositis, namely: *initiation*, occurring following administration of cytotoxic chemotherapy, it encompass the primary damage response and is a result of DNA and non-DNA damage and the generation of reactive oxygen species (ROS); *message generation*, involving the up-regulation of transcription factors including NFκB and subsequent activation of cytokine and stress response genes; *signalling and amplification*, producing proteins, such as tumour necrosis factor (TNF), interleukin-1β (IL-1β) and interleukin-6 (IL-6), which cause direct tissue damage and provide positive feedback to amplify the process; *ulceration*, resulting in painful ulcers, bacterial infiltration and an influx of macrophages and other inflammatory cells and finally *healing*, which spontaneously occurs upon cessation of chemotherapy [4].

Mucositis signalling pathways

The injury caused by cytotoxic chemotherapy in mucositis is mediated by a range of pathways including MAPK, NFκB and COX-2, Wnt, SAPK/JNK and ceramide signalling [1, 9]. Activation of these injurious signalling pathways leads to an excessive influx of immune cells, including macrophages and neutrophils, into the mucosa thus initiating an inflammatory response. Downstream up-regulation of pro-inflammatory cytokines, including TNF, IL-1β and IL-6, has also been reported throughout the entire AT mucosa following chemotherapy [11, 24]. Furthermore, their expression correlates with early damage to connective tissue and endothelium. In addition,

pro-inflammatory cytokines have the capacity to initiate epithelial signalling thus causing further tissue damage [21]. It has also been suggested that pro-inflammatory cytokines provide a positive-feedback loop by up-regulating genes associated with tissue injury, including NFκB.

Matrix metalloproteinases have been shown to function in several of the pathways which mediate mucositis development and tissue injury in general. Therefore, MMPs deserve careful consideration as possible mediators of mucositis development.

Matrix metalloproteinases

Function

Matrix metalloproteinases are a group of zinc-dependent endopeptidases. They were originally described as cleaving ECM components with a predominant role in ECM homeostasis [25–27]. However, recent research has identified a wide range of functions for those peptidases [12]. These functions include: regulation of cell growth, triggering the release of growth factors, regulating apoptosis, altering cell motility, affecting immune responses and modulating the bioactivity of cytokines and chemokines [12–14, 28]. MMPs were originally divided according to their ECM substrate specificity into five classes; which are the collagenases, gelatinases, stromelysins, elastases and membrane type MMPs. However, with the discovery of additional functions of MMPs, the more commonly used nomenclature is MMP-1 to MMP-28.

Regulation of MMPs

The levels of MMPs are tightly regulated at many stages including transcription, activation from precursor zymogens (post-translational) as well as by tissue inhibitors of metalloproteinase (TIMPs) [12, 25, 26]. Expression of most MMPs is normally low in tissues, however, they are induced when ECM remodelling is required or following injury [29]. MMPs are synthesised by a range of cell types including macrophages, neutrophils, fibroblasts and epithelial cells [12, 30]. They are secreted as latent, inactive zymogens and are converted to their activate form in the extracellular space [30, 31]. A latent MMP can gain catalytic activity through the disruption of the thiol-Zn^{2+} interaction [31]. Van Wart and Birkedal-Hansen referred to this mechanism as the 'cysteine-switch' and proposed that the thiol-Zn^{2+} interaction can be broken by three mechanisms: (1) modification of the free thiol by physiological (oxidants, electrophiles) or non-physiological (heavy metal ions, alkylating agents) compounds; (2) cleavage of the pro-domain by pro-protein convertases such as furin; and (3) inter- or intra-molecular autolytic cleavage of the prodomain by chemical or allosteric perturbation of the zymogen [32]. Moreover, MMPs work co-ordinately to create a cascade of activation where by an activated MMP has the capacity to catalyse the activation of other MMP zymogens [12, 31].

Matrix metalloproteinase activity is also regulated by TIMPs. These are the endogenous inhibitors of MMPs. To date four family members have been identified, namely: TIMP-1, -2, -3 and -4 [12, 29, 33, 34]. Whilst all members are capable of inhibiting MMPs, TIMP-1 and -2 appears to be the most active [30]. TIMPs are produced by the same cell types which secrete MMPs; including macrophages, neutrophils, fibroblasts and epithelial cells [30, 33]. TIMPs inhibit MMP activity by forming a 1:1 complex with the catalytic site of MMPs and chelating the active-site zinc [35]. In addition to their MMP inhibitory activity, there is also evidence that a decrease in TIMP levels, specifically TIMP-2, can act as an alternative mean for rapid generation of low levels of MMP-2 [36].

MMPs in cancer

The role of MMPs in tumour growth and metastasis has been widely studied, however, for the purpose of this review this will be discussed only briefly. MMPs have been shown to contribute to two facets of tumour behaviour including cancer dissemination and tumour angiogenesis. Moreover, increased expression of MMPs has been shown in a range of cancer types including lung, pancreatic, gastric, ovarian and breast cancers. MMP expression has also been associated with an increase in the probability of metastasis for those cancers [37]. It has been established that both tumour cells as well as the surrounding stromal cells are capable of producing MMP-1, -2, -3, -11 and -13 while inflammatory cells produce MMP-9 [37].

The healthy gastrointestinal tract and MMPs

Epithelial cells of the gastrointestinal tract (GIT) undergo continuous renewal. The process of cell turnover is tightly regulated by mucosal as well as submucosal signalling in order to maintain homeostasis and to compensate for disturbances which may occur in the GIT [38]. The ECM is a complex structural network containing fibrous proteins, proteoglycans and glycoproteins. It plays a vital role in providing support and regulation for the overlying epithelium [39]. Moreover, the ECM includes the interstitial matrix and basement membranes.

For many years, the primary role of the ECM was believed to provide structural organisation to the tissue

through supporting the overlying epithelium and segregating tissue [40, 41]. However, research into matrix biology revealed a vital role for the ECM, in particular the basement membrane, in regulating epithelial cell kinetics [40, 41] (Table 1). In the early 1990 s, cell culture studies demonstrated that detachment from the ECM molecule-containing basement membrane causes apoptosis in a variety of cell lines by induction of apoptosis-specific genes [28, 42]. Furthermore, *in vitro* studies have shown that the presence of ECM components promotes the expression of differentiation markers, such as sucrose and alkaline phosphatase, and imposes ultrastructural changes in immature intestinal IEC-6 cells [43, 44]. Subsequent studies identified the importance of direct epithelial cell-basement membrane interaction on gene regulation, cytoskeletal structure, differentiation and cell growth control [45, 46].

ECM components have been shown to be spatially expressed along the small intestinal and colonic crypt-villus axis and include: tenascin, laminin, fibronectin, collagen IV and perlecan [40, 47]. Beaulieu (1997) suggested that the spatial organisation of ECM molecules is the primary mechanism by which anchorage and migration of cells take place [40]. Furthermore, it has been suggested that an increase or decrease in the affinity of stem cells to those ECM components also accounts for the regulation of cell kinetics [47]. ECM-degrading MMPs have been implicated in providing regulation for ECM composition along the crypt-villus axis in a substrate-specific manner (Table 2) thus allowing for tight regulation of crypt cell proliferation, apoptosis and differentiation [25, 30].

MMPs and tissue remodelling in the gut

The distribution and expression of ECM components in the basement membrane plays a predominant role in regulating epithelial cell kinetics. Therefore, it is important that MMP and TIMP levels are continuously regulated to achieve a balance in tissue degradation and fibrogenesis. Furthermore, a skewed level of tissue MMPs and TIMPs has been implicated in the development of acute and chronic diseases of the gut [25, 26]. Previous research on inflammatory bowel disease (IBD) and Celiac disease (CD) has indicated a substantial increase in MMP-1, -2, -3 and -9 and a decrease in TIMP-1 and -2 expression in the small intestine and colon [15–17, 27]. Moreover, this alteration in expression is associated with extensive tissue remodelling in those regions and correlates with histopathological damage and the severity of the condition in patients [16]. Previous studies have also demonstrated that uncontrolled and excessive ECM degradation, which occurs as a consequence of elevated tissue MMPs and a skewed MMP:TIMP ratio, severely impairs AT histology and function by causing ulceration, malabsorption and diarrhoea; which are features of mucositis also [48].

Table 1 basement membrane components and their roles in regulating epithelial cell kinetics

ECM component	Spatial expression	Effect on cell kinetics
Collagen IV	Villus	Promote migration
Fibronectin	Highest in crypts and decreasing towards tip of villus	Promote proliferation, inhibit differentiation
Laminin-1 ($\alpha1\beta1\gamma1$)	Crypt-villus junction to villus tip	Promote differentiation
Laminin-2 ($\alpha2\beta1\gamma1$)	Crypt	Unknown
Tenascin	Highest in villus and decreasing towards crypt	Prevent migration

Table 2 MMPs involved in immune response and respective targets of activity

MMP	Common name	Substrate
MMP1	Collagenase 1	Aggrecan, collagen I, II, III, VII, X, XI, Fibronectin, Laminin, tenascin, IL-1β, pro-TNF
MMP2	Gelatinase A	Aggrecan, collagen I, III, IV, V, VII, X, XI, deocrin, elastin, fibronectin, gelatin, laminin, tenascin, IL-1β, pro-TNF, pro-TGFβ
MMP3	Stromelysin 1	Aggrecan, collagen III, IV, V, VII, IX, X, XI, deocrin, elastin, fibronectin, gelatin, laminin, tenascin, E-cadherin, IL-1β, pro-TNF
MMP7	Matrilysin	Aggrecan, collagen I, IV, deocrin, elastin, fibronectin, laminin, tenascin, E-cadherin, pro-TNF
MMP9	Gelatinase B	Aggrecan, collagen IV, V, XI, XIV, decorin, elastin, fibronectin, IL-1β, pro-TNF, pro-TGFβ
MMP12	Macrophage metalloelastase	Aggrecan, collagen I, IV, elastin, fibronectin, gelatine, laminin, pro-TNF
MMP14	MT-1 MMP	Aggrecan, collagen I, II, III, fibronectin, gelatine, laminin, pro-TNF

MMP expression following chemotherapy

The expression of MMPs following chemotherapy has not received a great deal of attention and the only attempts to clarify a role for MMPs in mucositis have been in patients receiving radiation therapy for head and neck tumours or allogeneic stem cell transplants [49, 50] where MMPs have not been shown to be altered in patients' saliva. Although there is a general lack of evidence for a role of MMPs in human and animal models of chemotherapy-induced injury, a role for MMPs has been described in cancer as well as inflammatory and degenerative processes, including rheumatoid arthritis, peridontitis and asthma. So it is plausible to suggest that MMPs may contribute to tissue injury and remodelling following cytotoxic chemotherapy.

A study published by Morvan and colleagues (2004) described the effects of an engineered biopolymer in preventing 5-fluorouracil-induced oral mucositis. Histopathological examination of tissue from animals administered with 5-fluorouracil (5-FU) demonstrated severe damage to the epithelium, connective tissue, muscle as well as the destruction of basement membranes [51]. Furthermore, an increase in the levels of MMP-activating plasmins, MMP-2 and MMP-9 and an accompanying decrease in TIMP-1 and TIMP-2 was observed [51]. Baseline levels of MMPs and TIMPs were maintained in animals that were given the biopolymer and this correlated with a significant reduction in severity of oral mucositis in the animals, thus providing further support for a role of MMPs in mucositis. Although this study investigated MMP and TIMP expression in oral mucositis, it is reasonable to suggest that similar expression patterns for those peptidases will be observed in the small intestine and colon following chemotherapy as the entire GIT (from mouth to anus) has the same embryological route of development thus sharing many commonalities [6].

Tissue injury and MMP synthesis

Although there is not sufficient data in the literature to explain all facets of MMPs function and contribution to the development and amplification of chemotherapy-induced tissue injury, there is growing evidence for an important role of MMPs in a variety of tissue injury models. In general, tissue injury, such as that caused by cytotoxic chemotherapy, triggers a range of signalling pathways which ultimately lead to the up-regulation of MMP expression [13]. Moreover, the signalling pathways that modulate MMP expression have been extensively researched [12, 52, 53]. It has been demonstrated that both MMPs and TIMPs respond to stimuli at the transcriptional level over a timeframe of several hours. This is suggestive of MMPs being components of genetic programs such as the wound repair response where they are downstream targets of immediate-early response genes that are induced within minutes of cell stimulation (Fig. 1) [12]. MMP promoter analysis studies have described the existence of a variety of functional elements on MMP promoters including binding sites for activator protein-1, Tcf/Lef-1 (site controlling Wnt signalling) and NFκB [12, 52–54]. MMP gene transcription studies have implicated MAPK signalling, NFκB signalling, Fos/Jun signalling and Wnt signalling in modulating MMP levels following injury [52, 55] and these have all shown strong association with mucositis development in animal models [9] as well as human studies [3].

Changes at the MMP gene transcription level is not the only mechanism by which MMP levels are increased following tissue injury. It has also been shown that an increased conversion of pro-MMP to MMP occurs in the ECM during tissue injury [13]. It is well established that leukocytes; which are recruited in response to unfavourable tissue stimulation, secrete oxidants [56]. According to the cysteine-switch mechanism proposed by Van Wart and Birkedal-Hansen, these oxidants have the ability to stimulate the modification of the free thiol on MMPs thus disrupting the thiol–Zn^{2+} interaction and resulting in a biologically active form of MMPs [32]. This type of MMP activation could therefore theoretically occur very early on following cytotoxic drug administration as ROS are produced following direct damage of chemotherapy to cells of the GIT.

MMPs and inflammation

Matrix metalloproteinases have been shown to contribute to the recruitment of inflammatory cells following primary tissue injury [25, 57]. Upon initiation of tissue injury, leukocytes are required to migrate across the endothelial cell barrier separating blood from tissue. This process involves complex morphological changes in leukocytes and the endothelial cell barrier as well as the formation of cell–cell and cell–matrix interactions. The process is mediated by high affinity binding of leukocytes to integrins and the induction of MMP-expressing injury response genes [25, 58]. Furthermore, MMP-2 and -9 have been shown to be up-regulated in effector leukocytes therefore facilitating their migration into the mucosa [58]. MMP-9 has also been implicated in neutrophil migration across blood vessel basement membranes [59].

A number of studies have documented the relationship between pro-inflammatory cytokines and MMP secretion [13, 55, 60]. A study conducted by Bamba et al. investigated the role of TNF, IL-1β and IL-17 on MMP3 secretion in colonic subepithelial myofibroblasts. Findings of this study suggested a causal relationship between an increase in pro-inflammatory cytokines and MMP secretion [60].

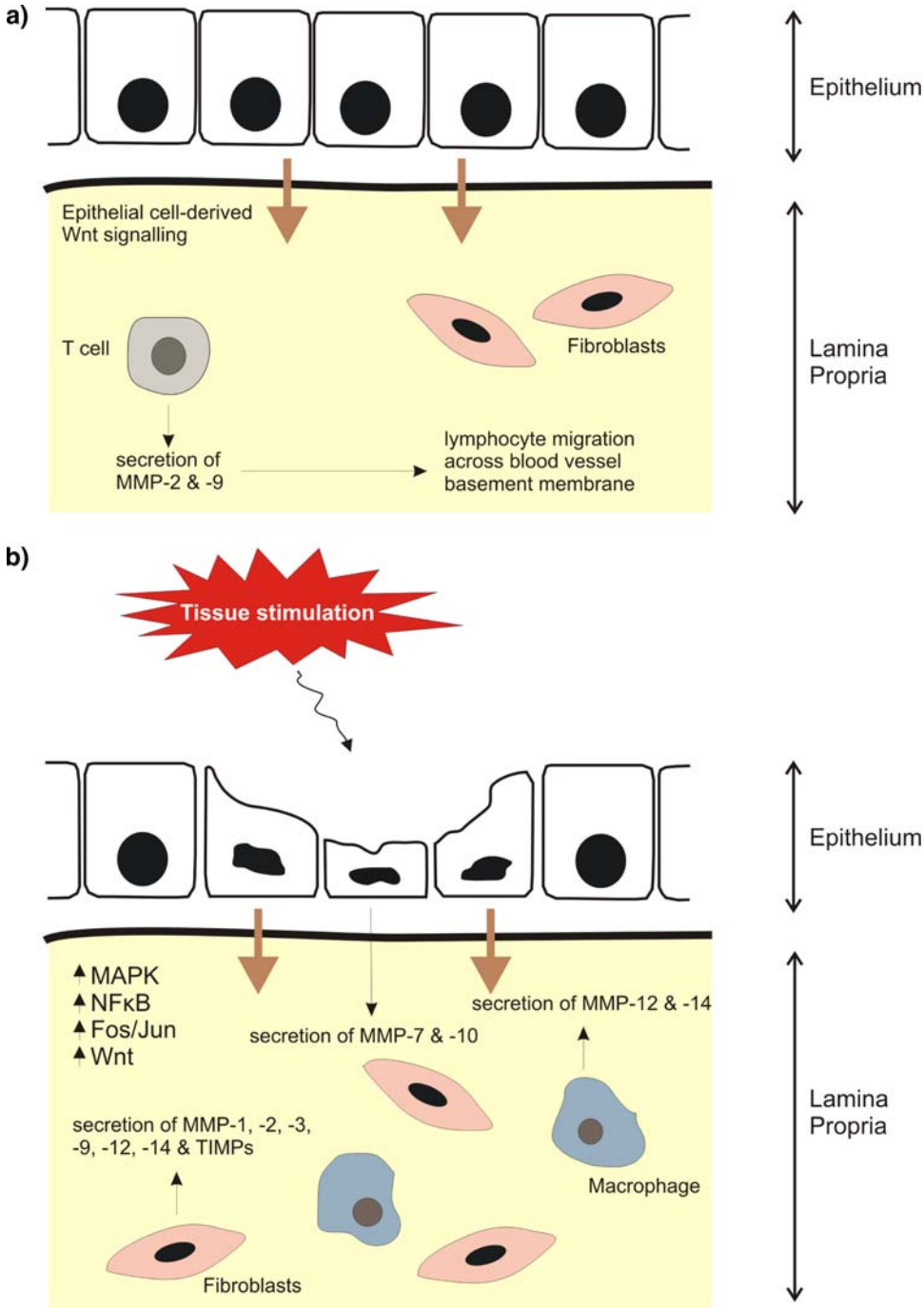

Fig. 1 Expression of MMPs in the **a** normal and **b** injured gut

Furthermore, MMPs have also been shown to mediate activation of pro-inflammatory cytokines in a positive-feedback manner [13]. TNF and IL-1β are expressed by T-cells and macrophages as pro-TNF and pro-IL-1β, respectively and require proteolytic processing to gain activity [13]. Moreover, several MMPs, including MMP-1, -2, -3, -9, -12, -14 and -17, have been shown to have TNF and IL-1β converting activity. The ability of MMPs to activate cytokines may therefore have implications in normal as well as pathological conditions, including those that occur in chemotherapy-induced mucositis.

Evidence for role of MMPs in mucositis

There is limited evidence in the literature for the modification of ECM components and the involvement of MMPs in the pathogenesis of mucositis. However, due to the already

established role of MMPs in numerous injury models, it is suggested that MMPs play a role in multiple phases of mucositis development.

Message generation and amplification phases

According to previous research, there seems to be some overlap of pathways that govern mucosal injury in the gut and MMP synthesis, in particular MAPK signalling, NFκB signalling, Fos/Jun signalling and Wnt signalling (Fig. 2). Moreover, independent studies have been undertaken to investigate the interplay between signalling systems and mediators of mucositis [9–11] and those that are required for the up-regulation of MMP expression [12, 13, 52, 53]. Previous studies have shown a role for ROS and the pro-inflammatory cytokines TNF and IL-1β in the message generation phase of mucositis [11] and the induction of MMP synthesis [60], separately, with no studies documenting a direct relationship between MMP synthesis and the development of AT mucositis. Furthermore, past studies have illustrated that MMPs proteolytically activate pro-inflammatory cytokines therefore provide positive feedback and amplifying the message generation phase.

Ulcerative phase

Sonis proposed that up-regulation of MMPs induced by injury response genes during the up-regulation and amplification phases of mucositis is responsible for some of the damage observed in mucosal and submucosal targets. The ulcerative phase of mucositis is characterised by breakage of the epithelial layer, influx of macrophages into the base of the lesion and possible bacterial colonisation [4].

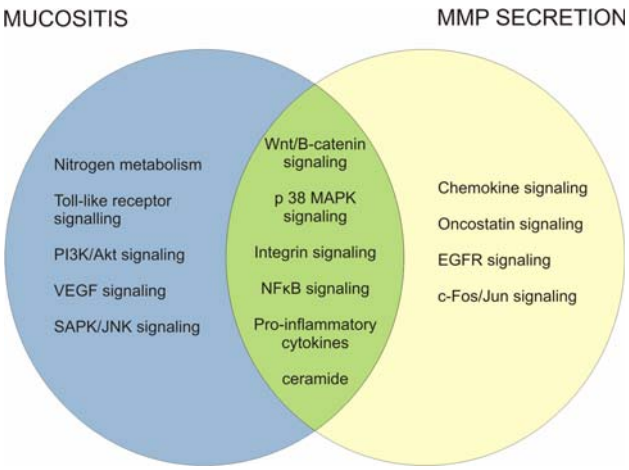

Fig. 2 Signalling pathways common to the development of mucositis and the secretion of MMPs

It is not clear what extent MMPs contribute to these events, however, an increase in MMPs could ultimately disrupt cell–ECM interactions thus leading to disregulation of cell proliferation, apoptosis and differentiation. Furthermore, an increase in MMPs, such as MMP-2, -9 and -12, could also lead to breaking of endothelial lining in mucosal and submucosal layers of the gut therefore mediating immune cell chemotaxis and local tissue inflammation.

Healing phase

Several MMPs have been shown to contribute to tissue restitution following injury. Furthermore, a study by Salmela et al. has shown that MMP-1, -7 and -10 are expressed by migrating enterocytes in an intestinal re-epithelialisation model [61]. MMP-3 has also been shown to contribute to wound healing as MMP-3 deficient mice fail to re-establish tissue integrity [62]. In wound healing models, MMPs have been suggested to control degradation of ECM components in order to allow cell migration and differentiation. Similarly, MMPs could contribute to tissue healing following chemotherapy-induced tissue damage.

Theoretical opportunities for intervention with MMP inhibitors

Cell–cell and cell–matrix interactions are vital biological processes; which have been shown to be compromised in many pathological conditions. MMPs are key enzymes in ECM degradation and therefore aberrant expression of these proteases leads to unfavourable biological events such as gut and respiratory inflammation, osteoarthritis, cancer metastasis and atherosclerotic plaque rupture. As a result, pharmaceutical companies have shown interest in the development of MMP inhibitors. There are two main classes of MMP inhibitors; namely broad spectrum MMP inhibitors and specific MMP inhibitors. Specific MMPs could potentially have a differential role in each stage of mucositis development, for example, MMP-2 and -9 are involved in damage onset while MMP-7 and -10 contribute to tissue repair following injury. Therefore, specific rather than broad spectrum MMP inhibitors should be investigated as possible therapeutic intervention. Currently, anti-mucotoxic drugs fall into four main categories; cell resistance modifiers, mechanism specific inhibitors, damage control agents and healing accelerators. Specific MMP inhibitors could potentially fall under ‘mechanism specific inhibitors’ where MMPs involved in tissue injury could be inhibited including MMP-2 and -9. However, this requires better characterisation of the specific MMPs involved in each phase of mucositis pathogenesis.

Conclusions

It has been previously shown that MMP expression and activation increases following tissue injury as a result of stress response gene up-regulation. Furthermore, an increase in tissue MMPs stimulates immune cell infiltrate and enhances cytokine activation. MMPs also degrade ECM components of the basement membrane and have the ability to impact cell proliferation, apoptosis and differentiation. Mucositis is characterised by inflammation as well as changes in cell kinetics, however, it is not known if these are associated with altered MMP expression. More definitive studies are required to elucidate the role of MMPs and ECM components in the histopathological and physiological alterations observed in gastrointestinal mucositis. However, it is hypothesised that MMPs will be shown to play a key role in mucositis development in the near future.

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