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REVIEW

Damage-associated molecular patterns in inflammatory bowel disease: From biomarkers to therapeutic targets

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Abstract

The chronic inflammatory process underlying inflammatory bowel disease (IBD), comprising Crohn's disease and ulcerative colitis, derives from the interplay of several components in a genetically susceptible host. These components include environmental elements and gut microbiota a dysbiosis. For decades, immune abnormalities have been investigated as critically important in IBD pathogenesis, and attempts to develop effective therapies have predominantly targeted the immune system. Nevertheless, immune events represent only one of the constituents contributing to IBD pathogenesis within the context of the complex cellular and molecular network underlying chronic intestinal inflammation. These factors need to be appreciated within the milieu of non-immune components. Damage-associated molecular patterns (DAMPs), which are essentially endogenous stress proteins expressed or released as a result of cell or tissue damage, have been shown to act as direct pro-inflammatory mediators. Excessive or persistent signalling mediated by such molecules can underlie several chronic inflammatory disorders, including IBD. The release of endogenous DAMPs amplifies the inflammatory response driven by immune and non-immune cells and

promotes epigenetic reprogramming in IBD. The effects determine pathologic changes, which may sustain chronic intestinal inflammation and also underlie specific disease phenotypes. In addition to highlighting the potential use of DAMPs such as calprotectin as biomarkers, research on DAMPs may reveal novel mechanistic associations in IBD pathogenesis and is expected to uncover putative therapeutic targets.

Key words: Damage-associated molecular patterns; Environmental factors; Epigenetics; Inflammatory bowel disease; Therapeutic targets

Core tip: Damage-associated molecular patterns (DAMPs) are basically endogenous stress molecules expressed or released as a consequence of cell or tissue damage. The release of endogenous DAMPs precipitates a secondary inflammatory response in inflammatory bowel disease (IBD), which may determine a self-sustaining chronic inflammatory process. DAMPs amplify the inflammatory response driven by immune and non-immune cells and promote several pathologic changes, which may be associated with specific disease phenotypes. Excessive or persistent DAMP-mediated signalling can result in epigenetic modifications, which may sustain chronic inflammation and also characterize IBD phenotypes. Preliminary studies targeting DAMPs have shown promising beneficial therapeutic effects both in human and experimental IBD.

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INTRODUCTION

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), constitutes a chronic inflammatory condition that primarily affects the gastrointestinal tract. Although the aetiology of IBD remains largely unclear, evidence to date supports a multifactorial background[1,2]. From a clinical perspective, IBD has been considered to be a heterogeneous condition, with a wide range of clinical manifestations that usually change throughout the course of the disease. Despite the remarkable accumulation of knowledge regarding disease mechanisms in the last decades, therapeutic options are still relatively scarce. Moreover, defining the best treatment for individual patients remains a challenge.

Within the context of chronic inflammation, particularly when severe injury ensues, the tissue damage occurring in cell death results in the release of a multitude of potentially pro-inflammatory endogenous molecules. Damage-associated molecular patterns (DAMPs) are such endogenous molecules released from cells in response to endogenous or exogenous stimuli. DAMPs can function as signalling mediators of stress responses and the immune response *via* specific membrane or intracellular receptors or after endocytic uptake[3,4]. DAMPs may originate from diverse cellular compartments, including the cytosol, nucleus, and mitochondria, and also from tissue components such as the extracellular matrix[5].

Evidence accumulated in the last decade indicates that abnormal signalling through receptors associated with DAMPs occurs in several diseases[6-8]. Such findings have attracted attention regarding the potential role of DAMPs in both IBD pathogenesis and clinical practice[9-12].

Here, we review mechanisms involving DAMPs in chronic intestinal inflammation and the potential use of DAMPs as biomarkers. Promising novel therapeutic targets for IBD are also discussed.

DAMPS AND THE INFLAMMATORY RESPONSE

The human body harbours an efficient defence system against potentially harmful elements in the environment. This protective mechanism is composed of several components, including cells programmed to combat exogenous elements utilizing a complex immunological system that consists of innate and adaptive responses. Cells of the innate immune system respond to a variety of molecules from different microorganisms known as pathogen-associated molecular patterns (PAMPs). Nevertheless, infectious and non-infectious challenges invariably result in host tissue damage, which directs the release of components normally found in intracellular compartments. Several molecules released into the extracellular milieu by damaged cells have been termed DAMPs[13,14].

DAMPs comprise various endogenous molecules that are capable of activating pattern recognition receptors (PRRs). DAMPs may be released after plasma membrane disruption secondary to several forms of cell death or may be actively secreted *via* non-classical pathways by cells under stress[15]. In addition to the ubiquitous origin of DAMPs, such as intracellular proteins and purinergic molecules in distinct sub-cellular compartments, DAMPs may also be derived from the extracellular matrix[5]. Although DAMPs are not recognized by the innate immune system under physiological conditions, extracellularly released DAMPs signal danger upon tissue damage and induce both inflammatory and repair processes[14]. However, within the context of significant tissue injury, the persistent release of DAMPs may fuel a stress-inflammation amplification loop that underlies the pathogenesis of several chronic inflammatory disorders.

PRRs can be activated by DAMPs within the scenario of "sterile inflammation", in which tissue damage occurs

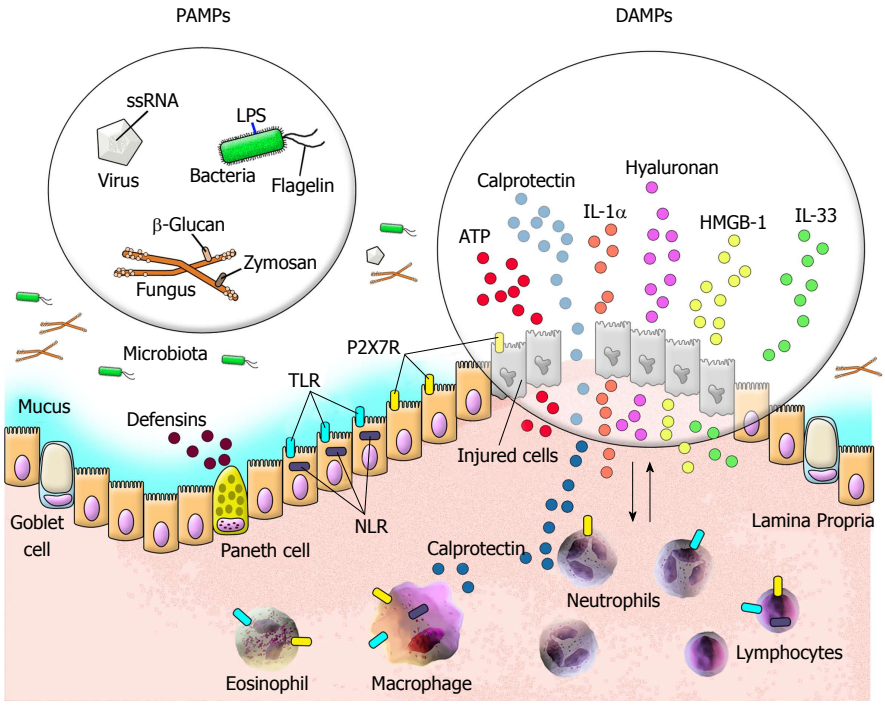

Figure 1 Participation of pathogen-associated molecular patterns and damage-associated molecular patterns in the induction of inflammatory responses in the intestinal mucosa. Pathogens such as viruses, bacteria and fungi present pathogen-associated molecular patterns that are able to stimulate cellular receptors such as toll-like receptors and nucleotide-binding and oligomerization domain-like receptors to promote the production of proinflammatory cytokines and recruitment of inflammatory cells. Upon tissue damage, injured cells release molecules known as damage-associated molecular patterns into the extracellular milieu to further stimulate and amplify the inflammatory response. TLR: Toll-like receptor; NLR: NOD-like receptor; IL: Interleukin; ATP: Adenosine triphosphate; DAMPs: Damage-associated molecular patterns; HMGB: High mobility group box; LPS: Lipopolysaccharide; PAMPs: Pathogen-associated molecular patterns.

in the absence of invasive microorganisms[16,17]. PRRs comprise several cell surface or endosomal receptors of four major types: Toll-like receptors (TLRs); cytoplasmic nucleotide-binding and oligomerization domain (NOD)-like receptors (NLRs) and inflammasomes; RIG-like receptors (RLRs); and C-type lectin receptors (CLRs)[18]. Although the precise mechanisms underlying the interaction between DAMPs and PRRs have yet to be clarified, it is interesting to note that regardless of their structural diversity, DAMPs and PAMPs are frequently recognized by the same receptors. After detecting PAMPs or DAMPs, PRRs activate intracellular signalling pathways, resulting in upregulation of pro-inflammatory genes and stimulation of mechanisms involved in the inflammatory response as well as antimicrobial actions[19] (Figure 1).

The pathways associated with NLR activation are poorly understood and remain under investigation. Nevertheless, two distinct mechanisms have been proposed: direct binding and indirect binding of PAMPs and DAMPs to receptors. These mechanisms are based on three models. The most studied model involves activation of the NLRP3 inflammasome, whereby the purinergic P2X7 receptor is stimulated by adenosine triphosphate (ATP), which triggers K^+ efflux and opening of the pannexin-1 pore. This allows passage of the NLRP3 agonist into the cytosol, leading to the direct activation of NLRP3[20] (Figure 2). The second model relates to the observation that crystalline and particulate structures can be phagocytosed and released into the cytosol following damage to the phagolysosome, thus directly activating NLRP3. The third model proposes that DAMPs and PAMPs induce production of reactive oxygen species (ROS), indirectly activating the inflammasome[21].

Overexpression of interleukin (IL)-1β and IL-18, as well as IL-18 and NLRP3 polymorphisms described in patients with CD, also supports the involvement of inflammasomes in IBD[22-24]. Studies using experimental models typically corroborate these findings. For instance, NLRP6-deficient mice develop spontaneous intestinal hyperplasia and show inflammatory cell recruitment and exacerbation of chemically induced colitis[25]. NLRP6 is highly expressed in the intestine; by preserving the integrity of the intestinal epithelial barrier, NLRP6 exhibits protective effects against the development of intestinal inflammation[26,27]. In accordance with these findings, most studies have reported that NLRP3-deficient mice are more likely to develop colitis[28,29]. However, another independent study has shown opposing results, suggesting a protective effect of NLRP3 deficiency against chemically induced colitis[30]. Independent of the exact role of the NLRP3 inflammasome in experimental colitis, the fact that NLRP3-, ASC-, and caspase-1-deficient mice do not develop colitis in the absence of chemical stimuli indicates that inflammasome impairment alone does not lead to intestinal inflammation[31]. Regardless, these data support the importance of PRR function in maintaining intestinal homeostasis and highlight the role of intracellular signalling *via* DAMPs in the pathogenesis

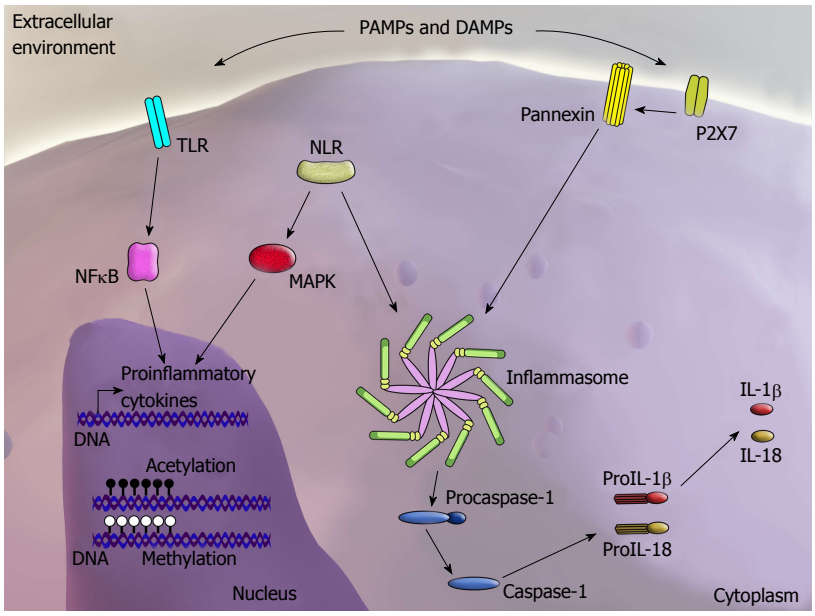

Figure 2 Intracellular signalling *via* damage-associated molecular patterns. Multiple mediators released by dying or stressed cells provide a secondary signal to amplify immune and inflammatory responses. Damage-associated molecular patterns (DAMPs) can activate proteins such as the purinergic receptor P2X7. P2X7 is capable of activating pannexin-1, a membrane channel involved in activation of the multiprotein inflammasome complex, promoting the inflammatory response. Immunological memory may develop via epigenetic reprogramming after exposure to pathogen-associated molecular patterns or DAMPs. This functional adaptation of the immune system may directly exacerbate inflammatory responses upon subsequent challenges. TLR: Toll-like receptor; NLR: NOD-like receptor; IL: Interleukin; NFκB: Nuclear factor kappa B; MAPK: Mitogen-activated protein kinase; PAMPs: Pathogen-associated molecular patterns.

of intestinal inflammation.

DAMPS IMPLICATED IN INTESTINAL INFLAMMATION

Several studies have contributed to our understanding of the role of DAMPs in IBD. DAMPs are currently thought to contribute to the development of intestinal inflammation, particularly *via* activation of lamina propria cells, which are directly involved in innate immunity[32]. In fact, several types of molecules identified as being involved during the course of IBD, such as calprotectin, lactoferrin, calreticulin, high-mobility group box 1 (HMGB1), ATP, IL-1α, IL-33, and fragments of the extracellular matrix, are considered DAMPs[5] (Figure 1). Below, we attempt to delineate the role of DAMPs in the pathogenesis of IBD by highlighting certain molecules and their potential importance as biomarkers of inflammatory activity and as therapeutic targets.

Calprotectin

Calprotectin, a calcium-binding protein belonging to the S100 family, is basically composed of S100A8 and S100A9 heterodimers. The S100 family comprises more than 20 members with multiple functions, with calprotectin typically being associated with intestinal inflammation. Calprotectin, which is also known as Mrp8/14, calgranulin A/B, and cystic fibrosis antigen, is commonly found in cells of the immune system, mainly in neutrophils but also in reactive monocytes and macrophages. This protein potentially functions as an antimicrobial agent[33-35]. During the inflammatory response, cells of the innate immune system release their intracellular contents into the extracellular milieu in a degranulation process; this results in increased concentrations of calprotectin at various body sites, including the intestinal lumen, and in faeces[36]. As a non-invasive tool to aid in the detection of intestinal inflammation, faecal calprotectin (FC) levels can be measured using enzyme-linked immunosorbent assays (ELISAs) or, more recently, a home-use kit associated with a smartphone application[37]. Such measurement has a relatively good correlation with clinical and endoscopic results in patients with UC[38] and in those with CD, for which FC has also been used to monitor the risk of disease relapse[39].

Lactoferrin

Lactoferrin, which binds iron, is an indicator of neutrophil degranulation and acts as an alarmin[40]. Because lactoferrin is relatively resistant to degradation and proteolysis, it can be measured in stool and serve as a biomarker of intestinal inflammation. Thus, lactoferrin has been utilised to differentiate functional diseases from IBD. However, similar to calprotectin, lactoferrin has been most highly correlated with colonic inflammation, as opposed to ileal activity[41].

Calreticulin

Calreticulin (CRT) is a calcium-binding protein and an endoplasmic reticulum (ER)-resident lectin-like chaperone that is induced by ER stress[42]. In addition, CRT has been shown to induce ER stress accompanied by a significant increase in proteasome activity[43]. Recently, CRT has

been recognized as a potent DAMP capable of influencing homeostasis through immune regulation. In this regard, new evidence has indicated that CRT can translocate to the cell surface and serve as a signal for immune-mediated cell death[44]. Moreover, a significant decrease in the basal transcriptional activity of nuclear factor kappa B (NF-κB) has been observed in CRT-deficient cells. In an experimental model of inflammation, the tubular epithelial cells of rats subjected to unilateral ureteric obstruction showed an upregulation of CRT[45].

HMGB1

In contrast to cellular components and endogenous DAMPs such as DNA, RNA, and ATP, another subset of intracellular proteins released from necrotic cells also appears to participate in sterile inflammatory processes. These proteins, including members of the IL-1 family such as IL-1α, IL-33, and HMGB1, are characteristically bifunctional, acting as cytokines and performing yet-unclear nuclear functions[46]. In contrast to the signalling mediated by DAMPs, which are usually recognized by PAMP receptors such as TLRs, activation of the HMGB1 signalling pathway occurs through interaction with several cell surface receptors. As a result, HMGB1 exerts effects on a multitude of processes, including cell proliferation, survival and death, as well as inflammation[47,48].

HMGB1 is a DNA-binding protein that may be translocated to the cytoplasm when cellular stress occurs. During chronic inflammatory processes, high rates of cellular necrosis result in the abundant release of HMGB1 into the extracellular milieu. As a consequence, extracellular HMGB1 participates in the induction of intestinal epithelial cell autophagy[49], increased expression of adhesion molecules, and secretion of proinflammatory cytokines and chemokines[50,51].

HMGB1 levels have been shown to be elevated in the dextran sodium sulphate (DSS)-induced colitis model[52]. In addition, genetically modified HMGB1-deficient mice (Vil-Cre Hmgb1$^{fl/fl}$) had more apoptosis of intestinal cells following induction of colitis with DSS[53].

IL-1α

IL-1α is an IL-1 family member synthesized as a precursor protein (pIL-1α) with a molecular weight of approximately 31 kDa that may be cleaved into mature 17-kDa forms. The two forms are biologically active and serve as ligands for the receptor IL-1R1[54]. These proteins are constitutively expressed in different immune cells as well as in intestinal epithelial cells[55]. IL-1α expression is upregulated in response to growth factors or to pro-inflammatory or stressful stimuli; the molecule then is translocated from the cytosol to the nucleus, where it acts as a pro-inflammatory transcription factor[54]. For example, upon stimulation with lipopolysaccharide (LPS) or tumor necrosis factor alpha (TNFα), IL-1α translocates to the nucleus to promote expression of inflammatory genes, including IL-8 and IL-6[56]. However, cells undergoing necrosis can release pIL-1α, which results in cell chemotaxis and inflammation[57]; therefore, pIL-1α functions as a DAMP. In fact, in the extracellular milieu, IL-1α appears to induce a pro-inflammatory response *via* binding with IL-1R1[58].

With regard to chronic intestinal inflammation, high levels of IL-1α have been detected in lamina propria mononuclear cells from patients with IBD[59] and in supernatants of colonic explant cultures from CD or UC patients[11]. In experimental colitis, release of IL-1α from damaged intestinal epithelial cells has been associated with the initiation and propagation of colonic inflammation[60]. IL-1α has also been shown to amplify gut inflammation in experimental colitis by inducing cytokine production in mesenchymal cells[61].

IL-33

IL-33 is a member of the IL-1 cytokine family that is predominantly expressed in stromal cells and in the epithelium lining surfaces in contact with the environment[62]. Primarily is described as a proinflammatory cytokine that induces the Th2 immune response and is involved in defence against parasitic infections. IL-33 has also been proposed as an inducer of Th1 cells, group 2 innate lymphoid cells, regulatory T (Treg) cells, and CD8$^+$ T cells[63]. In addition, IL-33 may act as a signalling molecule that alerts the immune system to danger or tissue damage[64]. IL-33 localises to the nucleus; however, once released into the extracellular milieu upon membrane disruption, it may act as a dual-function alarmin, similar to HMGB1 and IL-1 alpha[65].

IL-33/ST2 signalling in the gut has been implicated in the pathogenesis of inflammatory processes. In fact, abnormal expression of IL-33/ST2 has been detected in the inflamed mucosa of patients with IBD, as well as in experimental models of chemically induced colitis[66]. Because a predominant Th2 immune response underlies UC pathogenesis, several studies have attempted to investigate the role of IL-33 in this specific condition. For example, investigators found a significant increase in mucosal IL-33 mRNA expression in patients with active UC compared to healthy controls. Moreover, a significant reduction in IL-33 was detected after anti-TNF therapy, thus supporting the notion that enterocyte-derived IL-33 is induced and maintained by the inflammatory milieu[67].

ATP

Under normal conditions, nucleotides such as ATP are present in high concentrations intracellularly. However, upon stimulation by different stresses such as necrosis, apoptosis, hypoxia, or pathogen invasion, cells may release nucleotides into the extracellular milieu. ATP in the extracellular environment is thought to act as a messenger and behave as a danger signal capable of modulating immunity and inflammation[68] *via* activation of transmembrane receptors known as P2 receptors. The family of P2 receptors comprises P2Y (G-coupled proteins) and P2X (ionic channels)[69]. Among all P2 family members, P2X7 receptors, which are expressed

Table 1 Findings on the role of damage-associated molecular patterns in human and experimental inflammatory bowel diseases

DAMP	Human IBD	Experimental IBD
Calprotectin	Increased levels in the intestinal lumen and stools in both UC and CD[36,38,39]	-
Lactoferrin	Mostly correlates with colonic inflammation[41]	Beneficial therapeutic effects in colitis models[93,94]
Calreticulin	Related to inflammatory activity[44]	-
HMGB1	Increased levels in the stools of both adult and paediatric IBD patients[113]	Increased levels in DSS-induced colitis mice[52]
IL-1 alpha	Increased levels in the lamina propria of both UC and CD[59]	Associated with colonic inflammation initiation and amplification[60,61]
IL-33	Increased levels in the inflamed intestinal mucosa of IBD patients, especially in UC[66,67]	Increased levels in chemically induced colitis[66]; beneficial effects upon ST2 blockage[121]
ATP-P2X7	Overexpressed in IBD patients, particularly in CD[74]	Increases intestinal inflammation in chemically induced colitis[75]; P2X7-deficient mice essentially do not develop intestinal inflammation[74]
S 100 proteins	Increased faecal[95-98], mucosal[99], and serum[99-101] levels	
HSPs	Increased levels[102-105]	Beneficial therapeutic effects in colitis models[106]
Galectins	Increased serum levels in UC and CD[107]	Galectins 1 and 2 show anti-inflammatory action[108,109] Galectin 4: Antibody blockage reduces inflammation[110]
Hyaluronan	ECM components accumulate in the colon of IBD patients[82], particularly in UC[115]	ECM components accumulate in experimental colitis tissues[83]

DAMPs: Damage-associated molecular patterns; IBD: Inflammatory bowel disease; CD: Crohn's disease; UC: Ulcerative colitis; HSPs: Heat shock proteins; ECM: Extracellular matrix; IL: Interleukin; HMGB1: High-mobility group box 1.

on different cell types such as monocytes, macrophages, dendritic cells, lymphocytes, neurons, fibroblasts, and epithelial cells, have been studied the most[70].

Upon activation, ATP-P2X7 signalling promotes the release of pro-inflammatory cytokines such as IL-1β and IL-18[71], stimulates free radical production, and participates in cell cycle regulation and apoptosis induction[69]. We previously showed that the P2X7 receptor is positively modulated by IFN-gamma in intestinal epithelial cells[72] and that its activation induces apoptosis and autophagy *via* ROS production[73]. With regard to human IBD, we showed that P2X7 receptors are overexpressed in inflamed colonic mucosa, particularly in CD patients[74]. Moreover, we demonstrated that P2X7 receptors promote intestinal inflammation by triggering the death of mucosal regulatory T cells[75]. In addition, we found that systemic blockade of P2X7 receptors prevents the development of chemically induced colitis in rats[76], whereas P2X7-deficient mice essentially do not develop intestinal inflammation[74]. Taken together, these findings strongly support a role for ATP-P2X7 signalling in the pathogenesis of IBD and may offer avenues for the development of inflammatory biomarkers and new therapeutic options.

Extracellular matrix components and hyaluronan

The extracellular matrix (ECM) comprises a complex and dynamic non-cellular network that is present within all tissues. The ECM provides the architectural structure for cellular components and a microenvironment for the chemical and mechanical interactions necessary for tissue homeostasis. Although the ECM basically consists of water, proteins and polysaccharides, its composition is tissue specific[77]. Proteoglycans permeate most of the interstitial space within a tissue[78], and in the gastrointestinal tract, hyaluronan is a highly prevalent proteoglycan component of the ECM[79].

Hyaluronan, a non-sulphated glycosaminoglycan that interacts with different proteins, including ECM components and membrane receptors[80], has been shown to induce leukocyte recruitment in the extravascular space within the context of intestinal injury[81]. In fact, hyaluronan accumulates in the vicinity of infiltrating leukocytes in the colon, both in human IBD[82] and in experimental colitis tissues[83]. Under normal conditions, hyaluronan exists as a high molecular weight molecule that may function as an anti-angiogenic factor[84], prevent immune cell recognition, and block phagocytosis by macrophages[85,86]. In addition, high molecular weight hyaluronan prevents T cell-mediated liver injury[87] and promotes the persistence of tolerogenic regulatory T cells[88] in experimental models.

Conversely, hyaluronan displays an altered distribution in inflammatory settings and consists of a variety of polymers with different lengths and functions[89,90]. Small fragments resulting from hyaluronan degradation have been implicated in activation of the innate immune response *via* TLR2, whereas the intact hyaluronan molecule is capable of inhibiting activation of the same receptor[91]. In another study, investigators observed that fibroblasts from CD patients produce high levels of KIAA1199, a protein responsible for excessive hyaluronan degradation, which leads to the generation of pro-inflammatory fragments, potentially enhancing inflammation[92].

Table 1 summarises information on specific disease phenotypes and also presents details on human and experimental studies.

DAMPS AND EPIGENETIC REPROGRAMMING

Recent progress in epigenetics has suggested that ge-

nome modifications may be more dynamic than previously thought. For instance, immune cells, including monocytes and macrophages, and epithelial cells are known to promote an inflammatory response upon LPS stimulation. This phenomenon involves the reprogramming of cell-specific gene expression, which can occur through different mechanisms, including epigenetic modifications[111,112]. Nevertheless, in the case of LPS, epigenetic modifications are likely not exclusively associated with the acute response but also may be associated with the establishment of epigenetic memory, thus impacting the future response mediated by exposure to new microorganisms[113]. In parallel, tissue damage per se is known to induce a local inflammatory response, which may be followed by subsequent regenerative processes involving macrophages and other immune cells as well as non-immune cells[114]. In such circumstances, similar to the events that follow microbial stimulation[115], cells of the innate immune system develop immunological memory *via* epigenetic reprogramming after exposure to non-microbial ligands[116]. This functional adaptation of the immune system may direct exacerbated inflammatory responses upon subsequent challenges and may explain the long-term reprogramming of inflammatory genes induced by endogenous DAMPs[117] (Figure 2).

Atherosclerosis, a fundamental mechanism underlying most cardiovascular diseases and progressively recognized as an inflammatory disorder, is one ubiquitous example of epigenetic reprogramming. Indeed, the inflammatory nature of atheromatous plaques comprises interaction between elements such as modified low-density oxidized lipoproteins functioning as DAMPs and macrophage foam cells filled with cholesterol droplets; these foam cells produce chemokines that attract additional circulating leucocytes to atherosclerotic plaques[118]. Evidence for an epigenetic background underlying the atherogenic phenotype has been demonstrated by the observation that macrophages trained by exposure to beta-glucan display transcriptional activation at several loci encoding both inflammatory mediators and genes directly associated with basic metabolic processes in the development of atherogenesis[119]. In fact, the hypothesis that trained monocytes/macrophages may become pro-atherogenic has been further confirmed by the demonstration that oxidized LDL can train primary human monocytes to upregulate expression of proinflammatory cytokines, PRRs and LDL receptors[120].

Due to their wide range of participation in several disorders that directly or indirectly involve the immune system, regulatory T cells (Tregs), a subset of $CD4^+$ T cells that play a fundamental role in peripheral immune tolerance, continue to attract attention. New progress in this field points to potential Treg immune plasticity and regulation by receptors for PAMPs and DAMPs[121-123] as well as to the epigenetic regulation of Treg phenotypes and functions[124]. In light of these relatively novel findings, Yang *et al*[125] proposed an innovative concept in which Tregs might be subjected to re-shaping from a physiological phenotype into a pathological phenotype within the setting of diverse pathological conditions. Based on a similar line of evidence, macrophages are known to polarize into distinct phenotypes *in vitro* upon exposure to different stimuli; *in vivo*, these cells respond to signals, including PAMPs and DAMPs, that control their homeostatic functions[126,127]. Recently, polarization of macrophages in response to complex tissue damage and wound repair signals has been associated with expression of Rev-erb nuclear receptors. Interestingly, Rev-erbs repress subsets of genes activated by TLR ligands, IL-4, TGF beta, and DAMPs. Thus, Rev-erbs have been postulated to function as key molecules integrating signalling pathways involved in tissue injury to promote a wound repair phenotype[128].

The recent discovery that CRT possesses transacetylase activity, which is involved in a critical post-translational modification capable of shaping epigenetic regulation and signal transduction, suggests additional roles for CRT in diseases involving immune regulation. In this sense, CRT can also be considered a potential target for the development of anti-inflammatory therapies based on semi-synthetic acetyl donors such as polyphenolic acetates and related agents[129].

The above considerations represent a first attempt to relate the ability of endogenous signals such as DAMPs to promote trained immunity to IBD, offering a new principle for understanding the chronic and persistent nature of the inflammatory process that occurs in IBD. In the near future, the detailed epigenetic scenario in each IBD phenotype may become even more relevant, thus allowing for new therapeutic approaches directed towards the mediators or enzymes involved in the induction of relevant epigenetic modifications.

DAMPS AS BIOMARKERS AND THERAPEUTIC TARGETS

In light of the inconsistency among the currently available tests and the cost and potential risks of invasive procedures, contributing to a scenario of remarkable clinical variability, biomarkers of gut inflammation in IBD have been persistently investigated in recent decades. In addition, the fluctuating course of IBD creates a demand for more precise predictors of clinical outcomes to inform therapeutic decisions. In particular, the quantification of inflammatory activity, identification of specific disease behaviours, and prediction of responses and adverse effects due to a certain medication appear critical for the appropriate management of IBD.

Currently, FC and lactoferrin have been utilized as indicators of intestinal mucosal inflammation; together with other clinical and imaging approaches, these indicators, despite their limitations, contribute to the diagnosis and follow-up of patients with IBD[130]. Nonetheless, several other DAMPs have been proposed as promising

biomarkers for IBD[5].

Among IL-1 family proteins, HMGB1 released following cellular necrosis has been detected in chronically inflamed intestinal tissues and found abundantly in the stool of both adult and paediatric patients[131]. Notably, faecal HMGB1 has been supported as a reliable biomarker of intestinal inflammation; it significantly correlates with FC and may identify histological inflammation in IBD patients in clinical and endoscopic remission[132].

Another IL-1 family member, IL-1α, has been detected in the supernatants of intestinal explant cultures from patients with IBD[11]. IL-33, another member of the IL-1 family, is also released in the extracellular milieu upon cell or tissue damage, and it has been detected in the inflamed mucosa of IBD patients[66].

Because CRT is involved in processes related to inflammatory activity and translocates to the cell surface and signals immune-mediated cell death, CRT is both a DAMP[44] and a potential biomarker. In another category of DAMPs, a positive correlation between high concentrations of serum-derived hyaluronan-associated protein and intestinal inflammation has been found in intestinal samples and serum from experimental colitis models and patients with IBD, particularly those with UC[133]. Therefore, hyaluronan and possibly other ECM components are emerging as relevant DAMPs in intestinal inflammation and potential new biomarkers for IBD.

Considering the relatively disappointing results of current IBD therapies, one of the limitations of orthodox drug development is the lack of consideration of crucial aspects already known about IBD pathogenesis[134,135]. In this regard, DAMPs constitute interesting, underexplored factors, even though they are not the primary causative agents of IBD. Regardless, targeting DAMPs as a novel therapeutic approach for IBD appears to be an arduous but fascinating task. As such, current strategies propose to block the release of DAMPs, to inhibit their downstream signalling pathways, or to interfere with factors that may modulate the pathogenicity of the molecules involved[5].

Data regarding strategies targeting DAMPs for the treatment of inflammatory disorders are fundamentally based on results from *in vitro* studies and those involving experimental models. For example, tubular epithelial cells have been shown to overexpress CRT in a model of ureteral obstruction[45], and the association of CRT with renal fibrosis progression based on *in vitro* and *in vivo* approaches appears to implicate CRT in the molecular mechanisms that drive renal fibrosis progression[136]. Together, these studies suggest that CRT may become a new therapeutic target for fibrosis in chronic inflammatory disorders.

In chemically induced experimental colitis, HMGB1 targeting *via* either neutralizing antibodies or small molecules has been successful[137,138]. In addition, blockade of receptor for advanced glycation end products (RAGE), which is a receptor for multiple DAMPs, virtually suppresses inflammation in genetically predisposed IL-10-deficient mice, *i.e.*, a model of colitis[139]. Mitochondrial DNA (mtDNA), which shares many similarities with immunogenic bacterial DNA and is also recognized as a DAMP, is increased in the plasma of patients with UC and CD, and levels were significantly correlated with inflammatory mediators and endoscopic evidence of inflammation. Therefore, the investigators proposed that mtDNA may become a new biomarker for disease activity and that mtDNA-TLR9 may be a new therapeutic target in IBD[140].

With regard to IL-33, blockade of ST2 is reportedly beneficial in experimental models of chemically induced colitis[141]. From a clinical perspective, while the therapeutic success observed in animal studies targeting IL-33 ST2 may foster future trials directed towards IBD, specifically for patients with UC, and human studies have shown that loss of IL-33 expression in colonic crypts may be a useful marker of disease remission in UC[67]. Although the exact pathophysiologic importance of these findings has yet to be established, evidence supports dichotomous functions for the IL-33/ST2 pathway in IBD: The ability to enhance Th2 and Th17 responses in gut-associated lymphoid tissues while also stimulating mucosal healing following inflammatory tissue damage.

Recently, in the first phase Ⅱa study designed to assess the efficacy and safety of AZD9056, a selective orally active inhibitor of the purinergic receptor P2X7, for CD, investigators showed a beneficial risk profile with improvement of symptoms in patients with moderate-to-severe disease. However, changes in inflammatory biomarkers among patients with CD were not detected[142]. Although the beneficial effects observed in that study will likely prompt the development of new trials for CD, some specific points concerning the therapeutic use of P2X7 antagonists are noteworthy. Based on our previous experience with P2X7 blockade in experimental colitis, purinergic activation induces the death of Tregs[75], and the beneficial therapeutic effect is characteristically associated with prophylactic treatment, particularly when administered systemically[76]. Such discrepancies might be related to the specific actions of the ATP-P2X7 pathway during the course of the inflammatory process and also to the effects of purinergic signalling in epithelial versus immune cells of the intestinal mucosa.

Hyaluronan accumulation in the intestine of patients undergoing IBD flares[82] and excessive production of ECM fragments, especially smaller polymers, are likely to fuel chronic inflammatory conditions such as IBD[92]. Nevertheless, it is interesting to note that some DAMPs may have a dual role in innate immune defence. In the case of hyaluronan, it has been demonstrated that large molecules may provide protective effects mediated by CD44 and TLR4 in experimental IBD[143]. Furthermore, these molecules may act in host defence at the epithelial cell surface, thus promoting antimicrobial peptide production and improving regulation of the tight junction barrier in the gut[144].

CONCLUSION

In recent years, considerable advances have been achieved with regard to the pathogenic mechanisms in IBD.

However, a complete understanding of IBD pathogenesis will likely depend on more precise recognition and assimilation of the molecular and environmental constituents and the mechanisms by which they interact. In addition to potential use as practical biomarkers, proinflammatory activities and emerging roles in chronic inflammatory processes, including the ability to induce epigenetic modifications, DAMPs remain interesting targets for new discoveries about and innovative therapies for IBD.

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