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REVIEW

Involvement of heat shock proteins in gluten-sensitive enteropathy

Erna Sziksz, Domonkos Pap, Gábor Veres, Andrea Fekete, Tivadar Tulassay, Ádám Vannay

Erna Sziksz, Tivadar Tulassay, Ádám Vannay, MTA-SE, Pediatrics and Nephrology Research Group, H-1083 Budapest, Hungary
Erna Sziksz, Domonkos Pap, Gábor Veres, Tivadar Tulassay, Ádám Vannay, First Department of Pediatrics, Semmelweis University, H-1083 Budapest, Hungary
Andrea Fekete, MTA-SE, "Lendulet" Diabetes Research Group, H-1083 Budapest, Hungary
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Correspondence to: Erna Sziksz, PhD, MTA-SE, Pediatrics and Nephrology Research Group, Bokay Janos utca 53-54, H-1083 Budapest, Hungary. sziksz.erna@med.semmelweis-univ.hu
Telephone: +36-1-3343186 Fax: +36-1-3138212
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Abstract

Gluten-sensitive enteropathy, also known as coeliac disease (CD), is an autoimmune disorder occurring in genetically susceptible individuals that damages the small intestine and interferes with the absorption of other nutrients. As it is triggered by dietary gluten and related prolamins present in wheat, rye and barley, the accepted treatment for CD is a strict gluten-free diet. However, a complete exclusion of gluten-containing cereals from the diet is often difficult, and new therapeutic strategies are urgently needed. A class of proteins that have already emerged as drug targets for other autoimmune diseases are the heat shock proteins (HSPs), which are highly conserved stress-induced chaperones that protect cells against harmful extracellular factors. HSPs are expressed in several tissues, including the gastrointestinal tract, and their levels are significantly increased under stress circumstances. HSPs exert immunomodulatory effects, and also play a crucial role in the maintenance of epithelial cell structure and function, as they are responsible for adequate protein folding, influence the degradation of proteins and cell repair processes after damage, and modulate cell signalling, cell proliferation and apoptosis. The present review discusses the involvement of HSPs in the pathophysiology of CD. Furthermore, HSPs may represent a useful therapeutic target for the treatment of CD due to the cytoprotective, immunomodulatory, and anti-apoptotic effects in the intestinal mucosal barrier.

Key words: Gluten-sensitive enteropathy; Coeliac disease; Heat shock proteins; Gluten-free diet; Intestinal barrier

Core tip: The only current effective therapy for the treatment of coeliac disease (CD) is a gluten-free diet. However, therapies targeting heat shock proteins (HSPs) for the treatment of various autoimmune disorders and cancers have been developed and have shown promising results. As CD is an autoimmune disorder, these new therapies may prove beneficial as an alternative treatment strategy. This review highlights and discusses recent data concerning the involvement of HSPs in the pathophysiology of CD.

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INTRODUCTION

Coeliac disease (CD), or gluten-sensitive enteropathy, is an autoimmune inflammatory disorder characterized by partial or total villous atrophy and crypt hyperplasia of the small intestine in genetically predisposed patients. Ninety-five percent of affected individuals carry one of two specific human leukocyte antigen (HLA) class II alleles, either DQ2 (HLA-DQA1*05-DQB1*02) or DQ8 (HLADQA1*03-DQB1*0302)[1-4]. Since dietary gluten and related prolamins are present in different types of cereals (wheat, barley and rye), medicines, and various other products, including stamp and envelope adhesives, a lifelong exclusion of gluten presents a considerable challenge for patients with CD[5,6]. Although the worldwide incidence of CD has continued to increase over the past decade, most cases remain undiagnosed[7]. The increased incidence suggests that the disease manifestation is similar to that of other immune-mediated diseases, such as inflammatory bowel disease (IBD), allergies or asthma, and results from a combination of genetic predisposition and environmental factors. This hypothesis is supported by the fact that CD is often first detected following physical and emotional stress, such as from surgery, pregnancy, or viral infection[8]. Heat shock proteins (HSPs) are known to exert immunomodulatory effects, and have thus been targeted for the treatment of autoimmune disorders. Recent evidence suggests that the expression of HSPs is altered in CD. This review presents and discusses the role of HSPs and various stress factors in the pathophysiology of CD.

EFFECT OF STRESS ON THE PATHOGENESIS OF CD

Stress represents an acute threat to an organism, which initiates and mediates the physiological adaptations necessary to maintain homeostasis and ensure survival[9]. Stress can be caused by intrinsic factors, such as genes and endoplasmic reticulum stress, or extrinsic factors, such as heat, toxins, radiation, infection, mechanical force and metabolic disturbances. Stress factors affecting the gastrointestinal tract may induce inflammation and reduce its motility[10], resulting in disrupted mucosal integrity and impaired epithelial barrier function[11,12]. Such changes can lead to the development of CD in genetically predisposed individuals[13].

In CD, the transport of incompletely digested wheat gluten peptides, such as gliadin, across a damaged epithelial layer into the lamina propria[14] triggers oxidative stress and the release of pro-inflammatory cytokines[15]. However, gluten can induce adaptive as well as innate immune responses, such as enhancing the production of interleukin (IL)-15 in epithelial cells, which also leads to cell damage through the activation of intraepithelial cytotoxic CD8+ T-cells[16,17]. Activated transglutaminase 2 enzymes in the lamina propria[18] deamidate neutral glutamine residues of gluten, thus creating epitopes with increased immunostimulatory potential[16]. These deamidated peptides are presented to CD4+ T-helper cells by the disease associated HLA-DQ2 and -DQ8 molecules from macrophages, dendritic cells (DCs) and B lymphocytes[19], which promote the differentiation of B-cells producing anti-gliadin and anti-transglutaminase 2 antibodies[20]. T-cells may also produce pro-inflammatory cytokines, such as tumour necrosis factor (TNF)-α and interferon (IFN)-γ, and activate intestinal fibroblasts leading to further damage of the epithelial cell layer, mucosal matrix degradation and tissue remodelling[18]. Moreover, gliadin peptides can directly activate pattern recognition receptors such as Toll-like receptor (TLR) 2 and 4 on macrophages and DCs[21], leading to a further upregulation of proinflammatory cytokines and chemokines[22] (Figure 1). These inflammatory effects of stress lead to additional aggravation of the disease[23].

DEFENSE AGAINST STRESS: ROLE OF HSPs

Stress results in the activation of various proteins such as proteolytic system components, RNA/DNA modifying enzymes, metabolic enzymes, regulatory, transport, detoxifying and membrane-modulating proteins, and molecular chaperones, or HSPs[24]. HSPs were first discovered in *Drosophila melanogaster* in the early 1960s[25], and have since been observed in all organisms after exposure to cellular stresses[26], such as heat, UV light, cytotoxic agents[27,28], and nutritional (*e.g.,* the absence of glucose and glutamine)[29] and oxidative stress[30]. HSPs are expressed in many tissues, including heart[31], brain[26], muscle[32], lung[33], kidney[34], liver[35], and intestinal and colonic epithelium[36]. These highly conserved molecules are responsible for maintaining adequate protein folding[37] and influencing the degradation of proteins[38] and cell repair processes after damage[39]. Furthermore, HSPs are involved in the modulation of immune responses[40,41], autoimmunity[27], cell signalling[42], cell proliferation[43], apoptosis[44], and tumour cell differentiation and invasion[45]. Based on their molecular weight they can be classified into six major families: small HSPs (molecular weight < 30 kDa), HSP60s, HSP70s, HSP90s, HSP100s[24,46], and other non-ubiquitous HSPs[47] (Table 1).

Oxidative stress and HSPs

Environmental and chemical agents inducing oxidative stress can enhance the generation of reactive oxygen species (ROS)[48,49]. In CD, gluten itself can promote the generation of ROS by stimulating the expression of the inducible form of nitric oxide synthase (iNOS) and increasing nitric oxide levels[50,51]. This process contributes to subsequent mucosal damage and villous atrophy of the small intestine[52]. Interestingly, these same oxygen-free radicals, such as superoxide, also induce the expression of various HSPs which take part in the defence against oxidative stress[53]. The inducible form of HSP70 (HSP70i) reduces iNOS expression by specifically binding to iNOS

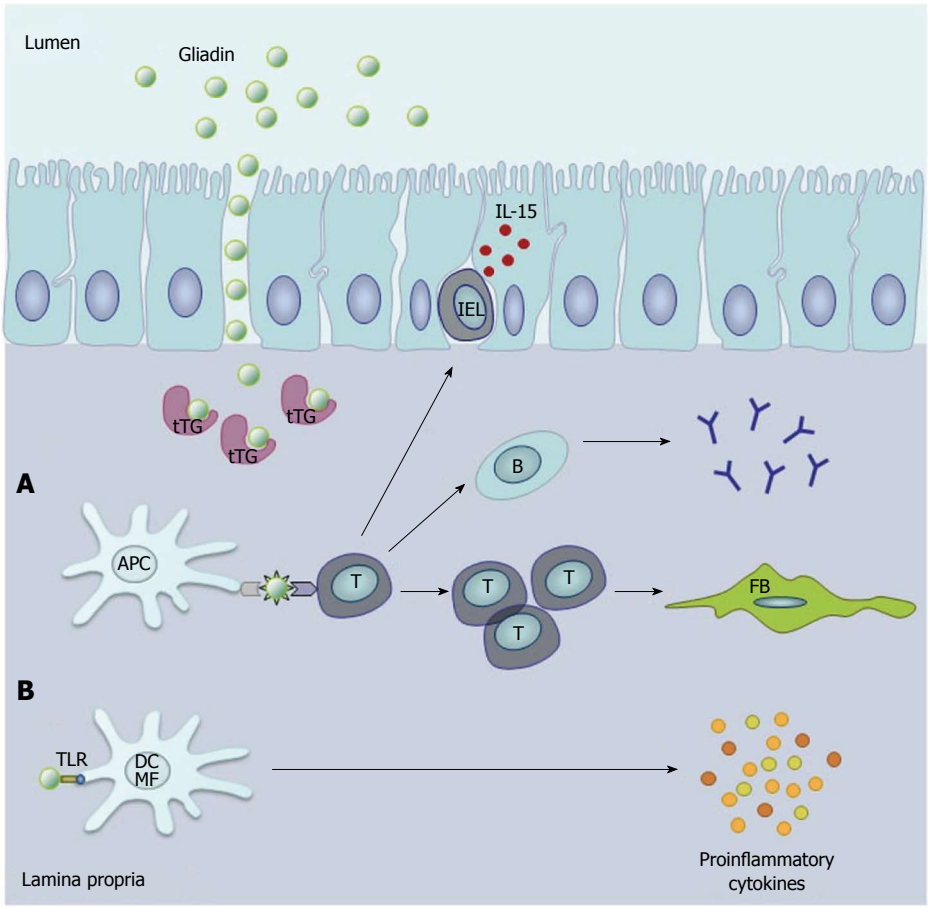

Figure 1 Key processes during the pathogenesis of coeliac disease. In the lamina propria. A: Gluten-derived gliadin peptides deamidated by tissue transglutaminase (tTG) are presented to T-cells by antigen presenting cells (APC). This process leads to the activation of anti-gliadin and anti-tTG antibody producing B-cells and other T-cells promoting the activation of intestinal fibroblasts (FB). Furthermore, gliadin enhances the production of IL-15, which activates intraepithelial T lymphocytes (IEL); B: Gliadin peptides can directly activate Toll-like receptor (TLR) 2 and 4 on macrophages (MF) and dendritic cells (DC), resulting in increased production of proinflammatory cytokines (Reproduced with permission from Sziksz *et al*[1]).

Table 1 Classification of heat shock proteins[46,113]

Family	Subunit MW (kDa)	Family members	Cellular localization
HSP100	80-110	HSP100, HSP104	Cytoplasm, nucleus, mitochondria, plasma membrane
HSP90	82-96	HSP90α, HSP90β	Cytoplasm, nucleus, mitochondria, endoplasmic reticulum
HSP70	67-76	HSP70, HSP72, HSP73, HSP80	Cytoplasm, nucleus, mitochondria, endoplasmic reticulum, lysosomes, extracellular compartments
HSP60	58-65	HSP60, HSP65	Mitochondria
Small HSPs	8-40	αB-crystallin, HSP25, HSP27, ubiquitin	Cytoplasm, nucleus
Others (not ubiquitous)	Various	HSP33	Various

MW: Molecular weight; HSP: Heat shock protein.

and its transcription factor Krueppel-like factor 6[54]; moreover, its upregulation was shown to inhibit nuclear factor (NF)-B activation, thereby providing cellular protection against stress[55]. In addition, glutamine-induced HSP72 was shown *in vivo* to protect against endotoxin-induced shock injury[56], and HSP90 has been shown to exert antioxidative and anti-apoptotic effects against chemical-induced hypoxic injury[57]. HSP60 contributes to the protection of small intestine by enhancing the cytoprotective function of intestinal epithelial cells against H_2O_2-induced injury[58]. Finally, HSP32, also known as heme oxygenase-1, degrades heme into vasoactive carbon monoxide, free iron and biliverdin, and is also a potent antioxidant[59].

Inflammation and HSPs

HSPs can act as "danger signals" for the immune system at sites of tissue injury[60]. HSPs were shown to contribute to antigen presentation and the proliferation and activation of macrophages and DCs[61], and natural killer cells[62]. HSP70 and HSP90 bind to TLRs on the surface of DCs and macrophages[63] resulting in enhanced expression of pro-inflammatory cytokines[64,65], and HSP60 stimulates the release of TNF-α, IL-12, and IL-1β, *via* TLR 4 signalling[66]. However, HSP60 can also activate anti-inflammatory processes through TLR 2 signalling,

upregulating the suppressive function of regulatory T-cells and shifting the cytokine secretion balance toward a Th2 phenotype[67,68], suggesting that the immunomodulatory effect can be cell and receptor type specific.

Altered expression of HSPs has been associated with intestinal inflammation. An increased epithelial expression of HSP70, HSP60 and HSP10 was observed in the colonic mucosa of patients with IBD[69,70]. This upregulation may be protective, as Tanaka *et al*[71] demonstrated that transgenic mice overexpressing HSP70 showed reduced apoptosis and suppressed expression of pro-inflammatory cytokines after dextran sulfate sodium-induced colitis. HSP47, a collagen-specific molecular chaperone, was also found in mesenchymal and submucosal cells in a murine model of colitis[72].

Apoptosis and HSPs

Apoptosis is essential for the maintenance of intestinal epithelial function, as it regulates the normal turnover of enterocytes[73]. The increased apoptosis of enterocytes in CD contributes to villous atrophy, which is mediated either by the direct toxicity of gliadin domains or by the gliadin-dependent activation of intraepithelial and lamina propria lymphocytes[74]. Gliadin-induced apoptosis can be blocked by Fas cascade inhibitors[75], although the activation of the Fas system can also contribute to cell survival in the gut by inducing the expression of HSP72 and HSP72-driven chemokines[76]. HSP70 can also promote cell survival by inhibiting the mitochondrial translocation of Bax and subsequent release of cytochrome c and activation of caspase-9 and -3[77,78], an intrinsic apoptotic pathway that is initiated by intracellular stress signals[79]. Furthermore, HSP70 is a natural inhibitor of c-Jun N-terminal kinase[80] and is also a modulator of the calcium signalling that play major roles in the regulation of apoptosis[80-83]. Furthermore, HSP60 has been identified as a novel mitochondrial permeability transition regulator. HSP60 is a component of a mitochondrial multi-chaperone complex that includes HSP90 and its related molecule TNF receptor-associated protein 1, which associates with and antagonizes the pro-apoptotic, mitochondrial permeability transition pore modulator, cyclophilin D, thereby contributing to the preservation of organelle integrity and prevention of cell death[84,85].

Intestinal epithelial integrity and HSPs

The intestinal mucosa forms a barrier that is essential for defending the intestine against the harmful effects of different stressors. Oxidative stress, inflammation and increased apoptosis all lead to mucosal damage and increased permeability[86]. The integrity of the epithelial barrier is determined by an apical junctional complex composed of tight and adherent junctions[87]. During heat stress, HSPs play a pivotal role in the preservation of the intestinal barrier by promoting the upregulation of the tight junction protein occludin[88,89]. HSP70s protect intestinal epithelial cells by preserving the integrity of the actin cytoskeleton and cell-cell contact, and HSP72 directly binds and stabilizes other tight junction-associated proteins on colonic epithelial cells, such as zonula occludens[90]. Other HSPs, including members of the HSP110 subfamily, have also been shown to bind to junctional proteins[91]. Tissue integrity is also influenced by matrix metalloproteinases (MMPs)[92], which have been observed as increased in intestinal tissues of patients with CD[93]. Extracellular HSP90α was shown to activate MMP-2, which was enhanced by HSP70 and HSP40, leading to increased cell migration[94]. HSP60 may also induce MMP production in macrophages[95].

HSPs AND CD

HSPs are differentially expressed throughout the gastrointestinal tract, with gastric and colonic epithelial cells showing high expression of HSP25 and HSP72, likely the result of continuously low acidic pH, mechanical stress and/or bacterial fermentation[96]. In contrast, the expression of HSPs in the small intestine is normally negligible[97], but the expression of HSP25 and HSP70 is markedly increased under stress[88]. The predominant localization of HSPs in intestinal epithelial cells suggests their primary role is in maintaining the integrity of the enterocyte layer, as demonstrated by Kojima *et al*[98] who showed that Bacteriodes fragilis treatment of young adult mouse colonocyte cells increased the expression of HSPs mediated by lipopolysaccharide and other bacteria-derived factors. Using horseradish peroxidase to evaluate human intestinal epithelial permeability, Yang *et al*[99] found that heat stress increased transport across an epithelial monolayer, which was inhibited by pretreatment with HSP70. Asea[65] and Cario *et al*[100] provided further supporting evidence by showing that HSP70 can behave as a ligand for TLR 2 and TLR 4[101], the activation of which can contribute to the maintenance of intestinal barrier function by preserving the integrity of tight junction proteins, such as zonula occludens 1, under stressful conditions.

The role of HSPs in the pathophysiology of CD is not well understood, owing in part to the lack of experimental models. However, our lab has shown increased mRNA and protein expression of HSP72 in the duodenal mucosa of children newly diagnosed with CD[102]. The most abundant expression of HSP72 was in villous enterocytes of the epithelium and immune cells of the lamina propria. Clinical symptoms were reduced with a gluten-free diet (GFD), which also reduced the level of intestinal HSP72, though levels were still higher than in control individuals. In contrast, Brottveit *et al*[103] reported that suspension of a GFD for three days did not alter the mRNA expression of HSP70 or HSP27 in the mucosa of adult CD patients. This apparent discrepancy may be due to the difference in patient age, or in the experimental setting, for example, comparing the effect of dietary gluten elimination in newly diagnosed CD patients *vs* the return of dietary gluten in patients maintained on a long-term GFD. Iltanen *et al*[104] found elevated expression of mitochondrial HSP65 in 80% of jejunal biopsies

Table 2 Involvement of heat shock proteins in coeliac disease

Samples	Investigation	Localization/major findings	Ref.
Duodenal biopsies from 16 children with newly diagnosed CD, 9 maintained on GFD, 10 controls	HSP72 mRNA expression, protein level and localization	HSP72 mRNA and protein are increased in CD, and decreased by GFD. HSP72 was localized in villous enterocytes of the epithelium and lamina propria immune cells	[102]
Duodenal biopsy specimens from 30 HLA-DQ2 (+) NCGS and 15 CD patients maintained on GFD	HSP27 or HSP70 mRNA expression, before and after challenge with gluten-containing bread daily for 3 d	mRNA expression of HSP27 and HSP70 in the duodenal mucosa was not different in any of the groups	[103]
Jejunal biopsies from 78 children with clinical suspicion of CD	Epithelial HSP65 expression	Increased mitochondrial HSP65 expression in the jejunal mucosa in 80% (16/20) of children with CD and in 24% (14/58) of non-CD patients. Strong correlation between HSP65, γδ + T-cells and serum IgA endomysial autoantibodies. HSP65 is a potential mucosal integrity modulator	[104]
Duodenal biopsies from 12 patients with CD and 10 controls	Small HSP αB-crystallin expression and distribution	Increased αB-crystallin in CD, localized in the supra-nuclear region of enterocytes in the duodenal mucosa	[105]
Blood samples from 128 patients with CD and 94 healthy individuals	*HSPA1A* gene (HSP70-1) polymorphism	Altered frequency of an intermediate HSPA1A allele in CD (64.5%) *vs* normal (37.2%). HSP70-1 gene is part of a high-risk haplotype for CD	[106]
Blood samples from 19 families with CD patients and 95 healthy individuals	HLA-linked *HSPA1B* gene (HSP70-2) polymorphism	Altered *HSPA1B* allele frequencies in CD *vs* normal and non-affected MHC haplotypes	[107]

CD: Coeliac disease; GFD: Gluten-free diet; HSP: Heat shock protein; NCGS: Non-coeliac gluten sensitivity; Ig: Immunoglobulin; HLA: Human leukocyte antigen; MHC: Major histocompatibility complex.

from children diagnosed with CD compared to 24% of specimens from children with a normal biopsy. The levels of HSP65 correlated with the number of + T-cells and serum IgA endomysial autoantibodies, suggesting that HSP65 may be an indicator of disease activity. Yeboah *et al*[105] examined the duodenal mucosa of CD patients and found a close correlation between the distribution of the small HSP αB-crystallin and the degree of villous atrophy, indicating its involvement in the modulation of mucosal integrity.

Single nucleotide polymorphisms in the 5' regulatory region of the gene encoding HSP70-1 (*HSPA1A*) have been linked with CD. Ramos-Arroyo *et al*[106] found a significantly higher frequency of an *HSPA1A* allele showing an intermediate electrophoretic mobility in patients with CD. Individuals expressing CD-associated HLA alleles that were homozygous for this intermediate *HSPA1A* allele were 12-fold more likely to develop CD, indicating that *HSPA1A* polymorphisms are an additional predisposing factor for CD as a component of a high-risk haplotype. Partanen *et al*[107] found significantly deviated gene frequencies of the *HSPA1B* (HSP70-2) gene cluster in 19 families of patients with CD compared to that of a normal population, indicating that a polymorphism of the HLA-linked *HSPA1B* gene may be involved in the pathophysiology of CD. The main scientific findings indicating involvement of HSPs in CD are summarized in Table 2.

HSPs AND THERAPEUTIC TREATMENTS

Although promising results have been found using HSP-based vaccines for the treatment of cancer patients[108], relatively little is known about the therapeutic potential of HSPs in the treatment of gastrointestinal diseases. There is evidence to suggest, however, that targeting of HSPs would be beneficial. The anti-ulcer drug geranylgeranylacetone (GGA) that reduced colitis in a mouse model was found to induce the intestinal expression of HSP70 and to suppress myeloperoxidase activity and reduce TNF-α and IFN-γ levels[109]. Furthermore, it was demonstrated that the upregulation of HSPs by GGA is protective against intestinal damage from non-steroidal anti-inflammatory drugs such as indomethacin[110]. Indeed, overexpression of HSP70 in mice decreased the number of indomethacin-induced apoptotic cells and the level of proinflammatory cytokines and chemokines (IL-1β, IL-6) in the small intestine, suggesting that HSP70 is protective and can reduce the extent of small intestinal lesions[36]. A strong correlation between the expression of HSPs and the advantageous effects of probiotics in IBD has also been suggested[111], and probiotics containing eight different naturally occurring strains of "beneficial" bacteria may induce the expression of HSP25 and HSP72 in colonic epithelial cells[88]. Moreover, probiotic *Lactobacillus GG* induces the expression of HSP72 in intestinal epithelial cells, contributing to the beneficial clinical effects through preservation of cytoskeletal integrity[112]. These data suggest that HSP-inducers are promising drugs to treat gastrointestinal diseases, including CD, or ameliorate their symptoms.

CONCLUSION

HSPs are a class of highly conserved, stress-induced chaperones that are responsible for proper protein folding and regulating protein degradation, cell repair, immune responses, cell signalling, cell proliferation, apoptosis, and tumour cell differentiation. The increased expression of various HSPs observed in CD suggests that their antioxidant and anti-apoptotic features are protective. Furthermore, HSPs may be involved in the pathophysiology of CD through their immunomodula-

tory effects, serving as "danger signals" for the immune system at sites of tissue injury.

Intrinsic apoptotic pathways initiated by intracellular stress signals can be blocked by HSPs, which likely contributes to the maintenance of intestinal homeostasis. HSPs suppress the expression of iNOS and reduce the level of nitric oxide, thereby providing cellular protection against stress. HSPs are also involved in tissue repair and remodelling by regulating the production of matrix metalloproteinases in the intestine, which are increased in patients with CD. In conclusion, HSPs appear to influence the key features of CD through their contribution to the maintenance of mucosal barrier integrity, inhibition of apoptosis, and regulation of inflammatory processes. Therefore, therapies targeting the expression of HSPs in the intestinal mucosa should be pursued for the treatment of inflammatory gastrointestinal diseases.

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