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Mini review

Role of heat shock proteins (molecular chaperones) in intestinal mucosal protection

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Abstract

Most studies into the pathogenesis of inflammatory bowel diseases (IBD) have primarily focused on the cytotoxic agents and processes involved in producing mucosal injury, including the immune system. However, less consideration has been given to the inherent mechanisms of cytoprotection and cellular repair in the intestinal mucosa. This review will focus on intestinal mucosal protection against cytotoxic agents and cellular stress mainly from the viewpoint of expression and function of heat shock proteins, in their role of "molecular chaperones," as internal cytoprotectants. Elucidation of such stress-responses in the intestinal mucosa may provide a better understanding of the mechanisms of cytoprotection and cellular repair, and present new strategies for IBD therapy.

Keywords: Heat shock protein; Molecular chaperone; Stress; Colon; Intestine; HSP; IBD; Crohn's disease; Ulcerative colitis

It had generally been assumed that the folding of newly synthesized polypeptides *in vivo* occurs spontaneously, without the need for accessory proteins or metabolic energy, as unfolded proteins had been shown to achieve their native conformations spontaneously *in vitro* [1]. Now, however, the folding of many newly synthesized polypeptides and degenerate peptides in the cell is considered to be assisted by a class of proteins (molecular chaperones) that function mainly to prevent off-pathway folding reactions that lead to aggregation. Mammalian heat shock proteins (HSPs) are classified into four families as shown in Table 1. Such HSPs, also referred to as molecular chaperones, are ubiquitous and highly conserved proteins from prokaryotic to eukaryotic cells in which they are rapidly induced in response to abrupt and adverse changes in their environment [2,3]. These HSPs are therefore considered to serve essential functions in cell survival and developmental processes. Recent *in vivo* studies, including ours, have provided further evidence of the cytoprotective functions of HSPs against environmental stresses and cytotoxic materials, and suggested that these functions are important for living cells to acquire tolerance to adapt environmental changes or pathogenic conditions in digestive organs [4–8].

With regard to the pathogenesis of mucosal injury, the balance between mucosal defense and the attacking agents or processes involved in producing the mucosal injury is considered important, especially in the context of the widely accepted "balance theory" [9] in the pathogenesis of gastric mucosal injury. In the gastric mucosa, HSPs, especially a 70-kDa heat shock protein (HSP70), have been known to protect gastric mucosa from toxic agents and ulcerogenic conditions [4,7,10,11]. Recently, HSPs, as intracellular cytoprotectants, have also been considered important in the epithelial cells of colonic mucosa [12–17]. In this review, we have mainly therefore focused on studies demonstrating the protective functions of HSPs in the colonic and small intestinal mucosa (Table 2).

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Table 1
Major HSP families in mammalian cells and their sub-cellular localization, functions and associated proteins [3]

HSP family	Subunit molecular mass (kDa)	Stress (−) → Stress (+)	Function, association
HSP90 family			
HSP100 (GRP94)	100	ER → ER	Glucose-regulated
HSP90α	86	CP → CP	Steroid receptors
HSP90β	84	CP → CP	Actin, p60v-src, FKBP52
HSP70 family			
HSP80 (GRP80)	80	ER → ER	Immunoglobulin
HSP75 (GRP75)	75	MIT → MIT	Glucose-regulated
HSP73 (HSC70)	73	CP → NUC	Protein folding (non-specific)
HSP72 (HSP70)	72	CP, NUC → NUC	Protein folding (non-specific)
HSP60 family	58, 60	CP, MIT → MIT	Protein folding (non-specific)
Small HSP family			
HSP47	47	MIT, CP → MIT, CP	Collagen specific
HSP32	32	CP, peri-NUC → CP, NUC	Heme oxygenase-1, degradation
HSP25	25	CP → CP	f-actin, αβ-crystallin
HSP8 (ubiquitin)	8	CP, MEMB → CP, MEMB	PDGF, histone

GRP, glucose-regulated protein; ER, endoplasmic reticulum; CP, cytoplasm; NUC, nucleus; MEMB, membrane; MIT, mitochondria; PDGF, platelet-derived growth factor.

Table 2
Induction and cytoprotective functions of HSPs in intestinal epithelial cells

HSP	Condition	Disease model	Function	Reference
HSP70	Hyperthermia, Zn, GGA	Acetic acid, DSS, TNBS	Protective	[12,20,16,17]
HSP60	Stress, TRH, 5-HT (colon and small intestine)	Acetic acid, Indomethacine	Non-protective	[25–27]
HSP32	Hyperthermia (small intestine)	Ischemia/reperfusion	Protective	[22]
HSP25	Short chain fatty acid, LPS	Oxidative stress (monochloramine)	Protective	[13–15]
HSP90	Cancer cells		Tumor growth, Anti-apoptosis	[43,44]
	Hyperthermia	Acetic acid	Non-protective	[12]

GGA, geranylgeranylacetone; TRH, thyrotropin-releasing hormone; 5-HT, 5-hydroxytryptamine; LPS, lipopolysaccharide; DSS, dextran sulfate sodium; TNBS, 2,4,6-trinitrobenzene sulfonic acid.

Regulation mechanism of heat shock proteins

The regulatory mechanisms of HSPs are summarized in Fig. 1 [3]. Environmental stresses induce the heat shock transcription factor (HSF), primarily HSF-1. The accumulation of aggregated or denatured proteins in the cytosol is thought to trigger the induction of HSF-1 as the first step in the stress response. Trimer formation of phosphorylated HSF-1 activates its movement into the nucleus where it binds to stimulate promoter lesion (heat shock element) and induce HSP gene expression. The produced HSPs subsequently bind to degenerated proteins, aggregated proteins, and newly synthesized polypeptides. On the other hand, formation of a HSP–HSF complex suppresses HSF-1 production in a negative feed-back regulatory system.

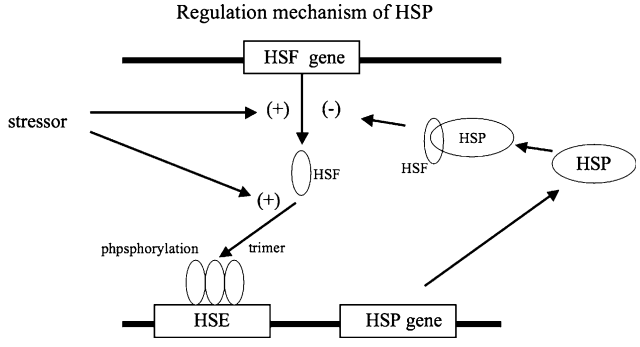

Fig. 1. Environmental stresses induce heat shock transcription factors (HSF), mainly HSF-1. The accumulation of aggregated or denatured proteins in the cytosol appears to trigger the induction of HSF-1 as the first step in the stress response. Trimer formation of the phosphorylated HSF-1 then activates its movement into the nucleus where it binds to stimulate the promoter lesion heat shock element (HSE) and to induce HSP gene expression.

HSP70 family

Cytosolic 70-kDa HSPs are present in cells as two different, but closely related, gene products: the stress-inducible form, HSP72 (known as HSP70), and a constitutively expressed form, HSP73 (known as the 70-kDa heat shock cognate protein, HSC70) (Table 1) [2]. In gastric mucosa, HSP70 has been demonstrated to have important cytoprotective functions both *in vitro* and *in vivo* [4,10,18,19]. We reported, for the first time, that preinduction of HSP70 (HSP72; stress-inducible HSP70) by systemic hyperthermia protected colonic mucosa from acetic acid-induced

mucosal damage in rats [12]. In this study, the contribution of other major HSPs, such as HSP60 and HSP90, to epithelial cytoprotection was minor since the cytoprotective ability was not related to expression of these two HSP families. We have also reported that HSP-induction, by intra-rectal administration of zinc derivatives (zinc L-carnosine), enhances the protective functions of colonic mucosa through NF-κB inactivation [20]. The results of our studies have been corroborated by other recent reports. For example, Ohkawara et al. reported that the induction of colonic HSP70 by zinc derivatives or geranylgeranylacetone (GGA) suppressed the severity of dextran sulfate sodium-induced colitis (DSS) or 2,4,6-trinitrobenzene sulfonic acid (TNBS) colitis in mice [16,17].

In the small intestinal mucosa, we have demonstrated that systemic hyperthermia induces HSP70 and HSC70 (heat shock cognate, HSP73). However, pre-induction of these proteins did not provide cytoprotective functions for small intestinal damage caused by indomethacin [21]. Recently, Sakamoto et al. reported the possible contribution of HSP70 to mucosal protection with co-induction of HSP32 (heme oxygenase-1) against ischemia/reperfusion injury in the rat small intestine [22]. These differences may depend on the severity of the experimentally induced lesions. More precise studies are required to elucidate the role of HSP70 in the small intestinal mucosa.

Thus, the importance of HSP70 as an internal cytoprotectant in the colonic mucosa has been amply demonstrated and is now widely accepted, especially as induction of HSP70 by different methods provides enhanced cytoprotective ability to various toxic agents. Furthermore, induction of colonic HSP70 by non-toxic agents, such as zinc L-carnosine [16,20] or geranylgeranylacetone [17], may be important for the development of new therapeutic strategies for colonic inflammatory diseases.

HSP60 family (chaperonin homolog)

The chaperonin, GroEL (58 kDa)/GroES (10-kDa co-chaperone), is the only chaperone system in *Escherichia coli* that is essential for growth [23]. The chaperonin mediates the folding of polypeptide chains in an ATP-dependent reaction. We reported for the first time the purification of a functional HSP60 from mammalian tissues (rat liver cytoplasm and mitochondria) [24]. Amino acid sequence analysis demonstrated that the cytoplasmic HSP60 had an N-terminal signal sequence that was absent from the mitochondrial HSP60. Both proteins however are known to possess chaperone activity *in vitro* and also *in vivo*. We have further reported that cytoplasmic HSP60 could act as a cytoprotectant in pancreatic acinar cells [8]. In the colonic mucosa, we found that HSP60 is specifically induced by increments of colonic motility or ischemia induced by 5-hydroxytryptamine (5-HT), thyrotropin-releasing hormone (TRH), or water-immersion stress. In contrast to HSP70 induction, however, specific pre-induction of HSP60 did not protect the colonic mucosa from acetic acid-induced mucosal damage [25,26]. Therefore, in the colonic mucosa, HSP60 and HSP70 have different functions in terms of chaperone-mediated cytoprotection.

Furthermore, in the small intestinal mucosa, HSP60 is specifically induced, with two peaks, by increments of intestinal motility or ischemia induced by TRH, 5-HT or water-immersion stress [27]. Small intestinal HSP60s have been reported to possess no cytoprotective ability against acetic-acid perfusion-induced mucosal damage [27]. What then is the role of HSP60 in the intestinal mucosa? HSP60 has been reported to act as a mediator in the intestinal immune system and in its modulation [28–30], although the specific details are beyond the scope of this review.

Other HSP families

HSP25

HSP25 is a member of the small HSP family that is expressed in nearly all organs under physiological conditions and which is also rapidly induced upon stress activation [31]. HSP25 has important chaperone properties similar to GroE/HSP60 and the HSP70 family, especially in the kidney and muscle. Overexpression of HSP25 has been shown to increase survival in response to a wide variety of potentially lethal agents [32]. Chang's group has vigorously examined the importance of this protein in colonic epithelial cells, and reported that specific induction of HSP25 by short chain fatty acids, interleukin-11 or lipopolysaccharide (LPS) protects colonic mucosa or cultured mucosal epithelial cells from oxidative stress damage [13–15]. Their series of studies emphasize that HSP25, in addition to the HSP70 family, could be a key chaperone in intestinal epithelial cells.

HSP32 (heme oxygenase-1)

Heme oxygenase (HO) is a crucial mediator of antioxidant and tissue-protective activities [33,34]. HO catalyzes the first step in the degradation of heme to carbon monoxide, iron, and biliverdin, which is immediately reduced to bilirubin. These products have important physiological effects; carbon monoxide is a potent vasodilator, and biliverdin and bilirubin are potent antioxidants [35]. The HO family consists of three distinct isoenzymes, HO-1, HO-2, and HO-3 [31]. HO-1, also known as a 32-kDa heat shock protein (HSP32), is widely distributed throughout the body and shows high levels of expression in the liver, spleen, and bone marrow. HSP32 is expressed in the gastric and intestinal mucosa, and is known to have tissue-protective activities in the gastric mucosa [36–39].

Sakamoto et al. reported that hyperthermia-induced HSP32 is the main contributor to cytoprotection against small intestinal mucosal damage following ischemia/reperfusion in rats [22]. This study, in which the administration of zinc protoporphyrin IX (HO-1 inhibitor) was shown to

reduce the protective effects of hyperthermia preconditioning, may be the first report demonstrating chaperone-mediated cytoprotection in the small intestinal mucosa.

HSP90

HSP90 functions as a multiprotein chaperone complex together with several co-chaperones, including HSP70, HSP40, and the HSP-organizing protein (HOP) [40]. This intermediate complex forms a mature chaperone complex containing p23, which catalyzes the conformational maturation of "client protein" substrates [41,42]. Numerous client proteins of the HSP90 chaperone heterocomplex are known to be involved in cell-cycle regulation, and in various signal-transduction and apoptotic pathways, including the EGFR signal transduction system and the Akt signalling pathway [43]. Recent studies of HSP90 have, therefore, focused on the contribution of HSP90 to tumorigenesis [44].

In a study evaluating the cytoprotective ability of HSP90, we reported that HSP90 expression did not correlate with the cytoprotective ability of the colonic mucosa against acetic acid-induced mucosal lesions [12]. Furthermore, Stahl et al. reported that there was no difference in HSP90 expression between normal and inflamed mucosa in human IBD, including Crohn's disease and ulcerative colitis [45].

Conclusions

This review has focused on intestinal mucosal protection against cytotoxic agents or cellular stress mainly from the viewpoint of the expression and function of heat shock proteins as internal cytoprotectants.

Many HSP families have been reported to possess cytoprotective abilities, as mediated by their chaperone functions, that are important for cell survival. As discussed in this review, some HSP families also play crucial roles in intestinal epithelial cells, and possess specific properties and expression patterns. We consider it essential to understand these differences in order to apply the unique characteristics of HSPs, as non-specific internal cytoprotectants, to chaperone-inducing therapy for disease treatment. Indeed, some diseases are considered to be the result of a dysfunction or decrease in molecular chaperones (chaperone diseases). We have also reported that antibiotic gentamicin-induced renal toxicity could be caused by the specific binding of this antibiotic to HSC70 (HSP73) and the consequent reduction in chaperone functions [46]. Some other cause-unknown diseases, including particular digestive diseases, may also result from such mechanisms. Binding substances that reduce chaperone functions may include drugs, chemicals, toxins, denatured proteins or peptides in the category of "chaperone-diseases." The elucidation of these post-genomic phenomena in the intestinal mucosa may provide us with a better understanding of the mechanisms of cytoprotection and cellular repair and create new strategies for the therapy of IBD.

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