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EDITORIAL

HSPA4, the "Evil Chaperone" of the HSP Family, Delays Gastric Ulcer Healing

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Even with the availability of potent anti-ulcer therapies such as histamine type 2 receptor antagonists or proton pump inhibitors, some patients suffer from ulcer recurrence or ulcer complications such as lack of healing or hemorrhage, prompting the formulation of a new concept addressing the quality of ulcer healing (QoUH), which incorporates the functional restoration of the mucosal architecture and the incidence of ulcer recurrence. Based on these observations, several gastroprotective agents were developed such as sucralfate, rebamipide, ecabet sodium in addition to potent phytoceuticals [1]. Gastric ulcer healing incorporates well-defined, interacting molecular and cellular repair processes such as epithelial cell proliferation and re-epithelialization, formation of granulation tissue, angiogenesis, matrix and tissue remodeling, and fine scar formation; all of these are orchestrated by coordinated release of growth and transcription factors. In addition to these repair mechanisms, circulating bone marrow-derived stem and progenitor cells and molecular chaperones is potentially important for ulcer healing, accelerating the regeneration of epithelial and connective tissue components [2]. In the stomach, there are three major components of gastric defenses, including a pre-epithelial mucus–bicarbonate–phospholipid barrier, an epithelial barrier composed of surface epithelial cells connected by tight junctions generating mucus, bicarbonate, phospholipids, trefoil peptides, prostaglandins, and heat shock proteins (HSPs) undergoing continuous cell renewal, and a subepithelial, endothelial barrier including sensory innervation, molecular acid sensors, and nitric oxide release [3]. As an additional fourth line of defense, the mucosal immune system, consisting of mast cells and macrophages, also significantly contributes to the inflammatory response to mucosal substances (Fig. 1).

Among these comprehensive defensive and ulcer healing mechanisms, HSPs were recently implicated as contributing to intracellular gastric defense. HSPs are a class of functionally related proteins involved in the folding and unfolding of other proteins. Their expression is increased when cells are exposed to elevated temperatures or other cell-damaging stresses such as inflammation, infection, exercise, exposure of cells to irritants or toxin, starvation, or hypoxia, induced primarily through transcription of heat shock factor. HSPs are named according to their molecular weight, HSP90, HSP70, HSP60, and HSP27 on the order of 60, 70, and 90 kDa in molecular size, respectively. Therefore, HSPs are referred to as stress proteins since their upregulation is part of the stress response. Our group had demonstrated beneficial contributions of HSP70, HSP60, and HSP27 to gastric cytoprotection, including accelerated ulcer healing, improved QoUH, and rescue from NSAID-induced gastric damage. Although some HSPs that are expressed under non-stressful conditions are important for the maintenance of normal cell integrity, HSPs generally improve cellular recovery from injury either by refolding partially damaged functional proteins or by increasing delivery of precursor proteins to important organelles such as mitochondria and the endoplasmic reticulum (ER) [4]. Therefore, most HSPs, especially HSP70, HSP60, and HSP27, might contribute to mucosal defense mechanisms and ulcer healing through either

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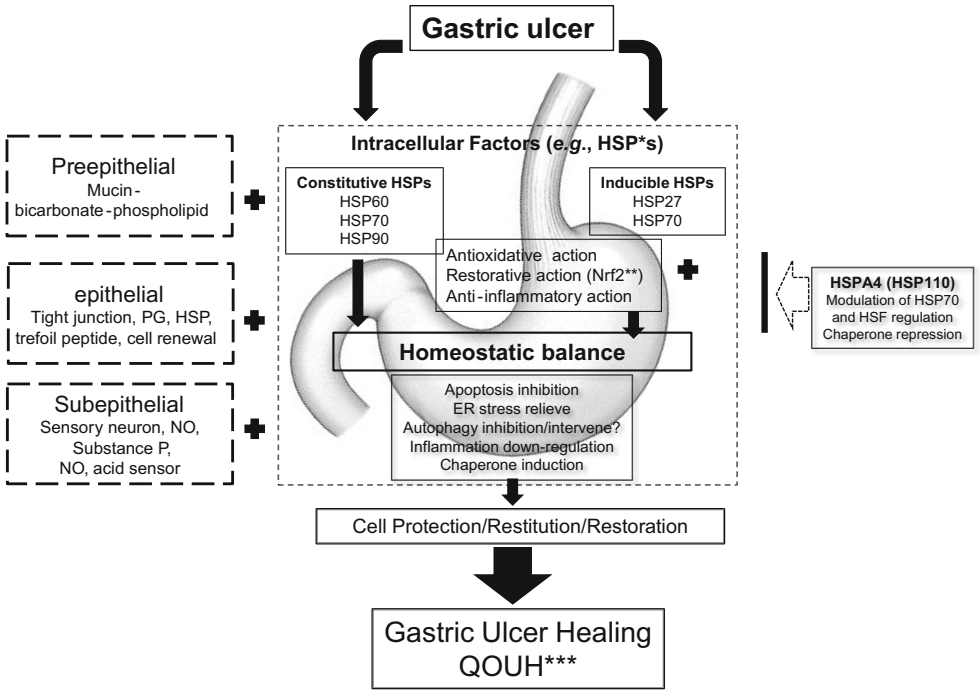

Fig. 1 HSP subfamily and HSPA4 (HSP110, Apg-2) regulate gastric mucosal defense mechanisms essential to gastric ulcer healing

protecting key enzymes related to gastric cytoprotection or accelerating epithelial repair.

In detail, several publications report that HSP70 is essential to gastric cytoprotection and ulcer healing. For example, inhibition of HSP70 aggravated gastric ulcer damage induced by *Helicobacter pylori* [5], protective effect of geranylgeranylacetone against indomethacin-induced gastric injury through HSP70 induction [6], and the cancellation of HSP70 was associated with aggravation of stress-induced gastric ulcer [7]. These studies supported the concept that induction of HSP70 protects the gastric mucosa from injury. Other than HSP70, small heat shock proteins (sHSP), with molecular masses of 12–43 kDa such as HSP27 in α- and β-crystalline oligomeric form, are important for stress tolerance. Many sHSP exert chaperone-like activity in preventing aggregation of target proteins, keeping them in a folding-competent state, and refolding them by themselves or in concert with other ATP-dependent chaperones, which are important for differentiation, proteasomal degradation, autophagy, and development. Nonetheless, the stress tolerance and anti-apoptotic properties of sHSP have beneficial and deleterious influences on human health and diseases. Moreover, abundantly expressed HSP90, a major molecular chaperone, is pivotal in supporting the correct folding of proteins, which unfortunately turns out to be mostly expressed in cancer cells, termed "HSP90-addiction" of cancer cells. Therefore, HSP90 inhibitors such as geldanamycin and its derivatives were developed to halt tumor progression through suppressing the cancer-promoting effects of HSP90, in sharp contrast to other HSPs, which are generally considered beneficial.

HSP70 protein 4 (HSPA4, mouse *Apg*-2, and a member of HSP110 family) is a protein that in humans is encoded by the *HSPA4* gene. HSPA4 interacts with histone deacetylatase 1 or histone deacetylatase 2 (HDAC1 or HDAC2), STIP1 homology and U-Box containing protein 1 (STUB1, C terminus of HSC70-interacting protein), NADH dehydrogenase (quinone 1), and apoptosis protease activating factor 1 (APAF1).

Sakurai et al. [8] in this issue of *Digestive Diseases and Sciences* assessed the involvement of HSPA4 in gastric ulcer healing, using either fibroblasts from wild-type and HSPA4-deficient mice or samples from patients undergoing endoscopic mucosal dissection of gastric cancer. The authors report that HSPA4 expression was inversely correlated with gastric ulcer healing. HSPA4 did downregulate the expression of stromal cell-derived factor 1 (SDF-1) and *Twist*, a master regulator gene of morphogenesis and epithelial mesenchymal transition, after which HSPA4 significantly inhibited cell migration, delaying gastric ulcer healing. HSPA4 increased the expression of Bcl-2 and Bcl-xL and attenuated apoptosis in the intestine. Its deficiency also activated STAT3 (signal transducer and activator of transcription 3) in cardiomyocytes. The authors concluded that HSPA4 deficiency significantly enhanced gastric ulcer healing, with the broader speculation that HSPA4 action differed according to cell and stress type, and microbiota

composition. The inverse effect of HSPA4 on gastric ulcer healing reinforces the concept that molecular chaperones can have adverse as well as beneficial effects.

Yet, since the authors only studied the influence of HSPA4 activity on the healing of acetic acid-induced gastric ulcers, further studies are needed to address the effect of HSP4 activity on the QoUH and the progression to precancerous lesions. Since several kinds of polyphenol-containing phytoceuticals and beneficial nutrients that are considered to be gastroprotective are reported to induce HSP70 as a gastric defense mechanism, injudicious attempts at uncontrolled enrichment of gastric defense mechanisms using poorly understood gastroprotective agents have the risk of inducing harmful molecular chaperones like HSPA4, with unanticipated damaging effects such as tumor induction.

Although the authors used the acetic acid ulcer model, non-steroidal anti-inflammatory drugs, which induce gastric ulcer formation based on ER stress with resultant apoptosis and autophagic cell death, should be used in the studies of HSPA4 induction. The biological benefits of the optimal modulation of chaperone activity might include rapid and high-quality ulcer healing manifest as lowered recurrence and reduced complications.

In conclusion, although catalytic unfolding chaperones of HSPs can act as primary cellular defenses against the formation of early misfolded and aggravated proteotoxic conformers accompanied by uncontrolled apoptosis and ulceration [9], antagonism of HSPA4 boosted host cytoprotective activities and accelerated gastric ulcer healing by reactivating nucleotide-activated exchange factor for HSP70. Taken together with the beneficial chaperone function of HSP70 in gastric ulcer healing, antagonism of HSPA4 contributed to accelerated gastric ulcer healing (Fig. 1).

References

1. Kangwan N, Park JM, Kim EH, Hahm KB. Quality of healing of gastric ulcers: natural products beyond acid suppression. *World J Gastrointest Pathophysiol*. 2014;5:40–47.
2. Tarnawski AS. Cellular and molecular mechanisms of gastrointestinal ulcer healing. *Dig Dis Sci*. 2005;50:S24–S33.
3. Laine L, Takeuchi K, Tarnawski A. Gastric mucosal defense and cytoprotection: bench to bedside. *Gastroenterology*. 2008;135:41–60.
4. Choi SR, Lee SA, Kim YJ, Ok CY, Lee HJ, Hahm KB. Role of heat shock proteins in gastric inflammation and ulcer healing. *J Physiol Pharmacol*. 2009;60:5–17.
5. Liu W, Chen Y, Lu G, Sun L, Si J. Down-regulation of HSP70 sensitizes gastric epithelial cells to apoptosis and growth retardation triggered by *H. pylori*. *BMC Gastroenterol*. 2011;11:146.
6. Suematsu S, Tanaka K, Namba T, et al. A role for HSP70 in protecting against indomethacin-induced gastric lesions. *J Biol Chem*. 2009;284:19705–19715.
7. Oh TY, Yeo M, Han SU, et al. Synergism of *Helicobacter pylori* infection and stress on the augmentation of gastric mucosal damage and its prevention with alpha-tocopherol. *Free Radic Biol Med*. 2005;38:1447–1457.
8. Sakurai T, Kashida H, Hagiwara S, Nishida N, Watanabe T, Fujita J, Kudo M. Heat shock protein A4 controls cell migration and gastric ulcer healing. Dig Dis Sci. (Epub ahead of print). doi:10.1007/s10620-015-3561-8.
9. Shaner L, Morano KA. All in the family: atypical Hsp70 chaperones are conserved modulators of Hsp70 activity. *Cell Stress Chaperones*. 2007;12:1–8.