HSPA12B and repairing the heart: beauty in simplicity

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This editorial refers to ‘HSPA12B attenuates cardiac dysfunction and remodelling after myocardial infarction through an eNOS-dependent mechanism’ by J. Li et al., pp. 671–681, this issue.

HSPA12B is a member of a newly identified subfamily of the Hsp70 family of heat shock proteins and is predominately expressed in endothelial cells. Blood pressure may play a role in its expression, as HSPA12B is expressed in endothelial cells in heart, adipose tissue, brain, kidney, and lung, but not in liver sinusoidal endothelial cells. In the heart and brain, vessels of all sizes express HSPA12B, whereas in lung and adipose tissue, expression is largely in capillaries. The cell-restricted expression of HSPA12B, which is otherwise not a feature of heat shock proteins, alone presages its importance to endothelial cell function and indeed studies have established that HSPA12B is required for angiogenesis, specifically in the processes of adhesion, migration, and tube formation. Endothelial cell HSPA12B expression seems to be dynamic and is increased in confluent HUVEC cultures kept in medium containing endothelial cell-specific growth factors, by heat shock, and during tubule formation. Protein levels are likely regulated by a post-transcriptional mechanism as well. Twenty-two putative client proteins have been identified for HSPA12B, including AKAP12 (A-kinase-anchoring protein 12) and hPDDXL (human podocalyxin-like), both of which are implicated in cell adhesion, and aryl hydrocarbon receptor nuclear translocator (ARNT).

HSPA12B also has protective actions in endothelial cells. Transgenic mice overexpressing the human hsp12b gene (including the endothelial cell-specific promoter) were found to be remarkably protected against endotoxin lipopolysaccharide (LPS)-induced cardiac dysfunction and inflammation. In addition, overexpression of human HSPA12B in mice protected against cerebral ischaemia–reperfusion injury. In both cases, phosphatidylinositol 3-kinase (PI3K)/AKT signalling, which was either enhanced or preserved and is known to have protective effect in endothelial cells, was implicated in the beneficial actions of HSPA12B. The mechanism by which HSPA12B impacts on PI3K/AKT signalling in endothelial cells is not known. One possibility may be in supporting the formation of angiopoietin-1 (Ang-1), known to activate PI3K/AKT signalling and have protective actions itself in endothelial cells. HSPA12B overexpression attenuated the decrease in Ang-1 expression in the heart induced by LPS, although levels were still significantly lower than in saline-treated wild-type and transgenic mice. LPS-induced decrease in eNOS protein levels was also attenuated by HSPA12B overexpression. Altogether, these findings demonstrate that HSPA12B overexpression has protective actions on endothelial cells under stress.

Li et al. report that transgenic mice expressing human HSPA12B specifically in endothelial cells exhibited remarkable improvements in cardiac function and remodelling (left ventricular enlargement, wall thinning, and fibrosis) up to 4 weeks after myocardial infarction compared with wild-type mice (Figure 1). Improvements were accompanied by less cardiac myocyte apoptosis and an increase in capillary and arteriolar densities. Transgenic hearts exhibited a further increase in levels of proteins known to have survival actions on cardiac myocytes and endothelial cells and/or to stimulate angiogenesis under conditions of ischaemic stress, namely eNOS, Ang-1, VEGF, and Bcl-2. Inhibition of eNOS by L-NAME blocked the positive actions of HSPA12B on cardiac function and remodelling, as well as cardiac myocyte apoptosis, VEGF production, and capillary formation. Thus, these events are downstream of, or sustained by, nitric oxide formation. Notably, L-NAME did not prevent the infarct-induced up-regulation of Ang-1, supporting the conclusion that Ang-1 production is a primary event in the protective actions of HSPA12B. Moreover, the observation that HSPA12B overexpression had no effect on eNOS levels in sham animals suggests that HSPA12B impacts on a stress-induced protein rather than an endogenously produced protein.

One of the more remarkable features of the study by Li et al. is perhaps its deceptive simplicity, which after all required the identification and exploitation of a cell-specific protein involved in dealing with stress or injury. That is no small feat. On the other hand, simplicity is oftentimes the barometer of utility and is not easily attained. Given the apparent lack of a phenotype of HSPA12B overexpression, it seems likely that HSPA12B, acting as a chaperone protein, enhances a normal reparative process that is ‘turned on’ in endothelial cells by injury. For instance, functioning as a chaperone, HSPA12B may enhance the stress-induced production of Ang-1 by cardiac endothelial cells.

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Therapeutic angiogenesis is a promising strategy for tackling chronic myocardial ischaemia and repairing the infarcted heart. However, delivery of angiogenic factors, in particular VEGF and Ang-1, is fraught with certain difficulties, such as achieving an adequate concentration in the heart, consistency, their short duration of action, and potential adverse or off-site effects such as vascular inflammation and tumour growth. Targeting angiogenesis using gene therapy addresses some of these concerns, particularly if expression is under control of a promoter that can be turned on and off, such as by hypoxia. However, safety issues remain with gene-based therapies. In addition, angiogenesis is a complex process involving the co-ordinated and temporal actions of a number of angiogenic factors. Getting it just right is no easy task. For that reason, exploitation of an endogenous process as achieved in the mature and functional vessels was actually achieved by HSPA12B over-expression in wild-type hearts. Like Hsp70, HSPA12B may have cytoprotective (e.g. anti-apoptotic) actions within endothelial cells and required for angiogenesis. HSPA12B likely has direct cytoprotective effects in endothelial cells and contributes to angiogenesis by additional means besides Ang-1 formation. Other not-yet-identified factors are expected to play a role in HSPA12B-related increases in eNOS expression and activity, as well as angiogenesis.

In conclusion, Li et al. have elegantly demonstrated that enhancing levels of a stress response protein expressed specifically in endothelial cells can concomitantly nurture recovery and attenuate deterioration following ischaemic insult to the heart, thus preserving heart function. Theirs is a ‘simple’ finding that may have profound significance for how ischaemic heart disease is treated.

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