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# Small heat shock proteins in smooth muscle

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*Abbreviations:*
HSE, heat shock response element
HSF, heat shock factor
HSP, heat shock protein
MAP kinase, mitogen-activated protein kinase
MK2, MAP kinase-activated protein kinase 2
MKK, MAP kinase kinase
PAK, p21-activated protein kinase
PKA, cyclic AMP-dependent protein kinase
PKG, cyclic GMP-dependent protein kinase

ABSTRACT

The small heat shock proteins (HSPs) HSP20, HSP27 and αB-crystallin are chaperone proteins that are abundantly expressed in smooth muscles are important modulators of muscle contraction, cell migration and cell survival. This review focuses on factors regulating expression of small HSPs in smooth muscle, signaling pathways that regulate macromolecular structure and the biochemical and cellular functions of small HSPs. Cellular processes regulated by small HSPs include chaperoning denatured proteins, maintaining cellular redox state and modifying filamentous actin polymerization. These processes influence smooth muscle proliferation, cell migration, cell survival, muscle contraction and synthesis of signaling proteins. Understanding functions of small heat shock proteins is relevant to mechanisms of disease in which dysfunctional smooth muscle causes symptoms, or is a target of drug therapy. One example is that secreted HSP27 may be a useful marker of inflammation during atherogenesis. Another is that phosphorylated HSP20 which relaxes smooth muscle may prove to be highly relevant to treatment of hypertension, vasospasm, asthma, premature labor and overactive bladder. Because small HSPs also modulate smooth muscle proliferation and cell migration they may prove to be targets for developing effective, novel treatments of clinical problems arising from remodeling of smooth muscle in vascular, respiratory and urogenital systems.


**Contents**



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## 1. Introduction

### 1.1. Chaperones

The small heat shock proteins HSP20, HSP22, HSP27 and αB-crystallin are widely expressed chaperone proteins. Chaperones interact with other proteins to facilitate normal functions including maintaining cytoskeletal structure, maintaining normal redox conditions and regulating translation, each of which facilitates cell survival (Arigo, 2007). During exposure of cells to chemical stressors such as oxidative stress chaperones preserve protein function by preventing denaturation and promoting proper protein refolding once the stress is alleviated (Welsh and Gaestel, 1998; Bryantsev et al., 2007). Chaperones also participate in folding of newly synthesized polypeptides, and in formation of a variety of multi-subunit protein assemblies. Some HSPs maintain proteins in unfolded states suitable for translocation across membranes. They also stabilize inactive or damaged forms of proteins that are induced by cellular signaling. Chaperone proteins are divided into several families according to their size — HSP 100, 90, 70, 60 and the small heat shock/α-crystallin proteins. The small HSPs are ATP-independent chaperones that exist in all organisms from bacteria to humans and are highly conserved (Jakob et al., 1993; Kappe et al., 2003). These proteins are essential for cellular viability following cellular stress, and their expression is frequently but not always increased by environmental stressors. One result of inducible expression is that organisms gain tolerance to changes in chemical and physical stimuli, in effect adapting to changes in the local environment of the cell. We suggest the small heat shock proteins contribute to smooth muscle function under normal conditions as well as enable smooth muscle to adapt to altered local environments in disease states. The review will focus on factors that alter small HSP expression, the macromolecular structure of small HSPs and the functions of small HSPs with an emphasis on the most frequently studied proteins — HSP27 and HSP20.

Rapid adaptation to the local environment is a major physiological role of smooth muscle cells. Force generated by smooth muscle cells dynamically stiffens the walls of the vasculature, airways and intestines to regulate flow of blood, air, food and waste products. In atherosclerosis, asthma and inflammatory bowel disease smooth muscle cells also undergo hyperplasia and hypertrophy as well as becoming secretory cells that exacerbate inflammation (reviewed by Johnson and Knox, 1997; Libby, 2003; Singer et al., 2004). In this review we summarize evidence that small HSPs are targets for signaling pathways that regulate major cellular processes that underlie the adaptive function of smooth muscle. Evidence is presented for a role of small HSPs in smooth muscle contraction, proliferation, cell migration and secretion of signaling proteins.

### 1.2. Functions of HSP27 and HSP20 in nonmuscle cells

Fig. 1 illustrates some of the cellular processes influenced by HSP27 and HSP20. Expression of HSP27 in nonmuscle cells is inducible by

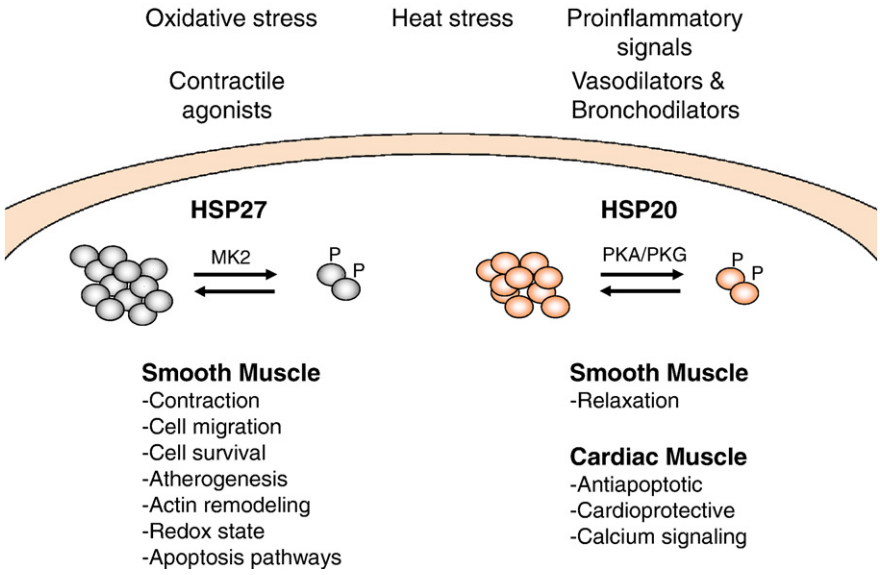


**Fig. 1.** Cellular processes modified by HSP20 and HSP27 in smooth muscles. Multiple extracellular signals impinge on smooth muscle cells to modify the macromolecular structure of small HSPs. Key protein kinases are shown that catalyze phosphorylation of these proteins which changes their molecular associations thus modifying a variety of downstream processes. HSP27 phosphorylation is catalyzed by MAPKAP kinase 2 (MK2) and HSP20 phosphorylation is catalyzed by cyclic nucleotide-dependent protein kinases (PKA and PKG). HSP27 has been shown to promote muscle contraction, increase cell migration and enhance cell survival under stress conditions. Activation of HSP20 causes smooth muscle relaxation and is cardioprotective.