Chapter 19

TURNING UP THE HEAT IN THE LUNGS
A key mechanism to preserve their function

Claudio Sartori and Urs Scherrer

Abstract: Life threatening events cause important alterations in the structure of proteins creating the urgent need of repair to preserve function and ensure survival of the cell. In eukariotic cells, an intrinsic mechanism allows them to defend against external stress. Heat shock proteins are a group of highly preserved molecular chaperones, playing a crucial role in maintaining proper protein assembly, transport and function. Stress-induced upregulation of heat shock proteins provides a unique defense system to ensure survival and function of the cell in many organ systems during conditions such as high temperature, ischemia, hypoxia, inflammation, and exposure to endotoxin or reactive oxygen species. Induction of this cellular defense mechanism prior to imposing one of these noxious insults, allows the cell/organ to withstand a subsequent insult that would otherwise be lethal, a phenomenon referred to as "thermo-tolerance" or "preconditioning". In the lung, stress-induced heat shock protein synthesis, in addition to its cyto-protective and anti-inflammatory effect, helps to preserve vectorial ion transport and alveolar fluid clearance. In this review, we describe the function of heat shock proteins in the lung, with particular emphasis on their role in the pathophysiology of experimental pulmonary edema, and their potential beneficial effects in the prevention and/or treatment of this life-threatening disease in humans.

Key Words: heat shock proteins, lung, acute respiratory distress syndrome, alveolar fluid clearance, epithelial sodium channel

Hypoxia: Through the Lifecycle, edited by R.C. Roach et al.
STRESS-INDUCED PROTEIN DENATURATION INCREASES THE EXPRESSION OF HSP

In 1962 Ritossa observed that exposing *Drosophila* to elevations of temperature produced "puffing" patterns of polytene chromosomes indicating increased gene activity (18). Approximately 10 years later, Tissières and colleagues demonstrated that these "puffing" patterns represented upregulation of genes encoding for heat shock proteins (HSP) (26). This heat shock response, now commonly referred to as the stress response, is ubiquitous in nature and consists of the transcription and translation of a set of HSPs, which possess a tremendous homology across virtually all living cells.

HSPs are proteins ranging from 8–110 kDa that are assigned to families on the basis of sequence homology and typical molecular weight (33, 34). In eukaryotes, there exist many families that comprise multiple members, differing in degree and kinetics of inducibility, intracellular distribution, tissue specificity and function (3, 4).

Table 1. Heat shock protein families, localization and function

<table>
<thead>
<tr>
<th>NAME</th>
<th>kDa</th>
<th>LOCALISATION</th>
<th>FUNCTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ubiquitin</td>
<td>8</td>
<td>Cytosol/nucleus</td>
<td>Degradation</td>
</tr>
<tr>
<td>HSP 27</td>
<td>27</td>
<td>Cytosol/nucleus</td>
<td>Molecular chaperone; cytoprotection</td>
</tr>
<tr>
<td>Heme Oxygenase</td>
<td>32</td>
<td>ER and cytoplasm</td>
<td>Resistance to oxidant stress</td>
</tr>
<tr>
<td>HSP 47</td>
<td>47</td>
<td>ER</td>
<td>Collagen chaperone</td>
</tr>
<tr>
<td>HSP 60</td>
<td>60</td>
<td>Mitochondria</td>
<td>Molecular chaperone</td>
</tr>
<tr>
<td>HSP 70</td>
<td>72</td>
<td>Cytosol/nucleus</td>
<td>Cytoprotection</td>
</tr>
<tr>
<td>HSP 90</td>
<td>90</td>
<td>Cytosol/nucleus</td>
<td>Regulation steroid receptor activity</td>
</tr>
<tr>
<td>HSP 110</td>
<td>110</td>
<td>Nucleolus/cytosol</td>
<td>Nucleoli protection from stress</td>
</tr>
</tbody>
</table>

MECHANISMS CAUSING INDUCTION OF HSP EXPRESSION

In addition to elevated temperatures, induction of HSP expression has also been observed under various other conditions such as ischemia, oxygen deprivation, inflammation, or exposure to endotoxin, reactive oxygen species, ethanol, heavy metals or other chemical denaturants. All these different forms of stress may induce protein conformational changes either directly or indirectly.

Accumulation of denatured or abnormally folded proteins itself is assumed to represent the key proximal signal for initiation of the stress response in a given cell or tissue (27). The exact underlying mechanisms by which denatured proteins initiate the stress response