Hsp10: anatomic distribution, functions, and involvement in human disease

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1. ABSTRACT

There is growing evidence that molecular chaperones/heat shock proteins are involved in the pathogenesis of a number of human diseases, known as chaperonopathies. A better molecular understanding of the pathogenetic mechanisms is essential for addressing new strategies in diagnostics, therapeutics and clinical management of chaperonopathies, including those in which Hsp10 is involved. This chaperonin has been studied for a long time as a member of the mitochondrial protein-folding machine. However, although in normal cells Hsp10 is mainly localized in the mitochondrial matrix, it has also been found during and after stress in other subcellular compartments, such as cytosol, vesicles and secretory granules, alone or in combination with other proteins. In these extramitochondrial locales, Hsp10 plays an active role in cell signalling. For example, cancer cells often show altered levels of Hsp10, compared to normal cells. Hsp10 may also be found in the extracellular space and in the bloodstream, with a possible immunomodulatory activity. This minireview focuses on some studies to date on the involvement of Hsp10 in human disease pathogenesis.

2. MOLECULAR CHAPERONES, HEAT SHOCK PROTEINS AND CHAPERONOPATHIES

Molecular chaperones, many of which are Heat shock proteins (Hsps), are an important class of molecules, highly conserved throughout evolution, with numerous intracellular functions (Table 1). The best-known role of these molecules is their involvement in the correct folding of polypeptide chains and in the assembling of proteins into functional higher order structures (1, 2). Prokaryotic and eukaryotic cells have evolved special multimolecular chaperone complexes that play a role in protein folding (3, 4). One of these is the Hsp60/Hsp10 molecular complex that captures unfolded, partially folded and/or misfolded proteins inside its central cavity, ensuring their correct structural conformation (3, 5).

The malfunction of the chaperoning system due to defective chaperones may lead to several diseases, now described as chaperonopathies (4, 6, 7). Chaperonopathies have been classified etiologically as genetic or acquired, and pathogenetically as by defect, excess, or mistake. The latter include various types of cancers in which chaperones
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Table 1. Main chaperones and their functions

<table>
<thead>
<tr>
<th>Chaperone</th>
<th>Subcellular localization</th>
<th>Known function</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-A crystallin</td>
<td>Cytosol</td>
<td>Structural protein of eye lens</td>
<td>62</td>
</tr>
<tr>
<td>αB crystallin</td>
<td>Cytosol</td>
<td>Anti-apoptotic, thermoprotection</td>
<td>63</td>
</tr>
<tr>
<td>Calnexin</td>
<td>Endoplasmic reticulum (ER)</td>
<td>Folding of glycoproteins</td>
<td>64, 65</td>
</tr>
<tr>
<td>Calreticulin</td>
<td>ER, cell surface</td>
<td>Folding of glycoproteins. Facilitates peptide loading to the class I molecule of the major histocompatibility complex</td>
<td>66-68</td>
</tr>
<tr>
<td>Grp96</td>
<td>ER, cell surface</td>
<td>Controls protein homeostasis in the ER. Implicated in the activation of dendritic cells and chaperoning of antigenic peptides in the process of antigen presentation</td>
<td>67, 69-71</td>
</tr>
<tr>
<td>Grp78</td>
<td>ER</td>
<td>Protein (e.g., immunoglobulin) folding</td>
<td>72, 73</td>
</tr>
<tr>
<td>Grp170</td>
<td>ER</td>
<td>Implicated in peptide transport in the ER</td>
<td>74</td>
</tr>
<tr>
<td>Hsp10</td>
<td>Mitochondria, cytosol, zymogen granules</td>
<td>Protein folding; modulation of immune system</td>
<td>75, 17, 31, 33, 16</td>
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<tr>
<td>Hsp22</td>
<td>Cytosol</td>
<td>Cell protection; maintenance of muscle integrity</td>
<td>76</td>
</tr>
<tr>
<td>Hsp27, HspB2</td>
<td>Cytosol</td>
<td>Anti-apoptotic; cytoprotection</td>
<td>77</td>
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<tr>
<td>Hsp40</td>
<td>Cytosol</td>
<td>Folding and refolding of denatured proteins, together with Hsp70/Hsc70</td>
<td>78</td>
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<td>Hsp47</td>
<td>ER</td>
<td>Synthesis/assembly of various collagens</td>
<td>79</td>
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<tr>
<td>Hsp60</td>
<td>Mitochondria, cytosol, cell membrane, vesicles, cell surface</td>
<td>Protein folding; protein folding; macrophage activator possibly through Toll-like receptors</td>
<td>80-82</td>
</tr>
<tr>
<td>Hsc70</td>
<td>Cytosol, nucleus</td>
<td>Protein folding; clathrin uncoating; peptide binding</td>
<td>83</td>
</tr>
<tr>
<td>Hsc72</td>
<td>Cytosol, nucleus</td>
<td>Cytoprotection and anti-apoptotic. Implicated in spermatogenesis</td>
<td>84</td>
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<tr>
<td>Hsc74</td>
<td>Mitochondria</td>
<td>Antigen presentation; radioresistance</td>
<td>85-87</td>
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<td>Hsp90α</td>
<td>Cytosol</td>
<td>Protein folding; cytoprotection; intracellular signalling (e.g., steroid receptor); cell-cycle control</td>
<td>88, 89</td>
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<tr>
<td>Hsp90β</td>
<td>Cytosol</td>
<td>Protein folding; Cytoprotection; Intracellular signalling (e.g., steroid receptor); Cell-cycle control</td>
<td>90, 91</td>
</tr>
<tr>
<td>Hsp10</td>
<td>Cytosol/nucleus</td>
<td>Binds to Hsc70 to form high-molecular-weight complex; involved in protein folding; thermotolerance; involved in embryogenesis</td>
<td>74, 92</td>
</tr>
<tr>
<td>Chaperonin II like molecule (TRiC)</td>
<td>Cytosol</td>
<td>Protein folding</td>
<td>93</td>
</tr>
<tr>
<td>PIase</td>
<td>Cytosol, ER</td>
<td>Protein folding inside ER; involved in disulfide bond rearrangement catalysis</td>
<td>94</td>
</tr>
<tr>
<td>PPIase</td>
<td>Cytosol, ER, mitocondria</td>
<td>Protein folding; interconverts the cis and trans isomers of peptide bonds with amino acid proline</td>
<td>95</td>
</tr>
<tr>
<td>Sacsin</td>
<td>Cytosol</td>
<td>Co-chaperone which acts as a regulator of the Hsp70 chaperone machinery and may be involved in the processing of the other ataxia-linked proteins</td>
<td>96</td>
</tr>
<tr>
<td>SEC63</td>
<td>ER</td>
<td>May perform post-translational protein translocation into ER</td>
<td>97</td>
</tr>
</tbody>
</table>

Modified with permission from (60). For complete guidelines for the nomenclature of the human heat shock proteins, see ref. 61. bMember of the serpin (serine protease inhibitor) superfamily.

benefit the tumors rather than the host (8). Some examples of chaperonopathies are given in Tables 2 and 3.

3. Hsp10 MOLECULAR ANATOMY AND FUNCTIONS

Most studies on chaperon function have been carried out using prokaryotic models, in particular the bacterial GroEL and GroES, which are the homologous of eukaryotic Hsp60 and Hsp10, respectively.

The GroEL chaperonin complex consists of two rings arranged in a barrel-shaped structure with a central cavity, the folding chamber. Likewise, GroES assembles into a ring. GroEL captures the unfolded protein and the GroES ring caps the cavity, initiating the folding process. After a few seconds, the folded protein and GroES are released (9). In eukaryotic cells, one or two ring-like structures (each with seven Hsp60 subunits) capped by one ring of seven Hsp10 subunits, form a bell-shaped chaperonin structure (5, 10).

Hsp10 is encoded by a nuclear gene (GeneID, 3336; gene map locus, 2q33.1) and transported into mitochondria (11). The human genes of Hsp10 and Hsp60 have been mapped to chromosome 2, placed head-to-head, and controlled by a bidirectional promoter (11). The transcriptional activity of the promoter in the Hsp60 direction is approximately twice of that in the Hsp10 direction under normal growth conditions, while, under heat stress the activity increases by approximately 12-fold in both directions, maintaining Hsp60 expression two-fold higher than Hsp10 (11).

Interestingly, in a recent study in which a mutant mouse line bearing an inactivating gene-trap insertion in the HspD1 gene encoding Hsp60, it was found that the expression of the nearby HspE1 gene, which encodes Hsp10, was concomitantly downregulated and the protein levels were reduced in many tissues (12). This mutation resulted in early embryonic death.

Hsp10 does not contain the typical mitochondrial-targeting sequence, but instead its N-terminal sequence forms an amphipathic alpha helix, stabilized by acetylation of the first Ala, which enables it to cross the mitochondrial membrane in the absence of a signal peptide (13, 14).

Although in normal cells Hsp10 is generally localized in the mitochondrial matrix, it has also been found in other subcellular localizations, such as in cytosol and secretory granules (15-17) (Figure 1). The mechanism by which Hsp10 accumulates in the cytoplasm is not known. Two possibilities are: 1) Hsp10 accumulates in the cytoplasm directly, without passing through the mitochondria; and 2) it enters into the mitochondria and is then translocated back into the cytoplasm (9).

In the cytosol, Hsp10 has further roles in addition to those accepted to play inside the mitochondria as a co-
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Table 2. Examples of genetic and acquired chaperonopathies

<table>
<thead>
<tr>
<th>Chaperones</th>
<th>Genetic chaperonopathies</th>
<th>Acquired chaperonopathies</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hsp22 and Hsp27</td>
<td>Neuropathies associated with sHsp mutations</td>
<td>Alexander disease</td>
<td>99</td>
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<tr>
<td>Hsp40 (DnaJ3)</td>
<td>Dilated cardiomyopathy</td>
<td>101</td>
<td></td>
</tr>
<tr>
<td>Hsp47</td>
<td>Fibrotic disorders</td>
<td>102</td>
<td></td>
</tr>
<tr>
<td>Hsp47, PDase</td>
<td>Posttranslational modification of PDase and protein misfolding disease</td>
<td>103</td>
<td></td>
</tr>
<tr>
<td>Hsp70</td>
<td>Inactivation of chaperones by exogenous toxins</td>
<td>104</td>
<td></td>
</tr>
<tr>
<td>Hsp72</td>
<td>Failure of inducible chaperones and disease</td>
<td>105</td>
<td></td>
</tr>
<tr>
<td>PPIase (peptidyl-prolyl cis-trans isomerase)</td>
<td></td>
<td>106</td>
<td></td>
</tr>
<tr>
<td>Sacsin</td>
<td>Ataxia of Charlevoix–Saguenay</td>
<td>107</td>
<td></td>
</tr>
<tr>
<td>SEC63</td>
<td>Pathology of protein transport into the ER</td>
<td>108, 109</td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Examples of chaperonopathies by excess, defect, or mistake

<table>
<thead>
<tr>
<th>Chaperones</th>
<th>Chaperonopathies by excess</th>
<th>Chaperonopathies by defect</th>
<th>Chaperonopathies by mistake</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hsp10, EPF</td>
<td>Cancer of large bowel, uterine exocervix, and prostate; mantle cell lymphoma; serous ovarian cancer; gestational trophoblastic tumor</td>
<td></td>
<td></td>
<td>31-36, 9, 37</td>
</tr>
<tr>
<td>Hsp20, HspB2, Hsp27</td>
<td>Alzheimer's disease (AD)</td>
<td></td>
<td></td>
<td>98</td>
</tr>
<tr>
<td>Hsp60</td>
<td>Age-related diseases</td>
<td>Cancer of large bowel, uterine exocervix, and prostate</td>
<td></td>
<td>31, 32, 110</td>
</tr>
<tr>
<td>Hsc70 and Hsp70</td>
<td>Multiple system atrophy; age-related diseases</td>
<td></td>
<td></td>
<td>111, 112</td>
</tr>
<tr>
<td>Hsp70</td>
<td>Breast cancer</td>
<td></td>
<td></td>
<td>113</td>
</tr>
<tr>
<td>Hsp90</td>
<td>Breast cancer</td>
<td></td>
<td></td>
<td>114</td>
</tr>
</tbody>
</table>

Table 4. Examples of roles of cytosolic Hsp10

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Function</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone</td>
<td>Osteoclast recruitment and bone resorption; bone collagen synthesis</td>
<td>115-118</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Suppression of ubiquitination of insulin-like growth factor-1 receptor and increase of insulin-like growth factor-1 receptor signaling</td>
<td>119</td>
</tr>
<tr>
<td>Epithelia</td>
<td>Inhibition of NF-κB-regulated gene expression; inhibition of the transcriptional activation mediated by WNT signalling; signal transduction</td>
<td>120, 121</td>
</tr>
<tr>
<td>Lung</td>
<td>Acetylation of polyamines and regulation of polyamine transport out of the cells</td>
<td>122, 123</td>
</tr>
<tr>
<td>Nervous, glia</td>
<td>Neurite outgrowth</td>
<td>124</td>
</tr>
<tr>
<td>Nervous, neurons</td>
<td>Nucleic acid metabolism</td>
<td>125</td>
</tr>
<tr>
<td>Testis</td>
<td>Lipid synthesis and steroid biosynthesis</td>
<td>126</td>
</tr>
</tbody>
</table>

Hsp10 localizes extracellularly during pregnancy. Extracellular Hsp10 is often referred to as Early Pregnancy Factor (EPF), because it has been found to be released during the first stages of gestation and it is involved in the establishment of pregnancy, in embryonic development, and in cell proliferation and differentiation (18-22). However, the mechanism by which Hsp10/EPF is released into the extracellular environment is not yet fully understood. We suspect that Hsp10 is released from cells by unconventional secretory pathways that involve lipid rafts and/or exosomes, as observed for other Hsps (23-30).

4. Hsp10 AND CANCER

Higher than average Hsp10 levels have been found in tumor cells in large bowel cancer (31, 32), exocervical cancer (31), prostate cancer (33), mantle cell lymphoma (34), and serous ovarian cancer (35). By contrast, in bronchial carcinogenesis, decreased levels of Hsp10 have been reported (36). It is not clear what determines an increase or a decrease in the expression of this protein in cancer cells. Table 5 shows a list of tumors, studied using various techniques, in which Hsp10 levels have been found to differ from those in the normal tissue counterparts. Figure 2 shows Hsp10 immunopositivity in normal (a) and tumor (b) cells from colon mucosa.

Clinical studies have demonstrated that circulating Hsp10 (EPF) can be found in a number of tumors, such as malignant trophoblastic tumor (37), invasive mole (38), choriocarcinoma (38), endodermal sinus tumor of the ovary (39), rhabdomyosarcoma (39), adrenal cortex carcinoma (39), ovarian carcinoma (40), and germ-cell tumor of the testis (41). In these neoplasms, Hsp10 measurement in sera may become a useful marker for clinical follow-up.
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<table>
<thead>
<tr>
<th>System</th>
<th>Tumor</th>
<th>Methods</th>
<th>Hsp10 levels (compared to normal tissues)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digestive</td>
<td>Large bowel carcinoma</td>
<td>IHC, WB</td>
<td>Higher</td>
<td>31, 32</td>
</tr>
<tr>
<td>Female reproductive</td>
<td>Ovarian cancer</td>
<td>IHC, WB</td>
<td>Higher</td>
<td>35</td>
</tr>
<tr>
<td>Hemolymphopoietic</td>
<td>Mantle cell lymphoma</td>
<td>Protein microarray; IHC; WB</td>
<td>Higher</td>
<td>34</td>
</tr>
<tr>
<td>Male reproductive</td>
<td>Prostate carcinoma</td>
<td>IHC</td>
<td>Higher</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>Testicular germ cell tumors</td>
<td>RIA</td>
<td>Higher (EPF-like)</td>
<td>41</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Bronchial adenocarcinoma</td>
<td>IHC; WB</td>
<td>Lower</td>
<td>36</td>
</tr>
</tbody>
</table>

Modified with permission from (9) Abbreviations: IHC, immunohistochemistry; WB, Western blotting; RIT, Radio Immuno Assay.

may act as either a pro- or an anti-apoptotic factor. In tumor cells, Hsp10 may induce programmed cell death. It has been reported that an interaction occurs between the Hsp60/Hsp10 complex and procaspase-3 in the mitochondria of Jurkat cells (42). When fragments of active caspase reached the mitochondrial intermembrane space after separating from the Hsp60/Hsp10 complex, these cells died. Therefore, it can be inferred that Hsp60-Hsp10 determines acceleration of caspase-3 maturation. Along the same lines, it has been demonstrated that Hsp10 knockdown induces apoptosis in mouse ovarian GCs, whereas overexpression of Hsp10 suppresses apoptosis (43). However, other data do not support this finding (44). For example, it has been reported that downregulation of Hsp10 could be one of the main causes of apoptosis in testis, while Hsp10 overexpression may suppress apoptosis and result in testis tumorigenesis (44).

Extracellular Hsp10 released from neoplastic cells may affect tumor cell division via a paracrine mechanism as suggested by a report showing that treatment of tumor cells with anti-EPF (Hsp10) monoclonal antibodies produced a significant decrease in cell growth and viability rates (45).

A number of studies have investigated the association between soluble Hsp10 and the immune system (for a Review, see Ref. 9 and 46). Suppression of immune function may be crucial for cancer progression. Indeed, the suppression of CD3-zeta expression induced by EPF has been shown to lead to inhibition of lymphocyte activation via the TcR complex, in turn enhancing cancer progression (40).

To the best of our knowledge, no studies have investigated the role of Hsp10(EPF) in tumor neoangiogenesis, which constitutes an interesting topic for research.

**5. Hsp10 AND AUTOIMMUNE DISEASES**

A variety of experimental animal models have been employed to assess the use of Hsp10 as a drug for immune response suppression. For example, it was shown that a reduction of lymphocyte infiltration after administration of *Mycobacterium tuberculosis* Hsp10 occurs in an experimental animal model (Lewis rat) of rheumatoid arthritis, known as adjuvant arthritis (47). Amelioration of clinical signs was accompanied by an increased titer of antibodies against *M. tuberculosis* Hsp10. A randomized double-blind clinical trial was carried out on patients with moderate-to-severe active rheumatoid arthritis, who received various intravenous doses of recombinant Hsp10 (twice a week for 12 weeks) and it was found that besides being well tolerated, Hsp10 administration improved clinical signs (48). These results suggest a possible use for Hsp10 in the treatment of rheumatoid arthritis. Similarly, experimental autoimmune encephalomyelitis, an animal model of multiple sclerosis (49), was used in rats and mice in order to evaluate the suppression of immune response by Hsp10 (EPF) and improvement of clinical signs was also reported, along with a reduced lymphocyte infiltration, which is responsible of demyelination in the central nervous system (50). In the same models, it was demonstrated a protective role of Hsp10 as a survival factor for oligodendrocytes (51). Likewise, an improvement of symptoms was observed in women affected by multiple sclerosis during pregnancy (52). It was also demonstrated that Hsp10 (EPF) can have an effect on delayed type hypersensitivity reaction in mice as two soluble factors (EPF-S1 and EPF-S2) (53).

On the basis of these findings, administration of Hsp10 has been considered to have potential in the treatment of autoimmune diseases. Some clinical trials have already been performed, demonstrating the usefulness of this protein in reducing inflammation in some autoimmune processes, such as multiple sclerosis (54), severe plaque psoriasis (55), and rheumatoid arthritis (56).

**6. Hsp10 AND CHRONIC INFLAMMATORY DISEASES**

Increased Hsp10 levels have been detected during chronic inflammatory processes, such as Ulcerative Colitis and Crohn’s disease (57). Immunohistochemistry and biochemical techniques showed increased levels of Hsp10 in mucosal biopsies from patients with both of the aforementioned conditions compared to normal controls. Hsp10 was localised in epithelial and lamina propria cells. The presence of this protein in lamina propria is a hallmark of inflammatory status (Figure 2c), in comparison with normal mucosa in which positive cells in lamina propria are rare (Figure 2a). Unpublished data from our group showed positivity for Hsp10 also in mucosal biopsies from patients with celiac disease and chronic obstructive pulmonary disease. All these observations should encourage research on the relationship between Hsp10 and chronic inflammatory disease pathogenesis.

**7. Hsp10 AND AGING**

Aging of human tissues is associated with an imbalance of Hsp levels and functions in a number of organs. This may determine a scrambling of the
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Figure 1. Hsp10 is normally present in the mitochondria (white arrows and inset). However, the chaperonin can also be found in the cytosol (black arrows) of normal cells. Cell: 16HBE (human bronchial epithelium). Bar: 1 micron.

Figure 2. Hsp10 is commonly detectable by immunohistochemical methods in normal and inflamed tissues, as well as in tumors. A: normal colon mucosa. B: Colon cancer. C: Nonspecific colitis. Hsp10 levels in inflammation and cancer are commonly higher in the affected than in the normal tissues. Bar: 50 micron.

interactions between Hsps and the immune system with age (8). In what regards Hsp10, few studies have investigated its variations in older people. In one of these studies, overexpression of Hsp10 was found to prevent skeletal muscle atrophy and weakness in old mice (58). These data would seem to demonstrate that development of age-related muscle weakness may be slowed down by Hsp10 overexpression, suggesting that a mitochondrial dysfunction, particularly a chaperoning machine defect, may be involved in the development of age-related muscle deficits.

In another study, the amount of Hsp10 was found to be increased in liver mitochondria after hyperthermic challenge in young but not old rats (59). The authors hypothesized that mitochondria in old animals are more vulnerable to the oxidative damage that occurs in response to heat stress since old-age mitochondria have compromised selfrepair ability.

8. CONCLUSION

Although the number of experimental projects on Hsp-chaperones involvement in human tissue homeostasis and disease has been constantly growing in the last decade, only a limited number of studies have investigated Hsp10. Nonetheless, these works have presented promising results for using this molecule as a diagnostic, prognostic, and therapeutic tool in the management of some human pathologies, such as cancer, autoimmune disorders, and chronic inflammatory diseases.

9. ACKNOWLEDGEMENTS

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Key Words: Heat shock proteins, Hsp10, Cpn10, Early pregnancy factor, Hsp60, Cancer, Autoimmune diseases, Review

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