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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

Table 1. Main chaperones and their functions

Chaperone	Subcellular localization	Known function	References
α-A crystallin	Cytosol	Structural protein of eye lens	62
α-B crystallin	Cytosol	Anti-apoptotic, thermoprotection	63
Calnexin	Endoplasmic reticulum (ER)	Folding of glycoproteins	64, 65
Calreticulin	ER, cell surface	Folding of glycoproteins. Facilitates peptide loading to the class I molecule of the major histocompatibility complex	66-68
Gp96	ER, cell surface	Controls protein homeostasis in the ER. Implicated in the activation of dendritic cells and chaperoning of antigenic peptides in the process of antigen presentation	67, 69-71
Grp78	ER	Protein (e.g., immunoglobulin) folding	72, 73
Grp170	ER	Implicated in peptide transport in the ER	74
Hsp10	Mitochondria, cytosol, zymogen granules	Protein folding; modulation of immune system	75,17,31,33, 16
Hsp22	Cytosol	Cell protection; maintenance of muscle integrity	76
Hsp27, HspB2	Cytosol	Anti-apoptotic; cytoprotection	77
Hsp40	Cytosol	Folding and refolding of denatured proteins, together with Hsp70/Hsc70	78
Hsp47[b]	ER	Synthesis/assembly of various collagens	79
Hsp60	Mitochondria, cytosol, cell membrane, vesicles, cell surface	Cytoprotection; protein folding; macrophage activator possibly through Toll-like receptors	80-82
Hsc70	Cytosol, nucleus	Protein folding; clathrin uncoating; peptide binding	83
Hsp72	Cytosol, nucleus	Cytoprotection and anti-apoptotic. Implicated in spermatogenesis	84
Hsc74	Mitochondria	Antigen presentation; radioresistance	85-87
Hsp90α	Cytosol	Protein folding; cytoprotection; intracellular signalling (e.g., steroid receptor); cell-cycle control	88, 89
Hsp90β	Cytosol	Protein folding; Cytoprotection; Intracellular signalling (e.g., steroid receptor); Cell-cycle control	90, 91
Hsp110	Cytosol/nucleus	Binds to Hsc70 to form high-molecular-weight complex; involved in protein folding; thermotolerance; involved in embryogenesis	74, 92
Chaperonin II like molecule (TRiC)	Cytosol	Protein folding	93
PDIase	Cytosol, ER	Protein folding inside ER; involved in disulfide bond rearrangement catalysis	94
PPIase	Cytosol, ER, mithocondria	Protein folding; interconverts the *cis* and *trans* isomers of peptide bonds with amino acid proline	95
Sacsin	Cytosol	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	96
SEC63	ER	May perform post-translational protein translocation into ER	97

Modified with permission from (60). For complete guidelines for the nomenclature of the human heat shock proteins, see ref. 61.
[b]Member 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 chaperonin 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-

Table 2. Examples of genetic and acquired chaperonopathies

Chaperones	Genetic chaperonopathies	Acquired chaperonopathies	References
Hsp20, Hsp27, HspB2		Physical association of chaperones with precipitates of abnormal proteins in neurodegenerative disorders Alzheimer's disease (AD).	98
Hsp22 and Hsp27	Neuropathies associated with sHsp mutations		99
Hsp27		Alexander disease	100
Hsp40 (DnaJ3)	Dilated cardiomyopathy		101
Hsp47		Fibrotic disorders	102
Hsp47, PDIase		Posttranslational modification of PDIase and protein misfolding disease	103
Hsp70		Inactivation of chaperones by exogenous toxins	104
Hsp72		Failure of inducible chaperones and disease	105
PPIase (peptidyl–prolil *cis–trans* isomerase)	Williams syndrome		106
Sacsin	Ataxia of Charlevoix–Saguenay		107
SEC63	Pathology of protein transport into the ER		108, 109

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

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

Modified with permission from (8)

Table 4. Examples of roles of cytosolic Hsp10

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

chaperonin for Hsp60. Some examples of these non-canonical roles are given in Table 4.

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 nonconventional 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.

The observation that Hsp10 levels are increased in some conditions has prompted studies to elucidate the significance of high levels of the chaperonin, focusing on apoptosis, cell proliferation, and immune tolerance. Hsp10

Table 5. Tumors in which Hsp10 levels have been found altered compared to normal tissue counterparts

System	Tumor	Methods	Hsp10 levels (compared to normal tissues)	References
Digestive	Large bowel carcinoma	IHC; WB	Higher	31, 32
Female reproductive	Ovarian cancer	IHC;WB	Higher	35
	Exocervical carcinoma	IHC; WB	Higher	31
Hemolymphopoietic	Mantle cell lymphoma	Protein microarray; IHC; WB	Higher	34
Male reproductive	Prostate carcinoma	IHC	Higher	33
	Testicular germ cell tumors	RIA	Higher (EPF-like)	41
Respiratory	Bronchial adenocarcinoma	IHC; WB	Lower	36

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 knock-down 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

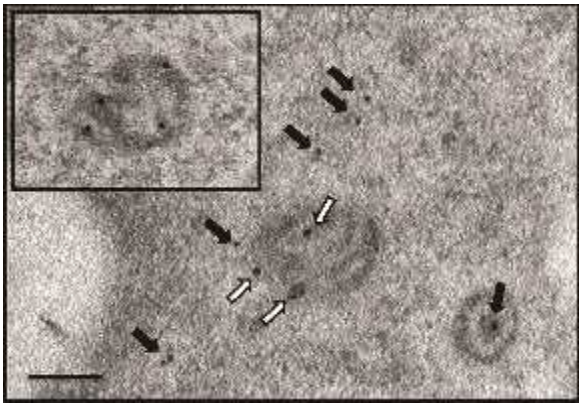

Figure 1. Hsp10 is normally present in the mitochondria (white arrows and inset). However, the chaperonin can also be found in the cytosol (black arrows) of normal cells. Cell: 16HBE (human bronchial epithelium). Bar: 1 micron.

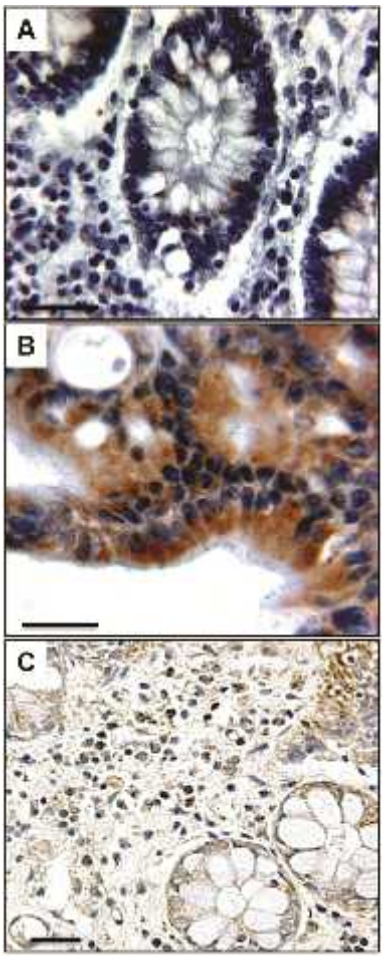

Figure 2. Hsp10 is commonly detectable by immunohistochemical methods in normal and inflamed tissues, as well as in tumors. A: normal colon mucosa. B: Colon cancer. C: Nonspecific colitis. Hsp10 levels in inflammation and cancer are commonly higher in the affected than in the normal tissues. Bar: 50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

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10. REFERENCES

1. Ellis R.J., van der Vies S.M .Molecular chaperones. *Annu Rev Biochem.* 60, 321-347 (1991)

2. Fribley A., Zhang K. and Kaufman R.J. Regulation of apoptosis by the unfolded protein response. *Methods Mol Biol.* 559, 191–204 (2009)

3. Horwich A.L., Fenton W.A., Chapman E. and Farr G.W. Two families of chaperonin: physiology and mechanism. *Annu Rev Cell Dev Biol.* 23 (2007)

4. Macario A.J.L. and Conway de Macario E. Sick chaperones, cellular stress, and disease. *N Engl J Med.* 353(14), 1489–1501 (2005)

5. Coluzza I., De Simone A., Fraternali F. and Frenkel D. Multi-scale simulations provide supporting evidence for the hypothesis of intramolecular protein translocation in GroEL/GroES complexes. *PLoS Comput Biol.* 4(2), e1000006 (2008)

6. Macario A.J.L., Grippo T.M. and Conway de Macario E. Genetic disorders involving molecular-chaperone genes: a perspective. *Genet Med.* 7(1), 3–12 (2005)

7. Macario A.J.L and Conway de Macario E. Chaperonopathies by defect, excess, or mistake. *Ann N Y Acad Sci.* 1113, 178–191 (2007)

8. Macario A.J.L., Cappello, F., Zummo, G., Conway de Macario, E. Chaperonopathies of senescence and the scrambling of the interactions between the chaperoning and the immune systems. *Ann N Y Acad Sci.* 1197, 85-93 (2010)

9. Corrao S., Campanella C., Anzalone R., Farina F., Zummo G., Conway de Macario E., Macario A.J.L, Cappello F., La Rocca G. Human Hsp10 and Early Pregnancy Factor (EPF) and their relationship and involvement in cancer and immunity: current knowledge and perspectives. *Life Sci.* 86(5-6), 145-52. (2010) Review.

10. Azem A., Diamant S., Kessel M., Weiss C. and Goloubinoff P. The protein-folding activity of chaperonins correlates with the symmetric GroEL14(GroES7)2 heterooligomer. *Proc Natl Acad Sci U S A.* 9226, 12,021–12,025 (1995)

11. Hansen J.J., Bross P., Westergaard M., Nielsen M.N., Eiberg H., Børglum A.D., Mogensen J., Kristiansen K., Bolund L. and Gregersen N. Genomic structure of the human mitochondrial chaperonin genes: HSP60 and HSP10 are localized head to head on chromosome 2 separated by a bidirectional promoter. *Hum Genet.* 112 (1), 71–77 (2003)

12. Christensen J.H., Nielsen M.N., Hansen J., Füchtbauer A., Füchtbauer E.M., West M., Corydon T.J., Gregersen N., Bross P. Inactivation of the hereditary spastic paraplegia-associated Hspd1 gene encoding the Hsp60 chaperone results in early embryonic lethality in mice. *Cell Stress Chaperones.* 15(6), 851-863 (2010)

13. Gupta R.S., Ramachandra N.B., Bowes T. and Singh B. Unusual cellular disposition of the mitochondrial molecular chaperones Hsp60, Hsp70 and Hsp10. *Novartis Found Symp.* 291, 59–68 (2008)

14. Jarvis J.A., Ryan M.T., Hoogenraad N.J., Craik D.J. and Høj P.B. Solution structure of the acetylated and noncleavable mitochondrial targeting signal of rat chaperonin 10. *J Biol Chem.* 270(3), 1323–1331 (1995)

15. Vélez-Granell C.S., Arias A.E., Torres-Ruiz J.A. and Bendayan M. Molecular chaperones in pancreatic tissue: the presence of cpn10, cpn60 and hsp70 in distinct compartments along the secretory pathway of the acinar cells. *J Cell Sci.*107(Pt3), 539–549 (1994)

16. Sadacharan S.K., Cavanagh A.C. and Gupta R.S. Immunoelectron microscopy provides evidence for the presence of mitochondrial heat shock 10-kDa protein (chaperonin 10) in red blood cells and a variety of secretory granules. *Histochem Cell Biol.* 116(6), 507–517 (2001)

17. Cappello F., Tripodo C., Farina F., Franco V. and Zummo G. HSP10 selective preference for myeloid and megakaryocytic precursors in normal human bone marrow. *Eur J Histochem.* 48(3), 261–265 (2004)

18. Morton H., Hegh V. and Clunie G.J. Immunosuppression detected in pregnant mice by rosette inhibition test. *Nature* 249(456), 459–460 (1974)

19. Nancarrow C.D., Evison B.M., Scaramuzzi R.J. and Turnbull K.E. Detection of induced death of embryos in sheep by rosette inhibition test. *J Reprod Fertil.* 57(2), 385–389 (1979)

20. Morton H., Morton D.J. and Ellendorff F. The appearance and characteristics of early pregnancy factor in the pig. *J Reprod Fertil* 69**,** 437–446 (1983)

21. Ohnuma K., Ito K., Miyake Y.-I., Tahakashi J.and Yasuda Y. Detection of early pregnancy factor (EPF) in mare sera. *J Reprod Dev.* 42(1), 23–28 (1996)

22. Ghaffari Laleh V., Ghaffari Laleh R., Pirany N. and Moghadaszadeh Ahrabi M. Measurement of EPF for detection of cow pregnancy using rosette inhibition test. *Theriogenology* 70**(**1), 105–107 (2008)

23. Hunter-Lavin C., Davies E.L., Bacelar M.M., Marshall M.J., Andrew S.M. and Williams J.H. Hsp70 release from peripheral blood mononuclear cells. *Biochem Biophys Res Commun.* 324(2), 511–517 (2004)

24. Lancaster G.I. and Febbraio M.A. Exosome-dependent trafficking of HSP70: a novel secretory pathway for cellular stress proteins. *J Biol Chem.* 280(24), 23,349–23,355 (2005)

25. Clayton A., Turkes A., Navabi H., Mason M.D. and Tabi Z. Induction of heat shock proteins in B-cell exosomes. *J Cell Sci*. 118(Pt16), 3631–3638 (2005)

26. Gastpar R., Gehrmann M., Bausero M.A., Asea A, Gross C., Schroeder J.A. and Multhoff G. Heat shock protein 70 surface-positive tumor exosomes stimulate migratory and cytolytic activity of natural killer cells. *Cancer Res.* 65(12), 5238–5247 (2005)

27. Mambula S.S. and Calderwood S.K. Heat shock protein 70 is secreted from tumor cells by a nonclassical pathway involving lysosomal endosomes. *J Immunol.* 177(11), 7849–7857 (2006)

28. Gupta S. and. Knowlton A.A HSP60 trafficking in adult cardiac myocytes: role of the exosomal pathway. *Am J Physiol Heart Circ Physiol.* 292(6), H3052–H3056 (2007)

29. Cappello F., Merendino A.M, Bucchieri F., Campanella C., David S., Pitruzzella A., Marcianò V., Zummo G., Burgio G., Corona D., Conway de Macario E. and Macario A.J.L. Secretion of chaperonin Hsp60 by human tumors. *The 4th Cell Stress Society International (CSSI) Congress on Stress Responses in Biology and Medicine, The 4th Annual Meeting of the Biomedical Society for Stress Response (BSSR) 6–9,* 238 (2009)

30. De Maio A. Extracellular heat shock proteins, cellular export vesicles, and the Stress Observation System: a form

of communication during injury, infection, and cell damage. It is never known how far a controversial finding will go! Dedicated to Ferruccio Ritossa. *Cell Stress Chaperones* 16(3), 235-49 (2011)

31. Cappello F., Bellafiore M., David S., Anzalone R. and Zummo G. Ten kilodalton heat shock protein (HSP10) is overexpressed during carcinogenesis of large bowel and uterine exocervix. *Cancer Lett.* 196(1), 35–41 (2003a)

32. Cappello F., David S., Rappa F., Bucchieri F., Marasà L., Bartolotta T.E., Farina F. and Zummo G. The expression of HSP60 and HSP10 in large bowel carcinomas with lymph node metastase. *BMC Cancer* 5, 139 (2005)

33. Cappello F., Rappa F., David S., Anzalone R. and Zummo G. Immunohistochemical evaluation of PCNA, p53, HSP60, HSP10 and MUC-2 presence and expression in prostate carcinogenesis. *Anticancer Res*. 23(2B), 1325–1331 (2003b)

34. Ghobrial I.M., McCormick D.J., Kaufmann S.H., Leontovich A.A., Loegering D.A., Dai N.T., Krajnik K.L., Stenson M.J., Melhem M.F., Novak A.J., Ansell S.M. and Witzig T.E. Proteomic analysis of mantle-cell lymphoma by protein microarray. *Blood* 105(9), 3722–3730 (2005)

35. Têtu B., Popa I., Bairati I., L'Esperance S., Bachvarova M., Plante M., Harel F. and Bachvarov D. Immunohistochemical analysis of possible chemoresistance markers identified by micro-arrays on serous ovarian carcinomas. *Mod Pathol.* 21(8), 1002–1010 (2008)

36. Cappello F., Di Stefano A., David S., Rappa F., Anzalone R., La Rocca G., D'Anna S.E., Magno F., Donner C.F., Balbi B. and Zummo G. Hsp60 and Hsp10 down-regulation predicts bronchial epithelial carcinogenesis in smokers with chronic obstructive pulmonary disease. *Cancer* 107(10), 2417–2424 (2006)

37. Fan X., Yan L., Jia S., Ma A., Qiao C. A study of early pregnancy factor activity in the sera of women with trophoblastic tumor. *Am J Reprod Immunol.* 41, 204–208 (1999)

38. Bojahr B., Straube W., Reddemann H. Case observations on the significance of early pregnancy factor as a tumor marker. *Zentralbl Gynakol.* 115, 125–128 (1993a)

39. Bojahr B., Straube W., Romer T. Early pregnancy factor (EPF) as tumour marker in two patients with trophoblastic tumour. *Arch Gynecol Obstet.* 252(4):215-8 (1993b)

40. Akyol S., Gercel-Taylor C., Reynolds L.C., Taylor D.D. HSP-10 in ovarian cancer: expression and suppression of T-cell signaling. *Gynecol Oncol.* 101, 481–486 (2006)

41. Rolfe B.E, Morton H., Cavanagh A.C., Gardiner R.A. Detection of an early pregnancy factor-like substance in sera of patients with testicular germ cell tumors. *Am J Reprod Immunol.* 3, 97–100 (1983)

42. Samali A., Cai J., Zhivotovsky B., Jones D.P. and Orrenius S. Presence of a pre-apoptotic complex of pro-caspase-3, Hsp60 and Hsp10 in the mitochondrial fraction of jurkat cells. *EMBO J.* 18 (8), 2040–2048 (1999)

43. Ling J., Zhao K., Cui Y.G., Li Y., Wang X., Li M., Xue K., Ma X., Liu J.Y. Heat shock protein 10 regulated apoptosis of mouse ovarian granulosa cells. *Gynecol Endocrinol.* 27(1), 63-71 (2011)

44. He Y., Shang X., Sun J., Zhang L., Zhao W., Tian Y., Cheng H., Zhou R. Gonadal apoptosis during sex reversal of the rice field eel: implications for an evolutionarily conserved role of the molecular chaperone heat shock protein 10. J *Exp Zool B Mol Dev Evol* 314(4), 257-66 (2010)

45. Quinn K.A., Athanasas-Platsis S., Wong T.Y., Rolfe B.E, Cavanagh A..C, Morton H. Monoclonal antibodies to early pregnancy factor perturb tumour cell growth. *Clin Exp Immunol.* 80, 100–108 (1990)

46. Lash G.E. and Legge M. Early pregnancy factor: an unresolved molecule. *J Assist Reprod Genet.* 14(9), 495–496 (1997)

47. Agnello D., Scanziani E., Di Giancamillo M., Leoni F., Modena D., Mascagni P., Introna M., Grezzi P., Villa P. Preventive administration of Mycobacterium tubercolosis 10-kDa heat shock protein (hsp10) suppresses adjuvant arthritis in Lewis rats. *Int Immunopharmacol. International* 2(4), 463-474 (2002)

48. Vanags D, Williams B., Johnson B., Hall S., Nash P., Taylor A., Weiss J., Feeney D. Therapeutic efficacy and safety of chaperonin 10 in patients with rheumatoid arthritis: a double-blind randomised trial. *Lancet.* 368 (9538), 855-863 (2006)

49. Raine C.S. Biology of disease: analysis of autoimmune demyelination: its impact upon multiple sclerosis. *Lab Invest. Laboratory Investigation.* 50(6), 608-635 (1984)

50. Zhang B., Harness J., Somodovilla-Torres M.J., Hillyard N.C., Mould A.W., Alewood D., Love S.G., Alewood P.F., Greer J.M., Cavanagh A.C., McCombe P.A., Morton H. Early pregnancy factor suppress experimental autoimmune encephalomyelitis induced in Lewis rats with myelin basic protein and in SJL/J mice with myelin proteolipid protein peptide 139-151. *J Neurol Sci.* 182(1), 5-15 (2000)

51. McCombe P.A. Recombinant EPF/chaperonin 10 promotes the survival of O4-positive pro-oligodendrocytes

prepared from neonatal rat brain. *Cell Stress Chaperones.* 13(4), 467-474 (2008)

52. Lorenzi A.R., Ford H.L. Multiple sclerosis and pregnancy. *Postgrad Med J.* 78(922), 460-464 (2002)

53. Rolfe B.E., Cavangh A.C., Quinn K.A., Morton H. Identification of two suppressor factors by early pregnancy factor. *Clin Exp Immunol.* 73, 219-225 (1988)

54. Broadley S.A., Vanags D., Williams B., Johnson B., Feeney D., Griffiths L., Shakib S., Brown G., Coulthard A., Mullins P., Kneebone C. Results of a phase IIa clinical trial of an anti-inflammatory molecule, chaperonin 10, in multiple sclerosis. *Mult Scler.* 15(3), 329-36, (2009)

55. Williams B., Vanags D., Hall S., McCormack C., Foley P., Weiss J., Johnson B., Latz E., Feeney D. Efficacy and safety of chaperonin 10 in patients with moderate to severe plaque psoriasis: evidence of utility beyond a single indication. *Arch Dermatol.* 144(5), 683-5 (2008)

56. Vanags D., Williams B., Johnson B., Hall S., Nash P., Taylor A., Weiss J., Feeney D. Therapeutic efficacy and safety of chaperonin 10 in patients with rheumatoid arthritis: a double-blind randomised trial. *Lancet* 368(9538), 855-63 (2006)

57. Rodolico V., Tomasello G., Zerilli M., Martorana A., Pitruzzella A., Gammazza A.M., David S., Zummo G., Damiani P., Accomando S., Conway de Macario E., Macario A.J.L., Cappello F. Hsp60 and Hsp10 increase in colon mucosa of Crohn's disease and ulcerative colitis. *Cell Stress Chaperones.* 15(6), 877-84 (2010)

58. Kayani A.C., Close G.L., Dillmann W.H., Mestril R., Jackson M.J., McArdle A. Overexpression of HSP10 in skeletal muscle of transgenic mice prevents the age-related fall in maximum tetanic force generation and muscle Cross-Sectional Area. *Am J Physiol Regul Integr Comp Physiol.* 299(1), R268-76 (2010)

59. Haak J.L., Buettner G.R., Spitz D.R., Kregel K.C. Aging augments mitochondrial susceptibility to heat stress. *Am J Physiol Regul Integr Comp Physiol.* 296(3), R812-20 (2009)

60. Li Z., Srivastava P. Heat-shock proteins. *Curr Protoc Immunol.* Appendix 1:Appendix 1T (2004)

61. Kamping H.H., Hageman J., Vos M.J., Kubota H., Tanguay R.M., Bruford E.A., Cheetham M.E.,Chen B., Hightower L.E. Guidelines for the nomenclature of the human heat shock proteins. *Cell Stress Chaperones* 14(1), 105-11 (2009)

62. Xi J.H., Bai F., and Andley U.P. Reduced survival of lens epithelial cells in the alphaA-crystallin-knockout mouse. *J. Cell. Sci.* 116, 1073-1085 (2003)

63. Quax-Jeuken, Y., Quax, W., van Rens, G., Khan, P.M., and Bloemendal, H. Complete structure of the alpha B-crystallin gene: Conservation of the exon-intron distribution in the two nonlinked alpha-crystallin genes. *Proc. Natl. Acad. Sci. U.S.A.* 82, 5819-5823 (1985)

64. Degen E. and Williams D.B. Participation of a novel 88-kD protein in the biogenesis of murine class I histocompatibility molecules. *J. Cell. Biol.* 112, 1099-1115 (1991)

65. Hochstenbach F., David V., Watkins, S., and Brenner M.B. Endoplasmic reticulum resident protein of 90 kilodaltons associates with the T- and B-cell antigen receptors and major histocompatibility complex antigens during their assembly. *Proc. Natl. Acad. Sci. U.S.A.* 89**,** 4734-4738 (1992)

66. Sadasivan B., Lehne, P.J., Ortmann, B. Spies, T., and Cresswell P. Roles for calreticulin and a novel glycoprotein, tapasin, in the interaction of MHC class I molecules with TAP. *Immunity* 5, 103-114 (1996)

67. Basu S., Binder R.J., Suto R., Anderson K.M., and Srivastava P.K. Necrotic but not apoptotic cell death releases heat shock proteins, which deliver a partial maturation signal to dendritic cells and activate the NF-kappa B pathway. *Int. Immunol.* 12, 1539-1546 (2000)

68. Ogden C.A., deCathelineau A., Hoffmann P.R., Bratton D., Ghebrehiwe, B., Fadok V.A., and Henson P.M. C1q and mannose binding lectin engagement of cell surface calreticulin and cd91 initiates macropinocytosis and uptake of apoptotic cells. *J. Exp. Med.* 194, 781-796 (2001)

69. Li Z. and Srivastava P.K. Tumor rejection antigen gp96/grp94 is an ATPase: Implications for protein folding and antigen presentation. *EMBO J.* 12, 3143-3151 (1993)

70. Suto R. and Srivastava P.K. A mechanism for the specific immunogenicity of heat shock protein- chaperoned peptides. *Science* 269, 1585-1588 (1995)

71. Binder, R.J., Han, D.K., and Srivastava, P.K. CD91: A receptor for heat shock protein gp96. *Nat. Immunol.* 1, 151-155 (2000)

72. Haas I.G. and Wabl M. Immunoglobulin heavy chain binding protein. *Nature* 306, 387-389 (1983)

73. Kaloff C.R. and Haas I.G. Coordination of immunoglobulin chain folding and immunoglobulin chain assembly is essential for the formation of functional IgG. *Immunity* 2, 629-637 (1995)

74. Wang X.Y., Kazim L., Repasky E.A., and Subjeck J.R. Characterization of heat shock protein 110 and glucose-regulated protein 170 as cancer vaccines and the effect of fever-range hyperthermia on vaccine activity. *J. Immunol.* 166, 490-497 (2001)

75. Czarnecka A.M., Campanella C., Zummo G., Cappello F. Mitochondrial chaperones in cancer: from molecular biology to clinical diagnostics. *Cancer Biol. Ther.* 5(7), 714-20 (2006)

76. Benndorf R., Sun X, Gilmont R.R., Biederman K.J., Molloy M.P., Goodmurphy C.W., Cheng H., Andrews P.C., Welsh M.J. HSP22, a new member of the small heat shock protein superfamily, interacts with mimic of phosphorylated HSP27 ((3D)HSP27) *J. Biol. Chem.* 276(29), 26753-61 (2001)

77. Arrigo A.P. and Landry J. Expression and function of the low-molecular weight heat shock proteins. *In The Biology of the Heat Shock Proteins and Molecular chaperones* (R.I.Morimoto, A.Tissieres, and C.Georgopoulos, eds.) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York. pp.335-373 (1994)

78. Ohtsuka K. and Hata M. Mammalian HSP40/DNAJ homologs: Cloning of novel cDNAs and a proposal for their classification and nomenclature. *Cell Stress Chaperones* 5, 98-112 (2000)

79. Tasab M., Batten M.R., and Bulleid N.J. Hsp47: A molecular chaperone that interacts with and stabilizes correctly-folded procollagen. *EMBO J.* 19, 2204-2211 (2000)

80. Bukau B. and Horwich A.L.The Hsp70 and Hsp60 chaperone machines. *Cell* 92, 351-366 (1998)

81. Ohashi K., Burkart V., Flohe S., and Kolb H. Cutting edge: Heat shock protein 60 is a putative endogenous ligand of the toll-like receptor-4 complex. *J. Immunol.* 164, 558-561 (2000)

82. Cappello F., Conway de Macario E., Marasà L., Zummo G., Macario A.J.L. Hsp60 expression, new locations, functions and perspectives for cancer diagnosis and therapy. Review. *Cancer Biol. Ther.* 7(6), 801-9 (2008)

83. Udono H. and Srivastava, P.K. Heat shock protein 70–associated peptides elicit specific cancer immunity. *J. Exp. Med.* 178, 1391-1396 (1993)

84. Melcher A., Todryk S., Hardwick N., Ford M., Jacobson M., and Vile R.G. Tumor immunogenicity is determined by the mechanism of cell death via induction of heat shock protein expression. *Nat. Med.* 4, 581-587 (1998)

85. Dahlseid J.N., Lill R., Green J.M., Xu X., Qiu Y., and Pierce S.K. PBP74, a new member of the mammalian 70-kDa heat shock protein family, is a mitochondrial protein. *Mol. Biol. Cell.* **5**, 1265-1275 (1994)

86. Wadhwa R., Taira K., and Kaul S.C. An Hsp70 family chaperone, mortalin/mthsp70/PBP74/Grp75: What, when, and where? *Cell Stress Chaperones* **7**, 309-316 (2002)

87. Liu Q., D'Silva P., Walter W., Marszalek J., and Craig E.A. Regulated cycling of mitochondrial Hsp70 at the protein import channel. *Science* 300, 139-141 (2003)

88. Rutherford S.L. and Lindquist S. Hsp90 as a capacitor for morphological evolution. *Nature* 396, 336-342 (1998)

89. Yamano T., Murata S., Shimbara N., Tanaka N., Chiba T., Tanaka K., Yui K., and Udono H. Two distinct pathways mediated by PA28 and hsp90 in major histocompatibility complex class I antigen processing. *J. Exp. Med.* 196, 185-196 (2002)

90. Ullrich S.J., Robinson E.A., Law L.W., Willingham M., and Appella E. A mouse tumor-specific transplantation antigen is a heat shock–related protein. *Proc. Natl. Acad. Sci. U.S.A.* 83, 3121-3125 (1986)

91. Udono H. and Srivastava P.K. Comparison of tumor-specific immunogenicities of stress-induced proteins gp96, hsp90, and hsp70. *J. Immunol.* 152, 5398-5403 (1994)

92. Manjili M.H., Henderson R., Wang X.Y., Chen X., Li Y., Repasky E., Kazim L., and Subjeck J.R. Development of a recombinant HSP110-HER-2/neu vaccine using the chaperoning properties of HSP110. *Cancer Res.* 62, 1737-1742 (2002)

93. Zhang J., Baker M..L, Schröder G.F., Douglas N.R., Reissmann S., Jakana J., Dougherty M., Fu C.J., Levitt M., Ludtke S.J., Frydman J., Chiu W. Mechanism of folding chamber closure in a group II chaperonin. *Nature*. 463(7279), 379-83 (2010)

94. William L. Kelley and Costa Georgopoulos. Chaperones and protein folding. *Curr Opin Cell Biol.* 4(6), 984-991 (1992)

95. Galat A. Peptidylprolyl cis/trans isomerases (immunophilins): biological diversity--targets--functions. *Curr Top Med Chem.* 3(12), 1315-47 (2003)

96. Parfitt D.A., Michael G.J., Vermeulen E.G., Prodromou N.V., Webb T.R., Gallo J.M., Cheetham M.E., Nicoll W.S., Blatch G.L., Chapple J.P. The ataxia protein sacsin is a functional co-chaperone that protects against polyglutamine-expanded ataxin-1. *Hum. Mol. Genet.* 18, 1556-1565 (2009)

97. Meyer H.A., Grau H., Kraft R., Kostka S., Prehn S., Kalies K.U., Hartmann E. Mammalian Sec61 is associated with Sec62 and Sec63. *J Biol Chem.* 275(19), 14550-7 (2000)

98. Wilhelmus M.M.M., Hoeller O., Wesseling P., de Waal R.M., Boelens W.C., Verbeek M.M. Specific association of small heat shock proteins with the pathological hallmarks of Alzheimer's disease brains. Neuropathol. Appl. Neurobiol. 32, 119–130 (2006)

99. Fontaine J.M., Sun X., Hoppe A.D., Simon S., Vicart P., Welsh M.J., Benndorf R. Abnormal small heat shock protein interactions involving neuropathy-associated HSP22 (HSPB8) mutants. *FASEB J.* 20, 2168–2170 (2006)

100. Der Perng M., Su M., Wen S.F., Li R., Gibbon T., Prescott A.R., Brenner M., Quinlan R.A. The Alexander disease-causing glial fibrillary acidic protein mutant, R416W, accumulates into Rosenthal fibers by a pathway that involves filament aggregation and the association of

alpha-beta-crystallin and HSP27. *Am. J. Hum. Gen.* 79, 197–213 (2006)

101. Hayashi M., Imanaka-Yoshida K., Yoshida T., Wood M., Fearns C., Tatake R.J., Lee J.D. A crucial role of mitochondrial Hsp40 in preventing dilated cardiomyopathy. *Nat. Med.* 12, 128–132 (2006)

102. Taguchi T. & Razzaque M.S. The collagen-specific molecular chaperone HSP47: is there a role in fibrosis? *Trends Mol. Med* 13, 45–53 *(*2007)

103. Uehara T., Nakamura T., Yao D., Shi Z.Q., Gu Z., Ma Y., Masliah E., Nomura Y., Lipton S.A. S-Nitrosylated protein-disulphide isomerase links protein misfolding to neurodegeneration. *Nature* 441, 513–517 (2006)

104. Paton Na.W., Beddoe T., Thorpe C.M., Whisstock J.C., Wilce M.C., Rossjohn J., Talbot U.M., Paton J.C. AB5 subtilase cytotoxin inactivates the endoplasmic reticulum chaperone BiP. *Nature* 443, 548–552 (2006)

105. Andringa G., Bol J.G., Wang X., Boekel A., Bennett M.C., Chase T.N., Drukarch B. Changed distribution pattern of the constitutive rather than the inducible HSP70 chaperone in neuromelanin-containing neurones of the Parkinsonian midbrain. *Neuropathol. Appl. Neurobiol.* 32, 157–169 (2006)

106. Maruyama T., Suzuki R. & Furutani M. Arachael peptydyl-prolyl *cis-trans* isomerases (PPIases) *Front. Biosci.* 9, 1680–1700 (2004)

107. Takiyama Y. Autosomal recessive spastic ataxia of Charlevoix-Saguenay. *Neuropathology* 26, 368–375 (2006)

108. Zimmermann R., Mueller L & Wullich B. Protein transport into the endoplasmic reticulum: mechanisms and pathologies. *Trends Mol. Med.* 12, 567–573 (2006)

109. Davila S., Furu L., Gharavi A.G., Tian X., Onoe T., Qian Q., Li A., Cai Y., Kamath P.S., King B.F., Azurmendi P.J., Tahvanainen P., Kääriäinen H., Höckerstedt K., Devuyst O., Pirson Y., Martin R.S., Lifton R.P., Tahvanainen E., Torres V.E., Somlo S. Mutations in SEC63 cause autosomal dominant polycystic liver disease. *Nat. Genet.* 36, 575–577 (2004)

110. Cappello F. HSP60 and HSP10 as diagnostic and prognostic tools in the management of exocervical carcinoma. *Gynecol Oncol.* 91(3), 661 (2003)

111. Kawamoto Y., Akiguchi I., Shirakashi Y., Honjo Y., Tomimoto H., Takahashi R., Budka H. Accumulation of Hsc70 and Hsp70 in glial cytoplasmic inclusions in patients with multiple system atrophy. *Brain Res.* 1136**,** 219–227 (2007)

112. Nardai G., Végh E.M., Prohászka Z, Csermely P. Chaperone-related immune dysfunction: an emergent property of distorted chaperone networks. *Trends Immunol.* 27**,** 74–79 (2006)

113. Rohde M., Daugaard M., Jensen M.H., Helin K., Nylandsted J., Jäättelä M. Members of the heat-shockprotein 70 family promote cancer cell growth by distinct mechanisms. *Genes Dev.* 19**,** 570–582 (2005)

114. Pick E., Kluger Y., Giltnane J.M., Moeder C., Camp R.L., Rimm D.L., Kluger H.M. High HSP90 expression is associated with decreased survival in breast cancer. *Cancer Res.* 67**,** 2932–2937 (2007)

115. Summers K.M., Murphy R.M., Webb G.C., Peters G.B., Morton H., Cassady A.I. and Cavanagh A.C. The human early pregnancy factor/chaperonin 10 gene family. *Biochem Mol Med.* 58(1), 52–58 (1996)

116. Meghji S., White P.A., Nair S.P., Reddi K., Heron K., Henderson B., Zaliani A., Fossati G., Mascagni P., Hunt J.F., Roberts M.M., Coates A.R. Mycobacterium tuberculosis chaperonin 10 stimulates bone resorption: a potential contributory factor in Pott's disease. *J Exp Med.* 186, 1241–1246 (1997)

117. Morton H. Early pregnancy factor: an extracellular chaperonin 10 homologue. *Immunol Cell Biol.* 76(6), 483–496 (1998)

118. Black A.J., Topping J., Durham B., Farquharson R.G., Fraser W.D. A detailed assessment of alterations in bone turnover, calcium homeostasis, and bone density in normal pregnancy. *J Bone Miner Res.* 15, 557–563 (2000)

119. Shan Y.X., Yang T.L., Mestril R., Wang P.H. Hsp10 and Hsp60 suppress ubiquitination of insulin-like growth factor-1 receptor and augment insulin-like growth factor-1 receptor signaling in cardiac muscle: implications on decreased myocardial protection in diabetic cardiomyopathy. *J Biol Chem.* 278, 45492–45498 (2003b)

120. Levanon D., Goldstein R.E., Bernstein Y., Tang H., Goldenberg D., Stifani S., Paroush Z., Groner Y. Transcriptional repression by AML1 and LEF-1 is mediated by the TLE/Groucho corepressors. *Proc Natl Acad Sci USA.* 95, 11590–11595 (1998)

121. Liu Y., Dehni G., Purcell K.J., Sokolow J., Carcangiu M.L., Artavanis-Tsakonas S., Stifani S. Epithelial expression and chromosomal location of human TLE genes: implications for notch signaling and neoplasia. *Genomics.* 31, 58–64 (1996)

122. Xiao L., Celano P., Mank A.R., Griffin C., Jabs E.W., Hawkins A.L., Casero Jr R.A. Structure of the human spermidine/spermine N^1-acetyltransferase gene (exon/intron gene organization and localization to Xp22.1) *Biochem Biophys Res Commun.* 187, 1493–1502 (1992)

123. Casero Jr R.A., Celano P., Ervin S.J., Wiest L., Pegg A.E. High specific induction of spermidine/spermine N^1-acetyltransferase in a human large cell lung carcinoma. *Biochem J.* 270, 615–620 (1990)

124. Kajkowski E.M., Lo C.F., Ning X., Walker S., Sofia H.J., Wang W., Edris W., Chanda P., Wagner E., Vile S.,

Ryan K., McHendry-Rinde B., Smith S.C., Wood A., Rhodes K.J., Kennedy J.D., Bard J., Jacobsen J.S., Ozenberger B.A. β-Amyloid peptide-induced apoptosis regulated by a novel protein containing a g protein activation module. *J Biol Chem*. 276, 18748–18756 (2001)

125. Hamajima N., Matsuda K., Sakata S., Tamaki N., Sasaki M., Nonaka M. A novel gene family defined by human dihydropyrimidinase and three related proteins with differential tissue distribution. *Gene* 180, 157–163 (1996)

126. Veitia R.A., Ottolenghi C., Bissery M.C., Fellous A. A novel human gene, encoding a potential membrane protein conserved from yeast to man, is strongly expressed in testis and cancer cell lines. *Cytogenet Cell Genet*. 85, 217–220 (1999)

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