The Prospect Of Heat Shock Protein (Hsp) As Biomarker Of Oral Disease

Prospek Heat Shock Protein (Hsp) Sebagai Biomarker Penyakit Gigi Dan Mulut

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Abstract

The prevalence of oral diseases is increasing and caused by many factors. It can be caused by environmental, genetic, malignancy or side effects of dental treatment. The research detect these disease has been done, but still not getting satisfactory results. Heat shock proteins (HSP) are intracellular proteins that mediate the cytoprotective function and other essential functions. This protein is expressed and synthesized under conditions of stress/harmful or nonstress. The oral disease is a form of adverse conditions, and the course will also trigger HSP expression.

Keyword: Heat shock protein (HSP), biomarker, oral disease

Abstract

Prevalensi penyakit gigi dan mulut semakin meningkat dan disebabkan oleh banyak factor. Hal tresebut dapat disebabkan lingkungan, genetic, keganasan ataupun efek samping perawatan gigi. Penelitian untuk mendeteksi penyakit-penyakit tersebut sudah banyak dilakukan, tetapi masih belum memberikan hasil yang memuaskan. Heat shock proteins (HSP) adalah protein intraselular yang memediasi fungsi sitoprotektif dan fungsi penting lainnya. Protein ini diekspresikan dan disintesis dibawah kondisi stress/berbahaya ataupun nonstress. Sedangkan penyakit gigi dan mulut merupakan salah satu bentuk kondisi yang merugikan dan tentu saja akan memicu ekspresi HSP.

Kata Kunci: Heat shock protein (HSP), biomarker, Penyakit gigi dan mulut

Introduction

Heat shock proteins (Hsps) are a family of highly homologous chaperone proteins that are induced in response to environmental, physical and chemical stressesand that limit the consequences of damage and facilitate cellular recovery. [1,2,3] The stresses that can trigger this response vary widely, and include heat or cold, osmotic imbalance, toxins, heavy metals and pathophysiological signals such as cytokines and eicosanoids. The cell-stress response is an evolutionarily ancient, ubiquitous and essential mechanism for cell survival. [2,3]

HSPs are expressed both constitutively (cognate proteins) and under stressful conditions (inducible forms). In addition to heat shock, a variety of stressful situations including environmental (ultraviolet radiation or heavy metals), pathological (infections or malignancies), or physiological (growth factors or cell differentiation) stimuli induce a marked increase in HSP synthesis, known as the stress response.[3,4]

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Exposure of cells to potentially damaging stresses such as UV or nutrient withdrawal induces signals able to mediate cell death, or alternatively, survival pathways that allow cells to tolerate and/or to recover from the damage imposed. This paradoxical activation of both pro and antiapoptotic events in response to the same stimulus ensures that neither aberrant cellular survival nor inappropriate cell death arises and, in doing so, averts the onset and persistence of the pathological state. [5]

The Activation of Heat shock Gen

Heat shock factor (HSF) is present in the cytoplasm as a latent monomeric molecule that is unable to bind to DNA. Under stressful conditions, the flux of non native proteins (which are non-functional, prone to aggregation, protease-sensitive, and bind to chaperones) leads to phosphorylation (P) and trimerisation of HSF. The trimmers translocate to the nucleus, bind the promoter regions of heat shock protein (hsp) genes and mediate hsp gene transcription. The activity of HSF trimers is downregulated by hsps (e.g. Hsp 70) and the heat shock binding protein 1 (HSBP1) that is found in the nucleus. [6]

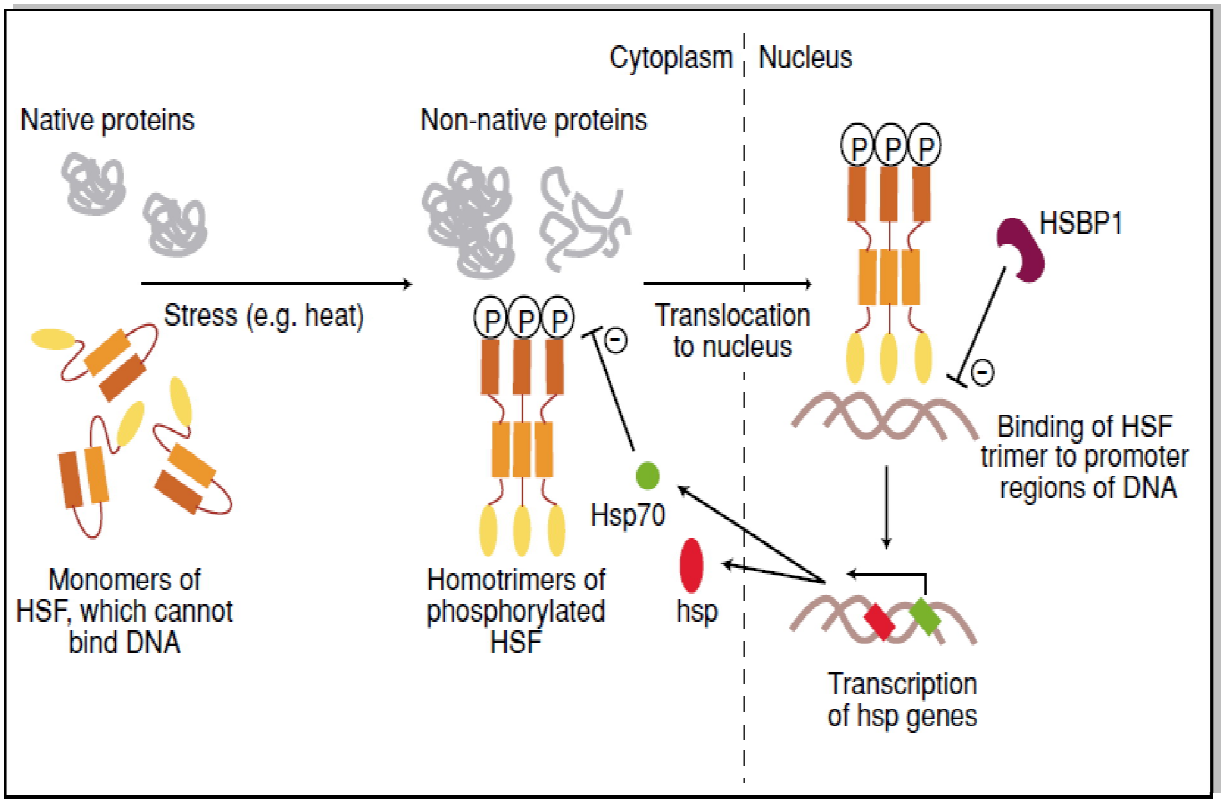

Figure 1. Regulation of Transcription of heat shock protein genes by heat shock factor. [6]

The Family of Heat Shock Protein

The primary function of the HSPs appears to serve as molecular chaperones in which they recognize and bind to nascent polypeptide chains and partially folded intermediates of proteins, preventing their aggregation and misfolding, or as chaperonins that directly mediate protein folding. The classification of HSPs is based on their related function and size (molecular mass). Using the nomenclature adopted after the Cold Spring Harbor Meeting of 1996, family names are written in uppercase, e.g., HSP70, whereas members of a family are conventionally written as Hsps, e.g., Hsp70. Major classes of

HSPs include the small HSPs, HSP40, 60, 70, 90, and 110 families. In mammalian species, the HSP60 (chaperonin) family consists of mitochondrial Hsp60 (mt-Hsp60) and cytosolic Hsp60 (T-complex polypeptide-1).[7]

Table 1. Key members of the heat shock protein family in humans [2,4,6]

HSP member	Location	Description
Small HSP		
Ubiquitin	Cytoplasm/nucleus	Facilitates targeting and removal of denatured proteins
Hsp10	Mitochondria	Cofactor for HSP60
Hsp27	Cytoplasm/nucleus	Involved in intracellular actin dynamics
β-crystallin	Cytoplasm	Involved in cytoskeletal stabilisation
HSP40		
Hsp40	Cytoplasm/nucleus	Regulates activity of HSP70, binds non-native protein
Hsp47	Endoplasmic reticulum	Processing of pro-collagen
HSP60		
Hsp60	Mitochondria	Molecular chaperone
HSP70		
Hsp72	Cytoplasm/nucleus	Highly stress inducible, protects against ischemia
Hsp73	Cytoplasm/nucleus	Constitutively expressed molecular chaperone
Hsp75	Mitochondria	Induced by stress including hypoxia
HSP90		
Hsp90	Cytoplasm (migrates to nucleus)	Part of the steroid receptor complex
HSP110		
Hsp110	Nucleolus/cytoplasm	Thermal tolerance
Hsp105	Cytoplasm	Protein refolding

The Expression and potential therapeutic Application of heat shock protein

The network of heat shock or stress proteins represents an emerging paradigm for the coordinated, multistep regulation of apoptotic signaling events to provide protection from and to facilitate cellular recovery after exposure to damaging stimuli. Heat shock proteins (Hsps) constitute a highly conserved and functionally interactive network of chaperone proteins, some of which are constitutively expressed and others of which are rapidly induced in response to a variety of chemical, environmental, and physiological stresses. Their collective ability to disaggregate, refold, and renature misfolded proteins offsets the otherwise fatal consequences of damaging stimuli. This protective function of Hsps has been suggested to reflect their ability to suppress several forms of cell death, including apoptosis.[5,6]

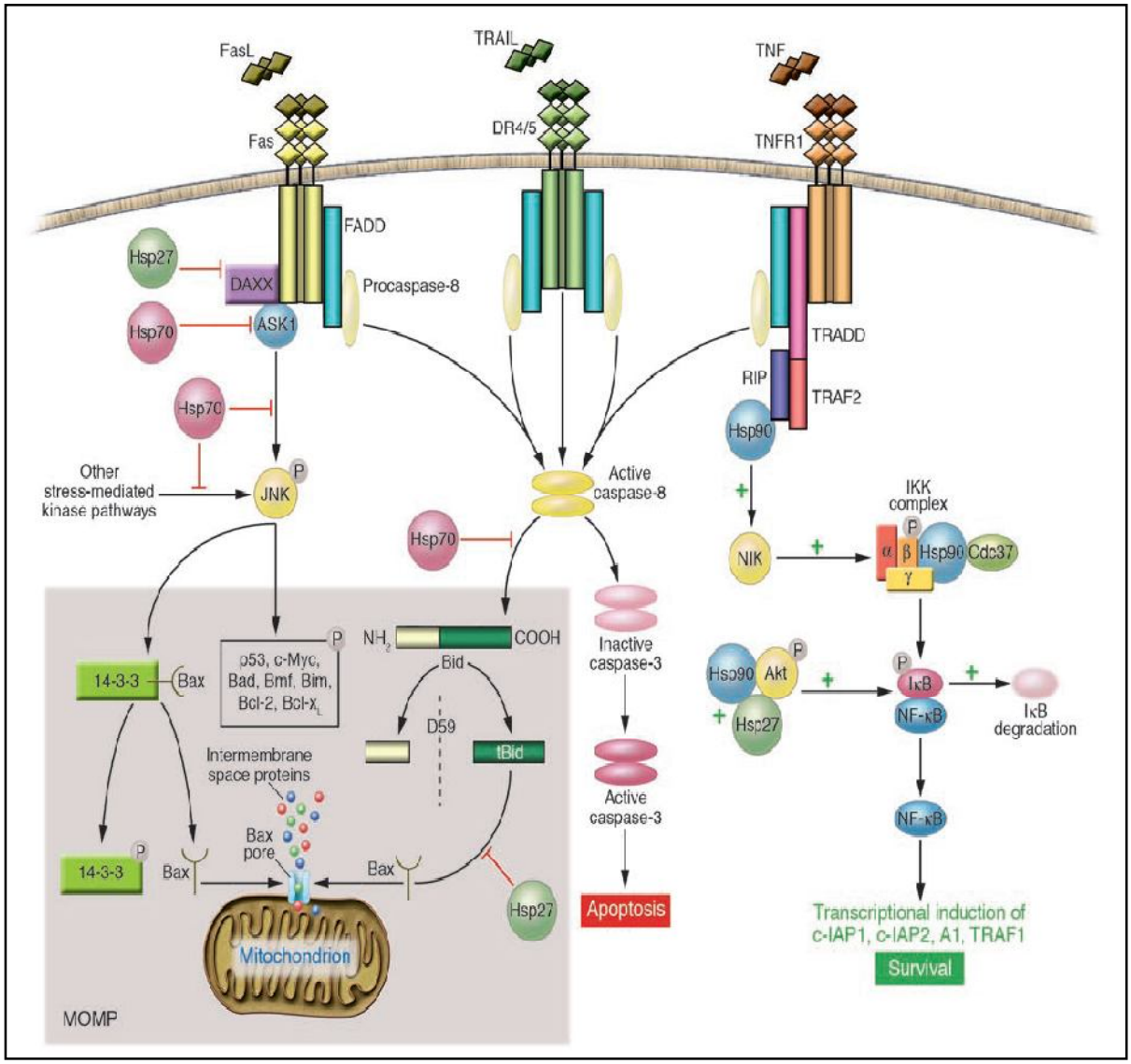

Figure 2. Regulation of the extrinsic pathway by Hsps.[5]

Hsps regulate at multiple points within the signaling pathways activated by ligation of a cell surface death receptor by the appropriate ligand. These include the maintenance of prosurvival signals generated via TNF-mediated activation of NF-κB and suppression of proapoptotic signaling events, e.g., JNK activity and Bid cleavage. Integration of the extrinsic and intrinsic pathways is mediated via the caspase-8–mediated cleavage and activation of Bid as well as activation of JNK, which can impact on numerous molecules that regulate mitochondrial integrity (shown in the shaded area). [5]

Hsps regulate several aspects of the intrinsic apoptotic pathway. These include both direct mediators — e.g., Bax — and indirect regulators — e.g., Akt — of mitochondrial membrane permeabilization to prevent MOMP as well as events downstream of mitochondrial disruption to regulate apoptosome assembly. Caspase-independent cell death may also be affected via Hsp-mediated suppression of AIF activity and inhibition of lysosome permeabilization and cathepsin release.[5]

Several studies showing the expression of HSP in some oral disease are summarized in Table 2

Table 2. Evidence for the involvement of HSP/Chaperonin in Oral disease

HSP	Disease
HSP 10	- growth factor of osteoclasts (M. tuberculosis chaperonin 10) [7]
HSP 27	- Osteoclastic resorption – calcium release [8] - Ameloblastomas, Salivary gland cancer, dysplastic lesions (Oral cancer), squamous cell carcinoma [9] - oral tongue squamous cell carcinoma [10]
HSP 60	- Ameloblastomas [9] - Periodontitis [11] - Cronic Periodontitis (+ microbial hsp 65) [12]
HSP 70	- Dental caries [13] - Ameloblastomas , Salivary gland cancer , squamous cell carcinoma [9] - oral squamous cell carcinoma [14,15] - dysplastic lesion and oral squamous cell carcinomas [16] - cancer of gingivo-buccal and tongue [17]
HSP 90	- Salivary gland cancer [9]
HSP 110	- Salivary gland cancer [9]

Conclusion

HSP may be a candidate as an oral disease biomarker and further research is needed to prove it again

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