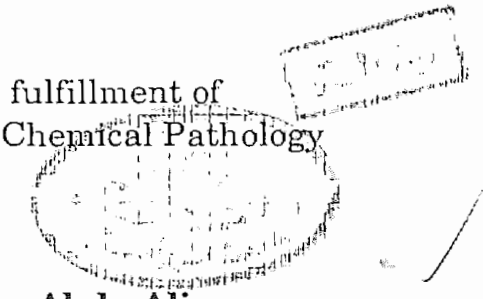
HEAT SHOCK PROTEINS: AN OVER VIEW

Essay

Submitted in the partial fulfillment of
Master Degree in Clinical and Chemical Pathology



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بسم الله الرحمن الرحيم

قالوا سبحانك لا علم لنا إلا ما علمتنا إنك إنت العليم الحكيم

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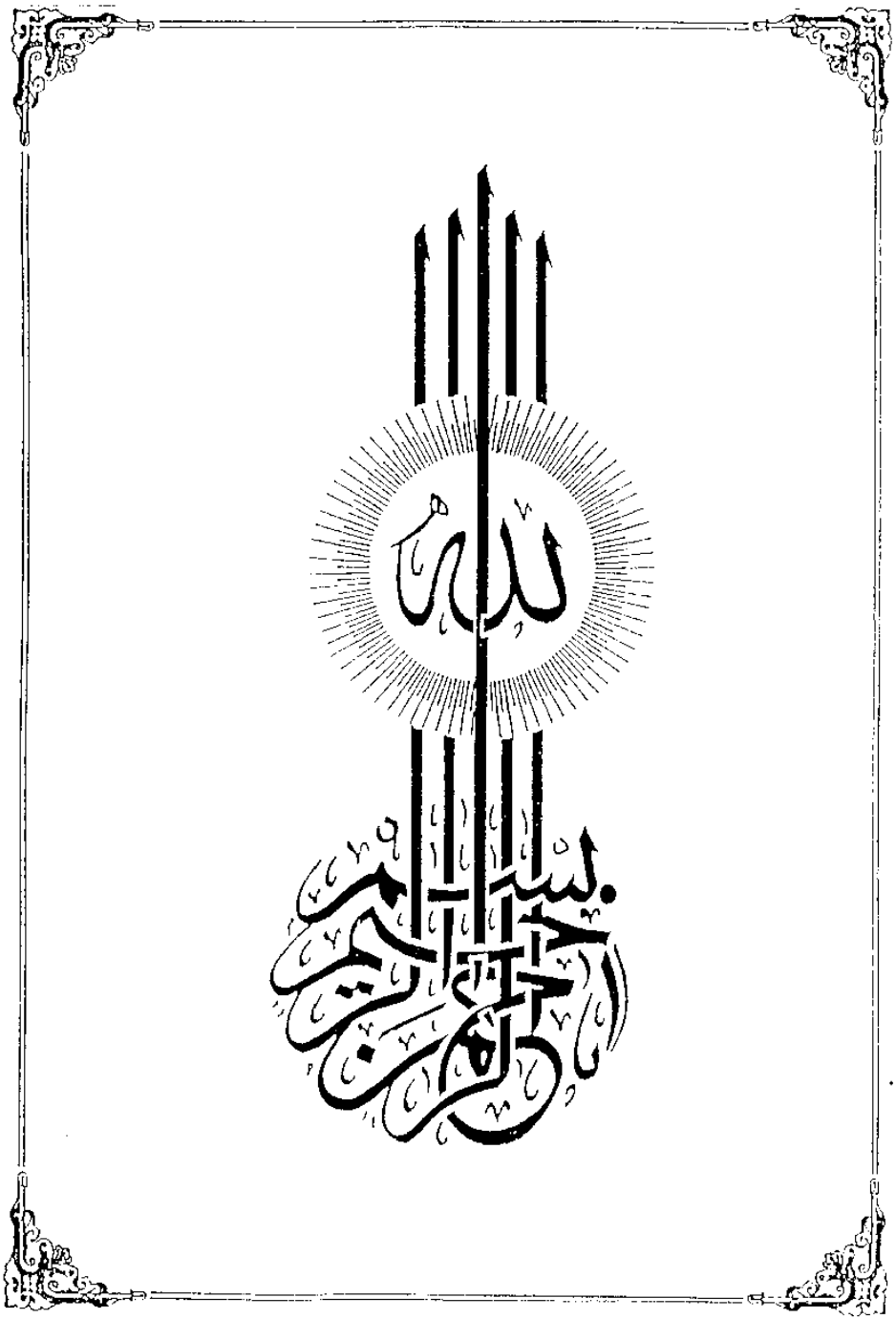

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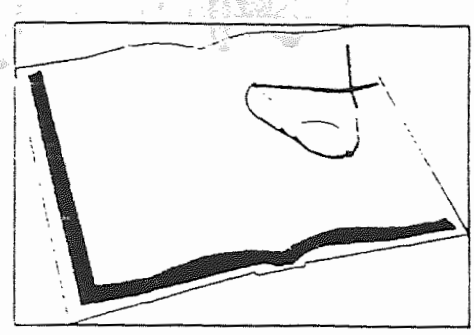
List of Errata

Page	Line	Wrong	Right
13	13	ER membrane hsp protein	ER membrane protein
19	9	hsp 82	hsc 82
22	15	thiolester	thiol ester
28	16	anorexia	anoxia
32	11	mamalian	mammalian
40	5	os	or
41	14	elone	clone
49	3	S.L.E and patients	S.L.E compared with patients
57	3	Leads disease	leads to disease

LIST OF ABBREVIATIONS

AA	Adjuvant arthritis
APCs	Antigen presenting cells
CTL	Cytotoxic T-lymphocytes
ER	Endoplasmic reticulum
hsc	Heat shock cognate
hsp	Heat shock proteins
IDDM	Insulin dependent diabetes mellitus
kDa	Kilodlalton
MHC	Major histocompatibility complex
NOD	Non obese diabetic
PCB	Polypeptide chain binding protein
RA	Rheumatoid arthritis
ReA	Reactive arthritis

CONTENTS



INTRODUCTION AND AIM OF THE WORK

INTRODUCTION

In 1962 Ritossa had discovered that a small temperature elevation, as well as treatment with particular chemicals, produced a stricking new puffing pattern on the giant salivary gland chromosomes of Drosophila fly. A small number of new puffs appeared, while most of the many puffs present before the heat shock regressed and often disappeared altogether. Experiments with radioactive markers (cytidine, uridine) showed that the newly induced puffs were the sites of intense transcription and the observations of Ritossa therefore indicated that mild heat shock as well as stresses induced by some chemicals led to profound alterations of gene expression. It is known that a small number of specific genes, the so-called heat shock genes, located at the sites of the heat shock-induced puffs, are vigorously activated under those conditions, while the expression of many of the genes active before the stress is precluded *(Bearman et al., 1956).*

It is now known that the products of the activated genes, the heat shock proteins (hsps), already present in small amounts in many cells in the absence of stress, rapidly increases under stress, and in some instances reaches fairly large concentrations *(Pauli et al., 1992).*

Following the early work on Drosophila, a similar heat shock response was observed in all organisms examined, from archae bacteria to man, showing that the response is universal *(Kellum and Schedl, 1991).*

Remarkable homologies of nucleotide sequences were found, not only between (hs) genes of very distant eukaryotes, but also between (hs) genes from prokaryotes and eukaryotes which is consistent with their having an essential role in cell survival. The (hs) genes appear to be among the most conserved genes *(Pauli et al., 1992).*

The immune dominance of hsp, and the existence of easily detectable immune reactions to autologous hsp, have led to various hypotheses about hsp as a link between infection and autoimmune disease *(Sinha et al., 1990).*

Hsp are not only imortant in situations of heat shock or stress, where they were detected first and where their name originates, but also appear to be essential for cell survival in normal situations.

One of the most prominent roles of hsp is in protein folding and degradation. This has led to the concept of hsp as

chaperonins (a chaperone provides nursing or guidance) *(Ellis et al., 1991).*

In their recent published article, Burel et al., (1992) had drown attention to the following points:

- Hsp synthesis is only one phase of a general adaptive response towards heat shock and similar stresses.
- Hsps are members of large families of proteins which have similar functions, but different expressions.
- Hsp synthesis can be regulated in a specific way, independently of any stress treatment, in different physiological conditions, for instance during gametogenesis or early development.
- Hsps and related proteins fulfil essential functions in the normal cell.
- The same functions are required in stressed cells.

AIM OF THE WORK

Our aim of this essay is to give a historical review after 3 decades of hsp research and to clarify the expression and the function of the different hsp families. Also to view hsp as target for the immune system and to explain their role in autoimmune diseases and immune regulation. We also try to summarize the role of hsp in health and disease.

REVIEW OF LITERATURE

A. CLASSIFICATION AND DISCRIPTION OF HSPS

The major mammalian hsps are classified into four families on the basis of their molecular weights and sequence homologies:

1. The large molecular weight hsp of 83-90 kDa (hsp 90 family).

2. Hsp 70 family ranging from - 66 to 78 kDa.

3. The hsp 60 family ranging from 60-65 kDa.

4. The small hsps a diverse group of proteins ranging from -15 to >30 kDa.

In addition to some larger hsps of -100 - 110 kDa *(Morimoto et al., 1990).*

The small hsp involve:

* 8-kDa protein: involved in protein degradation, ubiquitin.

* 27-kDa hsp: this hsp is structurally related to the α-crystallins of the lens *(Klonenz et al., 1991).*

* 28-kDa protein: consists of at least 4 major isoforms, three of which are phosphorylated. There is increased

phosphorylation in response to mitogens /tumor promoters *(Holland et al., 1993).*

* 32-kDa stress protein: was added by Levinson et al., 1980. The deduced amino acid sequence of 32 kDa has revealed the protein to be highly related to heme oxygenase which is an essential component in catabolism of heme. In addition the rat heme oxygenase gene itself contains a consensus hsp promoter element and exhibit some increased transcription after heat shock *(Muller et al., 1987).*

* 47-kDa hsp: located in the endoplasmic reticulum and has affinity for collagen. It has been described by Nagata et al., (1986).

* The hsp 60 machine: consists of two members in eukaryotes *(Geogopoulas and Mcfarland, 1993).*

* The hsp 70-kDa family: contains many different genes, (which are located inside HLA system) coding for different proteins expressed under different conditions and in different cell compartments. For instance, in mouse cells, the presently known members are:

- Hsp 68, the major inducible hsp, and
- Hsp 70 which is constitutively expressed and only slightly increased by stress.

These two proteins are cytoplasmic and nuclear in position. There are also two other proteins not induced by heat treatment:

- P 75 which is found inside the mitochondrial matrix *(Kang et al., 1990).*

- Grp 78 located in the lumen of endoplasmic reticulum. The synthesis of this protein is induced by a decrease in glucose concentration in the cell culture medium or by the addition of Ca++.

The number of genes coding for these different proteins is presently unknown but probably high. For hsp 68 more than 5 genes have been described, two of them coding for specific forms of hsp 68 expressed only during gametogenesis *(Zakeri et al., 1987).*