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Transcriptional regulation of small HSP—HSF1 and beyond☆

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ABSTRACT

The members of the small heat shock protein (sHSP) family are molecular chaperones that play major roles in development, stress responses, and diseases, and have been envisioned as targets for therapy, particularly in cancer. The molecular mechanisms that regulate their transcription, in normal, stress, or pathological conditions, are characterized by extreme complexity and subtlety. Although historically linked to the heat shock transcription factors (HSFs), the stress-induced or developmental expression of the diverse members, including HSPB1/Hsp27/Hsp25, αA-crystallin/HSPB4, and αB-crystallin/HSPB5, relies on the combinatory effects of many transcription factors. Coupled with remarkably different *cis*-element architectures in the *sHsp* regulatory regions, they confer to each member its developmental expression or stress-inducibility. For example, multiple regulatory pathways coordinate the spatio-temporal expression of *mouse αA-, αB-crystallin, and Hsp25* genes during lens development, through the action of master genes, like the large Maf family proteins and Pax6, but also HSF4. The inducibility of *Hsp27* and *αB-crystallin* transcription by various stresses is exerted by HSF-dependent mechanisms, by which concomitant induction of Hsp27 and αB-crystallin expression is observed. In contrast, HSF-independent pathways can lead to αB-crystallin expression, but not to Hsp27 induction. Not surprisingly, deregulation of the expression of sHSP is associated with various pathologies, including cancer, neurodegenerative, or cardiac diseases. However, many questions remain to be addressed, and further elucidation of the developmental mechanisms of *sHsp* gene transcription might help to unravel the tissue- and stage-specific functions of this fascinating class of proteins, which might prove to be crucial for future therapeutic strategies.

This article is part of a Directed Issue entitled: Small HSPs in physiology and pathology.

1. Introduction

Small heat shock protein (sHsp) family is characterized by the presence of an α-crystallin domain. The study of *sHsp* gene expression contributed in many ways to major breakthroughs in the understanding of the mechanisms of gene transcription, at a time where the concepts of transcription factors and of specific DNA-binding sites were only emerging. These discoveries have concerned the induction of these genes in response to stress, but also their striking expression in the development of diverse organisms from yeast to mammals.

1.1. *A little of history – cloning and transcriptional regulation of the small Hsp genes in response to stress and in development*

Together with *hsp83* and *hsp70* genes, the cloning of the *Drosophila sHsp* genes (*hsp22*, *hsp23*, *hsp26*, *hsp27* genes; Holmgren et al., 1981; Riddihough and Pelham, 1986) led to functional studies by transfection of cells or transformation of flies with hybrid genes, containing portions of the regulatory regions of the *Hsp* genes and reporter genes (Lis et al., 1981, 1983; Pauli et al., 1986; Pelham, 1982). In addition to a TATA box, these approaches contributed to the identification of the heat shock element (HSE; Fig. 1A), a very conserved regulatory sequence present in the 400 bp upstream *Hsp* genes, that is necessary and sufficient for their inducibility by heat shock, even in heterologous systems. First described as 5′CTnGAAnnTTCnAG3′ (Pelham, 1982), HSE was further refined as an inverted tandem repeats of the motif 5′nTTCnnGAAn3′ (Xiao and Lis, 1988), and more recently through genome-wide and bioinformatical analyses (Trinklein et al., 2004; Fig. 1B; Genomatix,

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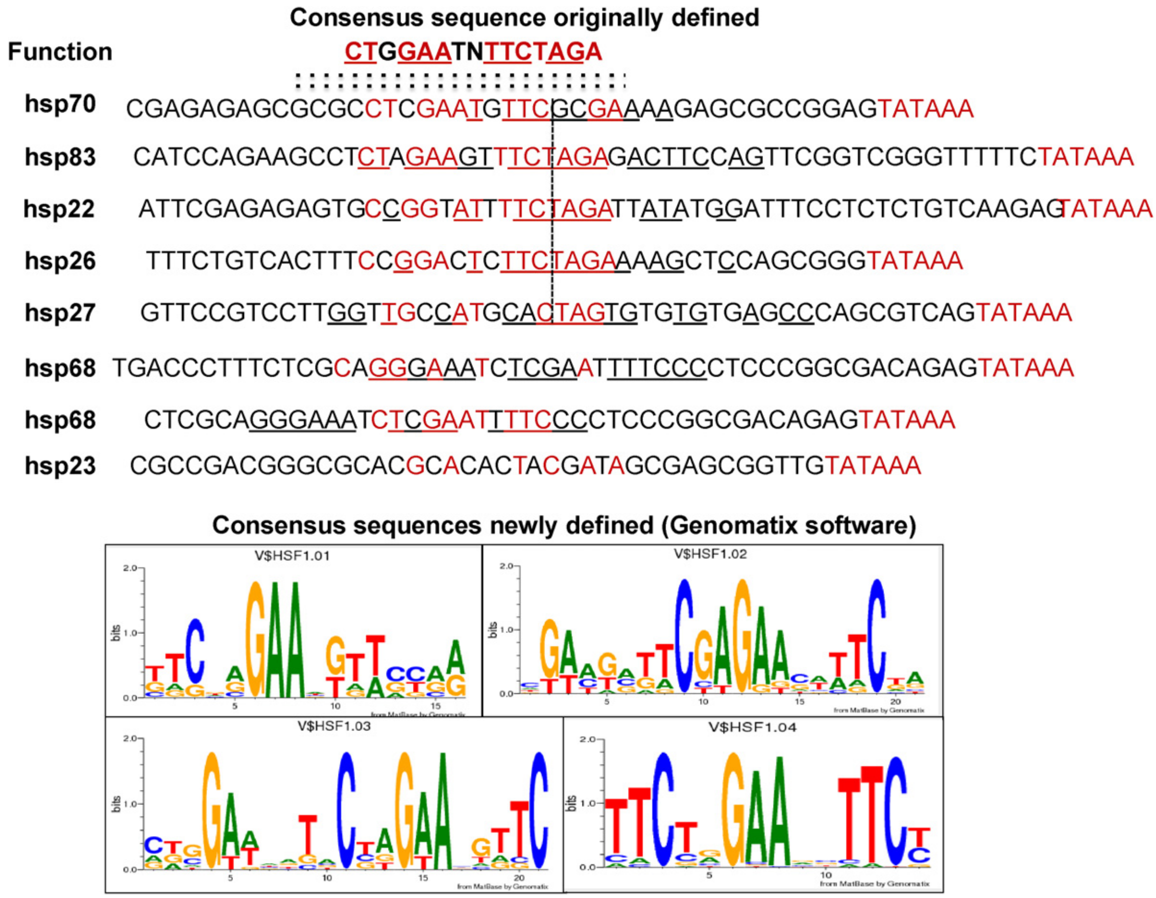

Fig. 1. (A) Historical definition of HSE. Homologies between the upstream regions of the *Drosophila hsp* genes from Pelham (1982). The nucleotides of the inverted repeats are indicated in red and the dyad axis of the major repeats is indicated by dots. (B) Current versions of HSE consensus matrices defined by Genomatix, according to data of the literature (MatBase; http://www.genomatix.de).

http://www.genomatix.de). The symmetry of this inverted repeat was suggestive of the binding of a regulatory protein, and the following years were an exciting period dedicated to the purification and identification of the transcription factor specifically binding HSE, heat shock factor (HSF; reviewed by Wu, 1995). The presence of multiple elements in the *Drosophila hsp70* gene promoter, 2 of which are necessary, and act in a synergistic manner, suggested cooperativity for HSF binding. In parallel, the study of the *sHsp* gene regulation brought new insights in the regulation of stress-induced chromatin rearrangements upon stress and during development.

(1) The case of *Drosophila* small *hsp* demonstrated the requirement of more than two HSEs for induction by stress, in relation with the more distal positions of HSEs from the TATA box (Bienz and Pelham, 1987). This brought the notion that long-distance effects of HSE require additional transcription factor binding sites, like SP1 (GC-box binding factor) (Bienz and Pelham, 1987).
(2) *Drosophila hsp26* presented an interesting model of chromatin organization that illustrated the notion of DNA-loop formation: the DNA segment, which separates the two HSE-containing hypersensitive sites, is wrapped around a nucleosome, which brings the two HSEs in close vicinity, allowing cooperative interactions between HSFs (Elgin, 1988 in agreement with Wu's results on *hsp70* and *hsp83*, reviewed in Wu, 1995).
(3) *Drosophila hsp26*, as *dHsp70*, is subjected to pausing of the RNA polymerase II, which is already engaged in non-stress conditions on the promoter of *Hsp* genes (Gilmour and Lis, 1986; Rasmussen and Lis, 1993; Rougvie and Lis, 1988).
(4) The investigation of *sHsp* gene expression gave the first best documented evidence for a HSE-independent regulation during development: ovarian induction and late third instar larval/prepupal *sHsp* expression was found to be regulated by ecdysone *via* elements distinct from HSEs (Cheney and Shearn, 1983; Cohen and Meselson, 1985; Hoffman and Corces, 1986; Lindquist, 1986; Michaud et al., 1997; Michaud and Tanguay, 2003; Riddihough and Pelham, 1986; Sirotkin and Davidson, 1982; Zimmerman et al., 1983).

In this review, we will describe the major recent findings about the transcriptional regulation of *sHsp* genes in development, stress, and diseases and will mainly focus on mammalian models (see Table 1). Unless otherwise stated, due to the poorly documented data on many sHsp gene regulation, like HSPB3 and HSPB7, we will mainly focus on HSPB1 and HSPB5.

1.2. Generalities about heat shock factors in stress, development and disease

Heat shock factors form a family of 4 well-described transcription factors (at least) in mammals (Akerfelt et al., 2010) which were named according to the first discovery of their activation by heat shock. Thanks to the universality and robustness of their response to HS, the stress-dependent activation of HSF became a 'paradigm': HSF triggers the expression of genes encoding heat shock proteins (Hsps) that function as molecular chaperones, contributing to establish a cytoprotective state to various proteotoxic stress and in several pathological conditions. Although it was believed for a few