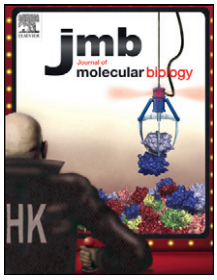

HSFs, Stress Sensors and Sculptors of Transcription Compartments and Epigenetic Landscapes

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Abstract

Starting as a paradigm for stress responses, the study of the transcription factor (TF) family of heat shock factors (HSFs) has quickly and widely expanded these last decades, thanks to their fascinating and significant involvement in a variety of pathophysiological processes, including development, reproduction, neurodegeneration and carcinogenesis. HSFs, originally defined as classical TFs, strikingly appeared to play a central and often pioneering role in reshaping the epigenetic landscape. In this review, we describe how HSFs are able to sense the epigenetic environment, and we review recent data that support their role as sculptors of the chromatin landscape through their complex interplay with chromatin remodelers, histone-modifying enzymes and non-coding RNAs.

Introduction

HSFs as integrators of stress signals and developmental and metabolic cues

Heat shock factors (HSFs) form a family of transcription factors (TFs) that were named for their activation by heat shock (HS) and their ability to bind heat shock elements (HSEs) on DNA. Thanks to the universality and robustness of their response to HS, the stress-dependent activation of HSF has become a "paradigm": HSFs trigger the expression of genes encoding heat shock proteins (HSPs), which function as molecular chaperones, contributing to the establishment of a cytoprotective state in situations of proteotoxic stress and under several pathological conditions (fever, aging, cancer, neuronal injury and so on).

Although it was believed for a few decades that the role of the HSFs was entirely dedicated to this protective mechanism, increasing evidence indicates that this ancient transcriptional program extends to the entire genome and contributes to unexpected functions in the absence of experimentally defined stress. Importantly, HSFs are also essential for development and reproduction [1,2].

The protective role of HSFs acts as a double-edged sword in two types of pathologies that plague the aging population. Indeed, HSF1 has a major role in longevity and a protective function in neurodegenerative disorders (reviewed in Refs. [3,4]). However, in sharp contrast, it promotes cancer by rewiring the transcriptome, enabling cells to adapt to the initial oncogenic stress and leading to drastic alterations in energy production, signal transduction, translation and protein metabolism [5–7].

Increasing evidence indicates that, to exert such a profound and wide-ranging influence on gene expression, HSFs act *via* broad epigenetic processes besides their well-characterized activity as transcriptional initiators. In this review, we aim to clarify the role of HSFs in sensing and remodeling the chromatin landscape in response to metabolic, developmental or stress stimuli.

HSF family members: Overlapping and specific features

HSFs share common structural domains and recognize similar sequences on DNA, and still they are subjected to different regulatory mechanisms and can accomplish overlapping but also high diverse biological roles in stress responses and developmental or pathological contexts [1,2,8].

Yeast, nematodes and flies each contain a single HSF, whereas four HSFs have been described in vertebrates. HSF1 is the main stress-responsive factor in mammals and essential to mount the heat shock response (HSR). HSF2 is quickly inactivated by HS but transiently modulates the HSF1-dependent induction of *HSP* [2]. HSF2 forms heterotrimers with HSF1 and can occupy more than half the HSF1 target sites genome-wide to fine-tune HSF1-dependent gene expression [9–12]. In chicken cells, cHSF3 is the major HSF and is activated at higher temperatures than cHSF1. cHSF3 controls cHSF1 activity and is indispensible for the induction of *HSP* genes, in contrast to cHSF1, which is responsible for the induction of non-*HSP* genes [13,14,8]. Although structurally a paralogue of cHSF3, mouse HSF3 does not activate HS genes but appears rather to be a functional orthologue of chicken HSF1 in activating the expression of genes other than the classic *HSPs* [15].

At their N-terminal moiety, HSFs share a highly conserved winged helix–turn–helix DNA-binding domain (DBD) containing a loop that provides an interface for cooperative interaction between the HSF subunits of the active HSF trimer and that modulates HSF transactivity [16–20] (reviewed in Ref. [2]). HSF DBD constitutes a hallmark of the HSF family, by conferring binding to the very conserved HSEs on the DNA (HSE; Fig. 1, reviewed in Ref. [2]). HSFs possess an atypical oligomerization domain composed of arrays of hydrophobic heptad repeats (HR-A and HR-B) that form a coiled coil, a structure common to many leucine zippers but that, in the case of the HSFs, leads to trimerization in a triple coiled-coil structure instead of dimerization [21–23]. The repression of spontaneous trimerization is driven by another heptad repeat (HR-C), located in the C-terminal domain that associates with HR-A and HR-B (Fig. 1; see Ref. [24]). HSF4 is devoid of this HR-C and can constitutively trimerize and bind DNA [25]. Present in a monomeric, inactive state in most cells under non-stress conditions, HSF1 trimerizes and binds to DNA in response to stress. HSF2 is also trimeric in its DNA-binding form but might be dimeric in its inactive state [26,27] (reviewed in Refs. [2,28]).

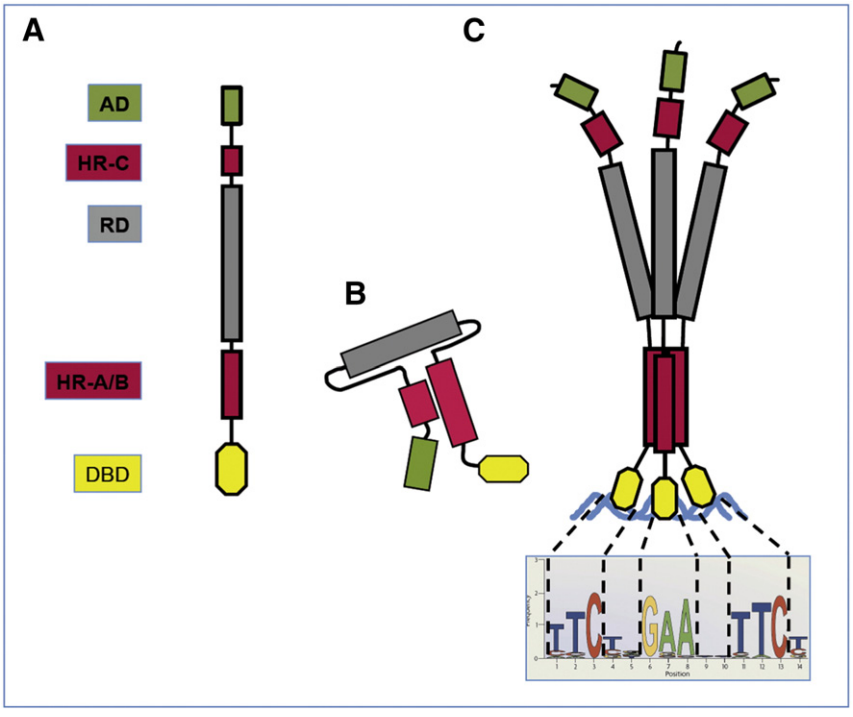

Fig. 1. (A) Conserved HSF domains (illustrated on the basis of human and murine HSF1). DBD: globular helix–turn–helix domain with a flexible wing (or loop) that allows cooperative DNA binding by HSF subunits for Refs. [95,170]. HR-A/B: heptad repeat A (HR-A) and heptad repeat B (HR-B), leucine-zipper domains that correspond to the trimerization domain and thereby mediate the formation of triple-coiled-coil trimeric HSF. HR-C: this heptad repeat, present in all HSFs, except *S. cerevisiae* HSF and mammalian HSF4, is responsible for maintaining HSF in a monomeric form by interacting with the HR-A/B domain under non-stress conditions. AD: domain responsible for transcriptional activation; RD: the regulatory domain that modulates AD activity. (B) Positioning of the DBDs of an HSF trimer on its consensus HSE sequence [115]. The HSE is composed of three inverted repeats of the pentanucleotide nGAAn in the proximal region of HSP genes and a pyrimidine/purine dinucleotide that separates a TTC triplet from a downstream GAA triplet. No constraints apply to the dinucleotide located between the GAA triplet and its downstream TTC triplet. The DBDs recognize the major groove of the DNA double helix of the HSE. Adapted from Wu [24] and Trinklein *et al.* [115].