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Plant Heat Shock Proteins - Origin, Evolution and Mechanism of Action for Biotechnological Implications in Crop Improvement

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ABSTRACT: Due to the present scenario of climate change, plants have to evolve strategies to survive and perform under a plethora of biotic and abiotic stresses, which restrict plant productivity. Maintenance of plant protein functional conformation and preventing non-native proteins from aggregation, which leads to metabolic disruption, are of prime importance. Plant heat shock proteins (HSPs), as chaperones, play a pivotal role in conferring biotic and abiotic stress tolerance. Moreover, HSP also enhances membrane stability and detoxifies the reactive oxygen species (ROS) by positively regulating the antioxidant enzymes system. Additionally, it uses ROS as a signal to molecules to induce HSP production. HSP also enhances plant immunity by the accumulation and stability of pathogenesis-related (PR) proteins under various biotic stresses.

KEYWORDS- plant, heat, shock, proteins, stress, biotechnological, antioxidant

I.INTRODUCTION

Heat shock proteins (HSPs) are specific proteins that are made when cells are briefly exposed to temperatures above their normal growth temperature. The synthesis of HSPs is a universal phenomenon, occurring in all plant and animal species studied, including humans. HSPs are also made by prokaryotic cells, namely, bacterial and archaean. Because HSPs can also be induced by oxidants, toxins, heavy metals, free radicals, viruses, and other stressors, they are sometimes called the 'stress proteins'. Most HSPs are molecular chaperones, which normally promote the self-assembly of newly synthesized polypeptide chains of proteins into a native spatial structure, the assembly of their complexes, and their transport through membranes as well as their participation in signal transduction. A nonlethal increase in temperature above the physiological norm for a biological species suppresses protein synthesis in the cell, activates the heat shock factor (HSF), and enhances transcription of heat shock genes, while exposure to a lethal temperature initiates apoptosis or programmed cell death. In turn, HSPs inhibit apoptosis and provide cells with thermal stability if stress reoccurs. In so doing, chaperones prevent irreversible aggregation of unfolded proteins and assist in the restoration of their native structure and/or degradation of denatured proteins. Response to heat shock is attenuated as the cell returns to normalcy after stress has been removed, HSF transforms to its inactive form and is transported to the cytoplasm, and 'bookmarked preinitiation complexes' are accumulated in the promoters of the genes encoding HSPs. HSP gene polymorphisms are associated with inflammatory, autoimmune, cardiovascular, and neurodegenerative diseases and, finally, aging.[1,2,3]

Hsp90 is one of the most highly connected proteins in the cell. Its function is naturally coupled to the activities of its diverse repertoire of clientele—kinases, E3 ubiquitin ligases, and transcription factors that are central to virtually every cellular and developmental pathway. By controlling and coordinating the activity of these client proteins, Hsp90 has the power to broadly impact phenotypic diversification and tumor heterogeneity—fueling malignancy and the acquisition of drug resistance. In principle, this diversification can occur by a variety of mechanisms, genetic, epigenetic, and posttranscriptional. The environmental regulation of Hsp90's function serves to couple these relationships to diverse stresses, providing a means through which external stimuli can create heritable phenotypic change.

In this chapter, we have surveyed many of the ways that this interface between environmental stressors, both internal and external, and the phenotypic diversification enabled by Hsp90 drives evolutionary change—often with profound effects on cancer and other human diseases. Much additional work is needed to reveal the precise molecular mechanisms that permit Hsp90 to remodel the genotype-to-phenotype map in cancers and uncover the most important types of genetic and epigenetic variation on which these mechanisms can act. Such an understanding will be of enormous value because, by revealing the mechanisms that highly mutated cells employ to survive and evolve new traits, we are likely to identify new Achilles' heels that are ripe for therapeutic intervention. Indeed, the insights gained from this work will hopefully allow

us to move away from the blunt and to date rather disappointing tool of global, maximally tolerated Hsp90 inhibition to the development of precise, tumor-specific, and more effective therapeutic strategies.

The stress heat shock protein 60 (HSP60) is phylogenetically highly conserved. Therefore, anti-HSP60 antibodies show significant cross-reactivity between microbial and eukaryotic, e.g. human, HSP60. Every healthy individual has protective antibodies against microbial HSP60 as well as bona fide autoantibodies against biochemically modified human HSP60. However, the titers of anti-HSP60 antibodies are significantly increased in persons with sonographically demonstrable atherosclerotic lesions. Such antibodies are of predictive value not only for morbidity, but also for mortality from atherosclerosis. However, anti-HSP60 antibodies, like other markers of inflammation, cannot be considered an atherosclerosis-specific parameter but rather as an additional tool for the early diagnosis of this “killer number one” disease.

Heat-shock proteins (HSPs) belong to a group of highly conserved families of proteins expressed by all cells and organisms from bacteria to humans in response to a variety of different stress stimuli, including heavy metals, inflammatory cytokines, amino acid analogues, oxidative stress, or ischemia [1].

The name of “stress proteins” would be more appropriate than “HSPs” but for historical reasons, due to the discovery of genes of the HSP family in salivary gland cells of *Drosophila* subsequent to heat shock [2,3], this name is still in use today. HSP expression may be constitutive or inducible. HSPs are generally considered as protective molecules against different types of stress. They have numerous intracellular functions including roles as molecular chaperones, promoting correct protein folding of newly synthesized or denatured proteins [4], inhibitors of apoptosis [5], or maintainers of cellular integrity by stabilization of the cytoskeleton [6]. Secretion or release of HSPs has also been described, and potential roles for extracellular HSPs reported. The compartmentalization of HSPs and their role as markers or actors in atherosclerosis will be discussed in this chapter. Several other reviews deal with HSPs and cardiovascular disease [7] including cardiac protection [8] or neuroprotection [4,5,6]

II.DISCUSSION

In nature, plants are often exposed to various kinds of abiotic stresses including low or high temperature, deficiency or excess of water, high salinity, heavy metals and ultraviolet radiation (Rucińska-Sobkowiak, 2010; Bitá and Gerats, 2013; Osakabe et al., 2013; He et al., 2018). Among these, HS has significant effects on plant growth, metabolism, and productivity (Rodríguez et al., 2015). HS causes protein misfolding and/or denaturation, leading to protein aggregation in plant cells by interactions between exposed hydrophobic amino acid residues of affected proteins (Nakajima and Suzuki, 2013). In response to HS, plants synthesize molecular chaperones including HSPs that recognize hydrophobic amino acid residues of non-native proteins and promote folding and refolding of denatured proteins. They are also responsible for assembling of multi-protein complexes, transporting, and sorting of proteins into correct compartments, controlling cell cycle and signal-transduction under various stress conditions. The different classes of HSPs play complementary and sometimes overlapping roles in protein stabilization under thermal stress. The HSPs are generally grouped into five major families based on their molecular weight: HSP100, 90, 70, 60 and the small HSPs (sHSPs)

III.RESULTS

Heat stress (HS) influences the alteration of membrane fluidity in plasma membrane (PM) in planta and activates the cyclic nucleotide-gated calcium channels (CNGCs), resulting in the movement of Ca²⁺ into the cytoplasm from the apoplasmic space. The Ca²⁺ ions are associated with protein calmodulin 3 (CaM3) during HS and the Ca²⁺-CaM3 complex binds to either calcium/calmodulin-binding protein kinase 3 (CBK3) or phosphatase PP7 to transduce cytosol heat-stress response (HSR) signals into the nucleus by modulating phosphorylation and dephosphorylation of the heat shock transcription factors (HSFs), respectively. The elevated levels of inositol-1,4,5-triphosphate (IP3) via the phosphoinositide-signaling pathway (PLC) lead to an influx of Ca²⁺ into the cytoplasm from the pool of intracellular Ca²⁺ ions including the ER and vacuoles in response to HS and induce the same CaM3 signaling pathway. ROS are generated by respiratory burst oxidase homolog B (RbohB) and D (RbohD) during HS. RbohB/D-produced O₂⁻ is converted into H₂O₂, which depolarizes PM as well as inducing the ROS/Redox signaling network which is involved in the activation of HSFs. Also, H₂O₂ is possibly increased in plant cells due to metabolic imbalances and the production of ROS, resulting in the accumulation of nitric oxide (NO) and the activation of calcium-channels that subsequently trigger the activity of CaM3[7,8,9]

Upon HS stimuli, HSP interacts with unfolded and aggregated proteins, thereby releasing HSF monomer. Heat shock factor monomers trimerize and bind to HSEs within promoter regions of heat shock genes. Heat shock factors undergo several post transcriptional modifications (PTMs) such as phosphorylation, which regulate the transactivation capacity of HSF. Under normal conditions, HSPs directly bind to HSF and provide negative feedback required to deactivate HSF. HSP70 and HSP40 together function as ATP-driven machines that prevent aggregation of misfolded polypeptides and participate in protein refolding. When denatured or misfolded proteins form aggregates, ClpB/HSP100 is crucial for protein disaggregation, refolding or degradation by protease especially during HS. Consequently, HSPs as chaperones play a pivotal role in conferring thermotolerance in plants. The dashed line indicates an unknown pathway.

Heat-stress response is known to be controlled by complex, tight networks, including selective enhancement and repression of gene expression in various metabolic processes, production of chaperone proteins for cellular protein homeostasis and other protective molecules that prevent targets from detrimental effectors such as ROS. The regulation of this network is critical for plant cells not only to adapt to various environmental conditions linked to temperature, humidity and light, but also to protect them from proteotoxic stresses. HSFs have a central function as major regulators in HSR by regulating transcription of a wide range of genes in several signaling and metabolic pathways (von Koskull-Döring et al., 2007; Guy et al., 2008). Heat shock factors are responsible for rapid synthesis and accumulation of HSPs, molecular chaperones for preventing protein aggregation and maintaining cellular protein homeostasis (Vierling, 1991; Wang et al., 2004; Gupta et al., 2010; Schleiff and Becker, 2011). Heat shock factor activity in each cell is controlled through sophisticated and complex feedback mechanisms and protein interactions, allowing for rapid adjustment and flexibility by diverse chaperones to changing environmental conditions (Akerfelt et al., 2010).[10,11,12]

The expression of HSPs is induced by HSFs that bind the HSEs in the promoters of heat shock responsive genes (Nover et al., 2001). Under normal conditions, monomeric HSFs are bound to HSP70 in the cytoplasm. When plants are exposed to HS, HSFs are released from HSP70-HSF complexes, and phosphorylated in the cytoplasm, and form a trimer for binding to HSEs in the nucleus (Liu et al., 2006). Overexpression of HSF genes in turn turns on almost all heat shock genes containing the HSE consensus sequence, conferring tolerance to HS. HSP70/90 plays an important role in the regulation of HSFA1 activity. HSP70/90 complex keeps HSFA1 inactive under normal conditions by repressing transactivation activity and nuclear localization of HSFA1 (Yamada et al., 2007; Hahn et al., 2011). Recently, the temperature-dependent repression (TDR) domain has been identified in the central region of HSFA1d, one of the Arabidopsis HSFA1s responsible for HS-dependent transactivation activity (Ohama et al., 2017). Overexpression of constitutively active HSFA1d, which lacks the TDR domain, induced the expression of heat shock proteins in the absence of HS, thereby conferring strong thermal stability in the overexpressing plants. Under HS conditions, HSFA1a is released from the HSFA1-HSP70/90 complex and activated. Of note, no TDR domain has been observed in mammalian HSFA1 proteins although the repression of the activities of HSFs by the HSP70/90 complex is generally conserved in both plants and animals. Activated HSFA1 directly and rapidly regulates expression levels of genes encoding important HS-responsive transcription factors (TFs) such as DEHYDRATION-RESPONSIVE ELEMENT BINDING PROTEIN 2A (DREB2A), HSFA2, HSFA7a, HSFBs, and MULTIPROTEIN BRIDGING FACTOR 1C (MBF1C) (Yoshida et al., 2011). Subsequently, DREB2A directly regulates the gene expression level of HSFA3 by creating a coactivator complex with NUCLEAR FACTOR Y, SUBUNIT A2 (NF-YA2), NF-YB3, and DNA POLYMERASE II SUBUNIT B3-1 (DPB3-1)/NF-YC10 (Chen et al., 2010; Sato et al., 2014). HSFA3 knockout or knockdown transgenic lines caused reduced expression of putative target HSP genes under HS, thus HSFA3 is regarded as an important HS-responsive TF (Schramm et al., 2008; Yoshida et al., 2008). Furthermore, HSFA2 contributes to high levels of modifications at specific histone tail residues (H3K4me2 and H3K4me3) of ascorbate peroxidase 2 (APX2), HSP22, and HSP18.2 (Sung et al., 2003; Charng et al., 2007; Lämke et al., 2016). Heat stress memory is maintained for several days, allowing plants to survive when they are exposed to the next HS conditions (Yamaguchi, 2021). Strong/rapid expression of sHSP genes including HSP21, HSP22, and HSP17.6C is observed in primed plants compared to non-primed plants (Yamaguchi et al., 2021). FORGETTER3 (FGT3)/HSFA3 is needed to retain HS memory for several days following HS exposure (Friedrich et al., 2021). A recent discovery showed that genes encoding stem cell regulators such as CLAVATA1 (CLV1), CLV3, and HSP17.6A, and the primary carbohydrate metabolism gene FRUCTOSE-BISPHOSPHATE ALDOLASE 6 (FBA6) are involved in the HS transcriptional memory in the shoot apical meristem (Olas et al., 2021). JUMONJI-C DOMAIN CONTAINING PROTEINs (JMJs) that code for H3K27me3 demethylases are regulators of heat acclimation through controlling the methylation status of HSP loci (Pan et al., 2007; Xiao et al., 2016; Yamaguchi et al., 2021; Yamaguchi and Ito, 2021).

Extreme HT causes protein misfolding and denaturation. Unfolded proteins can be degraded by the ubiquitin proteasome system or autophagy (Buchberger et al., 2010; Amm et al., 2014; Xu and Xue, 2019). It has been demonstrated that some ubiquitin E3 ligases and autophagy-related genes play a critical role in plant heat tolerance (Zhou et al., 2014; Li et al., 2015; Liu J. et al., 2016; Gil et al., 2017). Transgenic plants overexpressing ubiquitin or ubiquitin E3 ligases displayed enhanced BTT and/or ATT (Tian et al., 2014; Liu J. et al., 2016), and Zhang Y. et al. (2021) reported that silencing CARBOXYL TERMINUS OF THE HSC70-INTERACTING PROTEINS (CHIP), a chaperone-dependent ubiquitin E3 ligase caused reduced heat tolerance in tomato. CHIP plays a critical role in HSR through the misfolded proteins degradation induced by HS. Transgenic Arabidopsis seedlings overexpressing PROTEIN WITH THE RING DOMAIN AND TMEMB (PPRT1) encoding a C3HC4 zinc-finger ubiquitin E3 ligase showed enhanced BTT and ATT (Liu Y. et al., 2020). Moreover, virus-induced gene silencing (VIGS) of tomato AUTOPHAGY RELATED5 (ATG5) and ATG7 genes resulted in increased sensitivity of tomato plants to HS (Zhou et al., 2014).[13,14,15]

Understanding the dynamic behavior involving expression levels of TFs and HSPs under HS will help understand the whole regulatory network to adapt to HT.

IV.CONCLUSION

Climate change including global warming is causing abrupt changes in weather patterns, and extreme weather events that threaten crop yields. Elevated temperatures, in particular, will have a severe influence on the productivity and yields of vegetables in agricultural fields. It is, therefore, indispensable to understand the sophisticated mechanisms vegetable crops use to adapt to changing temperature environments, from the signal perception to gene expression in response to HS.[16,17,18,19]

As mentioned above, recent research has elucidated that an interplay of cooperative HSP, HSF, and HSR mechanisms orchestrate the expression of heat-responsive genes as the plant response to HS. Furthermore, research identifying TFs related to abiotic stresses and their molecular functions has contributed to the expansion of knowledge for the production of crops with desired traits through genetic manipulation and/or molecular breeding. Functional and cellular roles of some key TFs such as HSFA1s and DREB2A have been determined in transcriptional networks of HSR at the post-translational levels during HS. Nevertheless, the current information on the functional roles of HSP and HSF genes in vegetable crops is still insufficient for their practical application to breeding. Transcriptional regulation between HSPs and HSFs, and in-depth working mechanisms and pathways of heat-related proteins during HSR remain to be explored.[20]

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