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Molecular Mechanism and Role of Translational Values of Heat Shock Protein (HSP27) in Various Disease

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Authors' contributions

This work was carried out in collaboration among all authors. Authors SC, SSC, SR, SK, MM, MMAJ and BD are collected the research materials and written. Authors MMA and PA have designed and presented the article for current shape. All authors read and approved the final manuscript.

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ABSTRACT

HSP27, also known as HSPB1, was first discovered with a molecular weight 27kDa belonging to the four member gene family. Elevated levels of HSP27 are seen when different unfavorable conditions prevail such as increase in temperature and oxidative stress or exposure to heavy metals or organic solvents. They possess ATP-independent chaperone like activity which helps in maintaining protein homeostasis. It can also form large oligomers (300-600 kDa) containing different numbers of subunits. It is composed of total 205 amino acids. HSP27 undergoes post-

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translational modifications *i.e.* phosphorylation thereby converting large oligomers into dimers. It can act as an anti-apoptotic and antioxidant molecule during oxidative stress. The elevated form of HSP27 is also seen in some cancer belongs to breast, ovary, prostate, brain, colorectal, hepatocellular carcinoma, lung, liver, and cervical regions. Keeping in view of molecular roles of HSP27 signaling in various pathways, we have proposed their translational values in different diseases. In addition, we have also reported the existing scientific data on the HSP27 as the potential cancer biomarker and their therapeutic targets for improved prognosis and treatment in different diseases.

Keywords: Heat shock protein; chaperone; phosphorylation; apoptosis; cancer; biomarker.

1. INTRODUCTION

Heat shock protein (HSP) is a conserved protein involved in various stress mechanism of many organisms [1]. Based on their molecular weight, the HSPs resembled into other families named HSP100, HSP90, HSP70, HSP60 and other small HSPs (12-43kDa) [2,3,4,5]. HSP27 belongs to the small types of heat shock proteins with 4 members of gene encoded expressed in constitutively expressed in all organism [6,7]. Similarly, HSP27 is also observed by many investigators in all the kingdoms except *Mycoplasma genitalium* and *Helicobacter pylori* [8]. The preeminent levels of HSP27 are only observed in unfavorable conditions such as increase in temperature, oxidative stress or exposure to heavy metals or organic solvents [6] in organisms. HSPs possess chaperone-like activity which helps to continue the homeostasis process and prevents the formation of non-specific proteins in the accomplishment of their normal architecture [4,9]. Additionally, chaperone (large oligomers, 300-600 kDa) activity not only acts as stabilizing agents for the intracellular actin filaments but also plays a significant role in cell passage, aging, neurological disorders, autoimmune disease and neuro-protective disease and normal redox conditions [8,10-14] (Fig. 1). Moreover, heat shock proteins probably have anti-apoptotic activity, hampering activity of caspases, absolutely or laterally thereby interrupting the in and out process of apoptotic signaling by the interaction of key proteins [4,15].

2. STRUCTURAL OVERVIEW

HSP27 is a ATP independent chaperone composed of total 205 amino acids [4,13]. All HSPs contains 100aa residues which is homologous to α–crystalline protein composed of -crystalline domain (ACD) or small heat shock protein domain with variable N- and C- terminal domains obtained from the vertebrate eye lens [3,9]. These three domains i.e. N-terminal domain, ACD domain, C-terminal domain have been elaborated in Fig. 2. Moreover, these HSPs having a less conserved domain WDPF with N-Terminus (trp-asp-pro-phe) and C-Terminus (IXI/V motif) is important for oligomerization [16]. The primary structure of WDPF domain is (W/F)(D/F)PF-X0-8-(W/F)(D/E)(P/F)F, where X denotes non-conservative residues followed by a short variable sequence with primary structure PSRLFDQXFGEXLL existing on the C-Terminal [17].

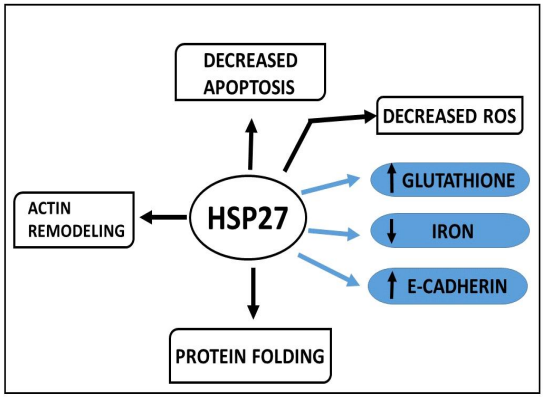

Fig. 1. Various role of HSP27 under unfavorable conditions

2.1 Molecular Characteristics, Gene Structure and Regulation

HSP27 gene is encoded by 205 amino acid protein with two HSE binding sites evolved by four members family. The size of transcript of HSP27 is 2.2kb which contains three exons [7]. The chaperone activity of HSP27 with respect to molecular mechanism, it is controlled transcription factors named as heat shock factors (HSF) [18]. These transcriptional activators are dependent or under the control mechanism of HSF. Further, HSF or transcriptional activators attached to the heat shock elements i.e. consensus sequences at the promoter region of

HSP family and enhanced the gene expression levels under unfavorable conditions. It is now noticed that HSF2 attached to HSE during mitosis while HSF1 in hemin treatment [13]. Rendering to the conventional model, misfolded proteins induced due to heat stress by HSF1 resulted the association with HSP. Conclusively, HSF1 is released and rapidly undertakes numerous roles like genetic modifications after mRNA processing in the nucleus region that binds to the heat shock promotes the expression level of HSP27 at promoter region [18].

HSP27 exists at the elemental stages in the tissues, and cells organized as large oligomers mainly exist in cytosol [4,19]. These large oligomers accounts for maintaining the chaperone activity of HSP27. HSP27 has capability to attach to inadequately folded proteins and further it transfers to HSP70, ATP-dependent chaperon [13]. The spectacle behind the formation of large oligomers from tetramers or dimers and formation of small tetramers or dimers from large oligomers is dephosphorylation and phosphorylation, respectively by oligomerization of HSP27 peptide [20].

Protein kinases C, D, G, (MAPKAP) and kinase 2/3 (MAP kinase protein activators) are mainly involved in the phosphorylation of HSP27 [21]. The choice of kinase depends upon the type of cell and conditions. Various types of stresses can activate the MAP kinase cascade played an important role in activation of p38 MAP-Kinase. The activated p38 MAP-Kinase further resulted in to the increased activity of MAPKAP-2 kinase catalyzes the phosphorylation of HSP27 proposed in Fig. 3 [17]. The reversible process in response to differentiating agents, mitogens, inflammatory cytokines, such as TNFα and IL-1β is further governed by phosphorylation of MAPKAP-kinase 2/3 [22]. It is noticed that when the phosphorylating sites of HSP27 were mapped, the involvement of Ser-15, Ser-82, Ser-78 and Thr-143 residues are evolved [20]. The dephosphorylation of HSP27 can occurs through the activation of phosphatases like PP2A, PP1 and PP2B [13].

3. HSP27 ROLE IN NUMEROUS DISEASE

3.1 Apoptosis

Studies confirmed that phosphorylated form of HSP27 played as a dynamic anti-apoptotic molecule and act as an anti-oxidant during oxidative stress [13]. HSP27 caused the low level of ROS (reactive oxygen species) by intervening the intracellular iron concentration and elevating the intracellular glutathione levels (Lianos et al. 2015). In Fas-FasL mediated apoptosis, HSP interacts with DAXX motif preventing the subsequent binding of Ask1 by DAXX resulted the cell death. Similarly, HFSP also play in the mitochondrial dependent apoptosis by interacting with Bax and cytochrome C (normal apoptosis caspase activator) that can regulate the apoptosis by interacting with STAT3 and CASP3 (Pro-Caspase3) [1,2,23]. During normal apoptosis caspase activator i.e. cytochrome C (mitochondria) binds with apoptotic protease activating factor1 (Apaf-1) and procaspase9 resulted in apoptosome, a caspase-3 activation complex [21]. Hence, we can correlate that the HSP27 has an ability to interact with cytochrome C, carried out the activation of pro-caspase-9, to form the apoptosome complex [13]. The diagrammatic view of the mechanism of apoptosome formation is shown in Fig. 4.

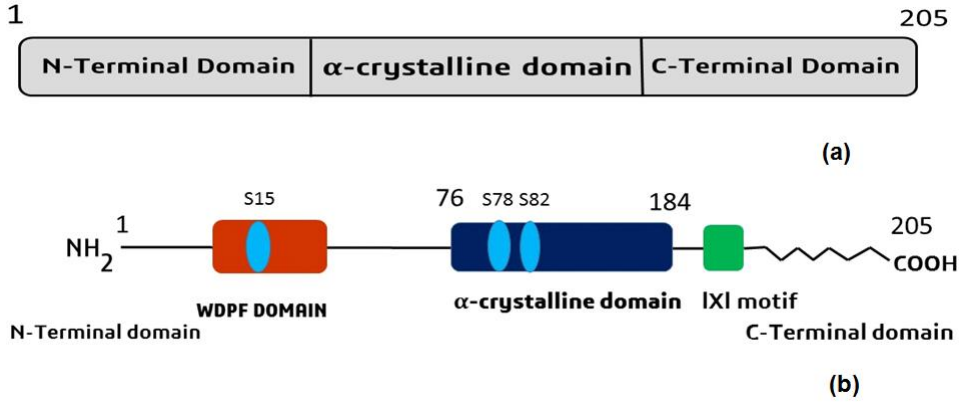

Fig. 2. Representing the three domains of the HSP27

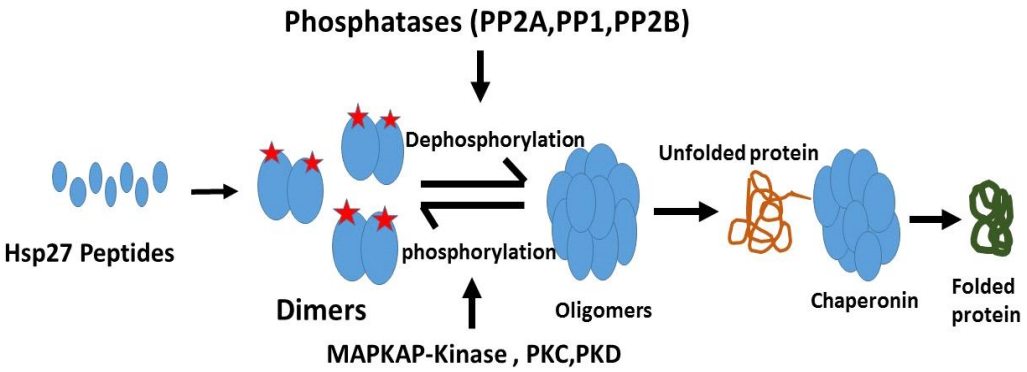

Fig. 3. Mechanism for phosphorylation and dephosphorylation of HSP27 by MAPKAP Kinase, PKC, PKD and phosphatases (PP2A, PP1, PP2B), respectively

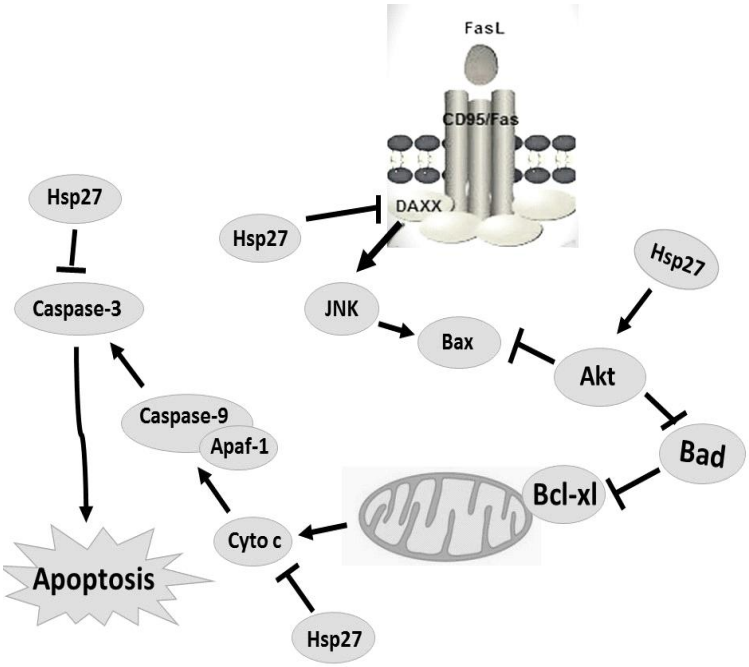

Fig. 4. Mechanism of apoptosis

3.2 Cancer

Studies conducted have been conducted and proved the role HSP27 in numerous cancer types; ovarian, prostate, colorectal, brain, breast, hepatocellular carcinoma, lung, pancreatic, liver and cervical [24-29]. Studies revealed that the overexpression of HSPs in various types of cancer is associated with tumor progression, making cells chemo resistant and as a prognostic or predictive marker [23,30]. The most common cause for the deaths due to gynecological malignancies is the ovarian cancer [31]. In ovarian cancer cells, an increased level of HSP27 is associated with its phosphorylation due to p38MAP kinase induced by HGF [32]. In prostate cancer the client protein i.e. androgen receptor (AR) [33] binds to the ARE (androgen response element) by the nuclear trafficking by increments HSP27 at the promoter region of specific genes to facilitates the up regulation of transcriptional activity, once it binds to the AR homodimer [34]. Similarly, in case of brain tumors HSP27 is expressed laterally and the Western blot analyses showed the presence of HSP27 in every meningioma tissues at histological grades of astrocytoma and with Ki-67 [4]. The breast cancer studies have also

confirmed significantly higher levels of HSP27 in the serum comparative to the control group [35]. An proteomic analysis of CRC propounds that induced the HSP27 level notable and confirmed its role in colorectal cancer [36]. Likewise, the immunohistochemistry experiments for lung cancer showed the expression of HSP27 in cytoplasm of the lung cancer developed brown-yellow granules in the nuclei or cytoplasm in lungs cells [37]. Same kind of studied have also been conducted for HBV, it was found that levels of HSP27 are increased in the serum of HCC patients infected by chronic hepatitis B virus and as compared to healthy individuals. It is due to the increased incursion and metastasis form in HCC through Akt-MMP2 signaling lead by HSP27 [38].

4. ASSOCIATED DISEASE

HSP27 are also linked with numerous diseases e.g. neurodegenerative, cardiovascular and kidney associated diseases [2].

4.1 Neurodegenerative

Neurodegenerative disease is the progressive loss of neurons categorized by accumulation of various polypeptide aggregates (amyloids, mis-folded proteins). The neurological diseases e.g. Alzheimer's, Parkinson, amyotrophic lateral sclerosis (ALS) and prion disease have been categorized by the occurrence of precise proteinaceous inclusions presence in neuron(s). In corresponding to increased levels of mis-folded proteinaceous inclusions, the levels of HSP expressions are usually affected and up regulated. In case of Alzheimer's disease, the high levels of HSP27 in the cerebral cortex while in Parkinson's disease, it also shows increased levels in the reactive astrocytes which is associated with HSP27. Similar kind of studied have also been reported in Charcot Marie tooth disease (neurological disorder) caused by a mutation in small types of HSPs *i.e.* HSPB1 [39]. Here it has been noticed that the members of small HSPs have well played the particular role in neuroprotective behavior to their non-chaperone functions [18,40,41].

4.2 Cardiovascular Disease

An important role of HSP27 has been seen in the ischemic conditioning of the myocardium and limiting the progress of oxidative stress caused by reperfusion. An elevated levels of HSP27 corresponds to the cardio-protection activity by sustaining the veracity of microtubules and actin cytoskeleton [42]. The presence of phosphorylated HSP27 in concurrence present in smooth muscle cells through tropomyosin played an important role in defensive and stabilizing the cytoskeleton and against ischemic injury [43].

4.3 Atherosclerosis

Physiological response to biochemical stress increases the expression of HSP27 with vascular smooth muscles cells in human atherosclerotic plaques. There are several beneficial role of HSP27 in atherogenesis in term of both cellular and humoral component systems have been reported [44]. In this case the mammary arteries are in phosphorylated form plays important role in apoptosis, proliferation and migration of human vascular endothelial cells, vascular smooth muscles; which prevents plaque rupture by HSP27 regulations which in turn binds and stabilize the actin microfilament. In few studies, HSP27 probably reacts with IKK protein and prevents atherosclerotic inflammatory responses by inhibiting NF- κB activation [42].

5. TRANSLATIONAL VALUES AND FUTURISTIC ROLE OF HSP27

HSP plays a crucial role in tumorigenesis and cancer progression, these molecules therefore are potentially ideal therapeutic targets for cancer treatment [45]. HSP27 might be a striking target for neuroprotection directly or indirectly implicated for all kinds of neurodegenerative diseases [40]. HSPs may also turn a piece of auto antigens that intensify the immune responses in vascular injuries. It is suggested that tolerization of these antigens may constrain atherogenesis and thus may be use as a practical therapeutic target [13] (Ghayour-Mobarhan et al. 2012). The overexpression of HSP27 may also protects the ischemic injury by employing its antioxidant virtues and also acts as biomarker of several diseases [2]. In numerous neurodegenerative diseases such as Alzheimer's, Parkinson's and prion-oriented diseases, the HSPs are bound by the ruinous metal factor involved in neuro signaling. In normal range of Cu^{2+} levels in brain is from 15-80 µm but the concentration of Cu^{2+} recorded more than 300 µm resulted Alzheimeric brain. The amyloid fibril aggregation of amyloidogenic peptides (α-synuclein and Aβ peptides) implicated in synucleopathies including Parkinson and Alzheimer's disease, are enhanced by Cu^{2+} (Fig. 5). The better attraction

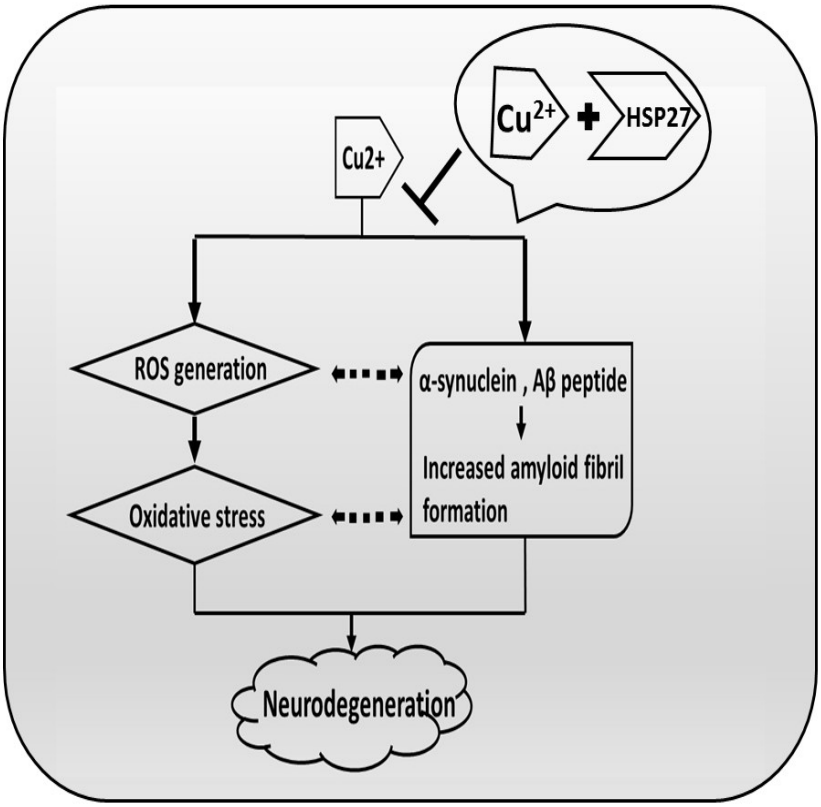

Fig. 5. Mechanism of Cu^{2+} ion action on HSP27

has been practical proven by the binding of HSP27 to the Cu^{2+} which cripples the redox activity, fostering to beneficial cryoprotective effects. Once HSP_{27} binds to Cu^{2+} it knock outs the cu^{2+} from the amyloidogenic target i.e. α-synuclein, Aβ peptides, thus subsequently prevents amyloid fibril formation thereby clampdown reactive oxygen species generation [46].

6. CONCLUSION

HSP27 is the affiliated with small heat shock kind of proteins (HSPs) with molecular chaperone activity played an important role in protein folding. In consonance with the other functions of HSP27 may include actin remodeling, oligomerisation, decreased apoptosis and decreased reactive oxygen species. Although several studies have been carried out to understand the role of HSP27 in various disorder, it is now emphasized on the basis of recent data of HSP27 may be used as a prognostic and therapeutic competency biomarker targeting HSP27, a better understanding of its phosphorylated state in apoptotic signaling. HSP27, therefore can be an enticement for its expansion as a multitarget therapeutic agent.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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