HSP70&HSP90 in Viral Infection

Subjects: Virology
Contributor: Waldemar Pluta

Heat shock proteins (HSPs) are a large group of chaperones found in most eukaryotes and bacteria. They are responsible for the correct protein folding, protection of the cell against stressors, presenting immune and inflammatory cytokines; furthermore, they are important factors in regulating cell differentiation, survival and death. Although the biological function of HSPs is to maintain cell homeostasis, some of them can be used by viruses both to fold their proteins and increase the chances of survival in unfavorable host conditions.

Keywords: HSP70 ; HSP90 ; viral infection

1. Introduction

The discovery of Heat Shock Proteins (HSPs) is attributed to the Italian geneticist Ferruccio Ritossa [1], who during his research mistakenly increased the incubation temperature of Drosophila melanogaster larvae, which resulted in an increased transcription of genes of proteins unknown at that time. Less than 10 years later it was noticed that the proteins discovered by Ritossa prevented damage to cells which were associated with abnormal proteins resulting from heat shock [2]. Later studies have shown that HSP can be induced not only by temperature but also by other stressors, including starvation, hypoxia, physiological or environmental attacks, chemical or UV exposure and the invasion of pathogens [3].

Their main role is to protect cells against stressors by participating in the correct folding of newly formed proteins, repairing misfolded proteins and by participating in the transport of proteins to their site of action [4]. HSPs usually make up about 5–10% of the total protein in most cells but their intracellular concentration may increase within a few minutes under the influence of stressors up to 20 times in order to suppress or attenuate undesired effects [5][6].

In physiological conditions and in the absence of stressors, HSPs are associated with heat shock factors (HSF), especially HSF-1. An increase in the number of damaged proteins causes the detachment of HSP from HSF in order to bind the damaged protein. Consequently, there is an increase in the number of free HSFs in the cell, which function as transcription factors and bind to heat shock DNA elements, triggering the expression of HSP, a so-called heat shock response HSR. This increase in HSP expression means that free HSF is rebound, reducing HSP gene transcription and inhibiting HSF binding to DNA. This approach enables HSPs to independently regulate their own expression. During cellular stress, the level of HSP in the cytoplasm increases and their transport takes place mainly to the cell nucleus, where they protect DNA, pre-mRNA, pre-ribosomal and nuclear proteins against damage and degradation. They also participate in the activation of specific genes [4].

Although HSPs are protective proteins, they can be turned against the organism in which they are found. Viruses lacking their HSPs use the host's HSP to fold their proteins and increase the effectiveness of infection. A better understanding of the mechanisms of viral infections in which HSPs participate would allow for the development of more effective antiviral drugs based on these proteins. HSP70 and HSP90 inhibitors show great therapeutic potential. The aim of this review is to present the latest reports on the role of HSP70 and HSP90 in viral infections and to present these proteins as an effective therapeutic target.

2. Characteristics of Selected HSP's

As one of the most ubiquitous molecular chaperones located in all the cellular compartments of eukaryotes, HSP70s regulate every aspect of cellular proteostasis, including: the folding of both nascent and misfolded proteins; protein assembly and the regulation of their activity; the translocation into mitochondria, chloroplasts and the endoplasmic reticulum; the degradation of and prevention from dismantling protein aggregates [7][8]. HSP70 is composed of two large, functional domains: the N-terminal nucleotide-binding domain (NBD) and the C-terminal substrate-binding domain (SBD). The NBD is about 44 kDa and provides energy to power HSP70 activity by binding and hydrolyzing ATP to ADP. It is divided into two lobes (I and II), which are further divided into two subdomain regions (IA, IB and IIA, IIB). The

characteristic structure of subdomains forms a V-shaped cleft where the nucleotide binds. In turn, SBD (25 kDa) is a tweezers-like binding site for polypeptide substrates and is divided into two domains called α and β. A 12-kDa β-SBD is organized such as a sandwich and is made up of two antiparallel β-sheets of four strands each. The β-domain contains the substrate-binding site used for binding misfolded proteins which is located between the two β sheets. The substrate-binding pocket is highly hydrophobic and displays a high affinity for hydrophobic substituents such as Leu. α-SBD is a 15-kDa α-helical subdomain which forms a lid that covers the substrate-binding cleft and stabilizes the loop regions of the β-subdomain. The domains are connected by the interdomain linker, which is composed of 10–12 highly conserved hydrophobic amino acids which assume an unstructured conformation in the ADP-bound state and a β-stranded conformation in the ATP-bound state [7][9][10]. SBD is similar in shape to tweezers, allowing HSP70 to interact with polypeptides and protein complexes regardless of their size. Moreover, this domain can stabilize these units by interacting with folding intermediators and folded pieces of proteins. Interaction with folded proteins is not constant and is regulated by an allosteric mechanism. It involves the hydrolysis of ATP and the rebinding of ATP in NBD with the binding and release of substrate polypeptides. The allosteric mechanism of HSP70 can be modified by J domain proteins (JDP) and nucleotide exchange factors (NEF) [11].

Such a wide spectrum of activity of HSP70s proves that these proteins, in order to adapt to the conditions of growth and stress in the cell, are able to act on a variety of substrates [8]. There are at least 14 proteins within the human HSP70 family, which differ in terms of expression level, amino acid composition and subcellular localization. Proteins can be stress induced (e.g., HSPA1 and HSP6) or constitutively expressed (e.g., HSPA5, HSPA8 and HSPA9). The chaperone activity of a protein consists of the hydrolysis of ATP. The interaction with unfolded protein begins with the binding of HSP70 to its substrates. The initially low affinity increases significantly after ATP is hydrolyzed to ADP by the cochaperone HSP40. Finally, with the help of nucleotide exchange factors, ADP dissociates to reset the cycle [12]. The most important functions of the HSP70 isoforms are presented in **Table 1** .

Isoform	Location	Function	References
HSPA1	**cytoplasm nucleus lysosomes**	**inhibiting the accumulation of protein aggregates; protection of the mitotic cell against division abnormalities; stabilization of the lysosomal membrane; inhibition of the release of lysosomal hydrolases into the cytosol**	**[13][14][15][16] [17][18]**
HSPA1L	**cytoplasm nucleus**	**unknown**	
HSPA2	**nucleus**	**chaperone for the cyclin B/cdc2 complex during meiotic cell division orphases for the transition protein 1 and -2 (DNA packaging proteins)**	**[19][20][21]**
HSPA5	**endoplasmatic reticulum**	**facilitates the transport of the newly synthesized protein into the lumen of the endoplasmic reticulum and their subsequent folding**	**[22][23][24]**
HSPA6	**cytoplasm nucleus**	**unknown**	
HSPA8	**cytoplasm nucleus**	**maintenance of organization, folding of nascent polypeptides, translocation of proteins across membranes, autophagy mediated by chaperones, prevention of protein aggregation under stress conditions and disassembly of clathrin-coated vesicles**	**[25][26]**
HSPA9	**mitochondrium cytoplasm endoplasmatic reticulum**	**interacting with incoming proteins and helping them to fold properly after transmembrane transport**	**[27][28]**

A characteristic feature of all HSP90 family proteins is the identical domain structure. It consists of the N-terminal domain (NTD), the middle domain (M domain) and the carboxy-terminal domain (CTD). NTD contains in its structure an ATP binding site that is essential for the ATPase activity of HSP90. It is required for the chaperone cycle and protein binding of the HSP90 client [29][30]. The MD domain has a characteristic way of controlling the functions of HSP90 through the binding of phosphate to the ATP specified for NTD. Thus, the MD domain influences the ATPase activity of HSP90 [31]. There are two key sites in the CTD domain: one for calmodulin binding [32], and the other for HSP9 homodimerization [33]. In addition, there is a nucleotide binding site that opens after taking the N-terminal site and serves as an allosteric regulator of N-terminal ATPase activity [34].

The functions of HSP90 are modulated by numerous post-translational modifications. These include acetylation, phosphorylation, sumoylation and S-nitrosylation. Certain changes in the acetylation state are key regulators of co-chaperone binding [35], including HSP90 hyperacetylation, causing the inability to bind to co-chaperone p23, loss of guardian activity and impaired activation of the glucocorticoid receptor (GR) [36][37]. Phosphorylation has been shown to

slow down the conformational cycle of HSP90 and to influence client maturation and interactions with the co-chaperone [38]. Protein phosphatase PP5 is the co-chaperone of HSP90 that affects the phosphorylation status. In the absence of PP5, a state of hyperphosphorylation occurs, which negatively affects the maturation of the client [39]. S-nitrosylation of HSP90 in CTD inhibits the ATPase reaction and reduces the activating effect of HSP90 on client endothelial nitric oxide synthase (eNOS). It can be concluded that there is an eNOS feedback mechanism [40]. S-nitrosylation affects the ATPase activity of HSP90 as well as its chaperone activity [41]. The most important functions of the HSP90 isoforms are presented in **Table 2** .

Isoform	Location	Function	References
HSP90	**cytoplasm, cell nucleus**	**folding and preventing protein aggregation; stabilization of citrate synthase, rhodanase and protein kinase CK-II; aryl hydrocarbon receptor maturation; abrogates v-Src kinase activity; protection of the kinase against the action of phosphatases; cross-linking of actin filaments; protection of tubulin against thermal denaturation; protection of myosin from heat stress**	**[42][43][44][45][46][47][48][49][50][51][52]**
GRP94	**endoplasmatic reticulum**	**promoting the folding of secretory and membrane proteins; shifting toll-like receptors and integrins; calcium binding**	**[53][54][55][56]**
TRAP1	**mitochondrium**	**maintenance of mitochondrial integrity and protection against mitochondrial apoptosis; protection against cell death caused by overproduction of ROS; preventing protein aggregation in mitochondria and supporting protein folding**	**[57][58][59][60]**

3. The Role of HSP70 and HSP90 in Viral Infections

Heat shock stress has been shown to enhance replication in the U937 cell line by increasing the expression of HSP70 and HSP90 on the cell surface, especially in lipid rafter microdomains. Interestingly, the increase in HSP70 and HSP90 expression induced by heat stress did not result in increased DENV binding, but facilitated viral entry. The findings suggest that HSP70 and HSP90 are necessary for DENV entry into the cell, and that heat shock stress is optimal for cell replication in the U937 cell line [61].

In addition to the role of HSP90 in the stabilization of viral polymerase and in nuclear transport, HSP90 promotes influenza A-mediated apoptosis. It activates the caspase cascade, essential for viral replication, pathogenesis and virulence [62][63][64][65]. HSP90 has also been shown to counteract the degradation of influenza A (NA) neuraminidase and increase its stability [66][67]. The formation of the HSP90-NA complex increases the viability of the cells, which leads to more virus production [68].

Studies have shown that HSP70 can inhibit IAV replication by disrupting viral polymerase binding to viral RNA [69] or by preventing the RNP complex from being exported to the nucleus [70].

Human hepatitis B virus (HBV) belongs to the Hepadnaviridae family and can cause acute and chronic liver disease. The core protein (HBc) plays an essential role in the viral life cycle, which is organized into two domains: the C-terminal domain that regulates viral replication and the N-terminal domain that is involved in the core assembly [71][72].

4. Conclusions

Members of the HSP70 and HSP90 families are involved in viral infections in many different ways. First, they support viruses when entering host cells by forming complexes on the cell surface. They also support viruses during their replication by directly interacting with the viral polymerase. HSP70 and HSP90 are important for viral gene expression. They are involved in assembling the capsid of some viruses. Viruses use the HSP70 and HSP90 proteins to fold their proteins and increase their chances of survival under unfavorable host conditions. A comprehensive knowledge of the use of chaperones during viral infection would provide new insight into viral replication mechanisms and potential therapies. The use of newer and more effective inhibitors directed against HSP70 and HSP90 proves that they are a very good therapeutic target in viral infections.

References

1. Ritossa, F. A new puffing pattern induced by temperature shock and DNP in drosophila. Experientia 1962, 18, 571–573.

2. Borkovich, K.A.; Farrelly, F.W.; Finkelstein, D.B.; Taulien, J.; Lindquist, S. hsp82 is an essential protein that is required in higher concentrations for growth of cells at higher temperatures. Mol. Cell. Biol. 1989, 9, 3919–3930.
3. Hoekstra, S.P.; Bishop, N.C.; Leicht, C.A. Elevating body termperature to reduce low-grade inflammation: A welcome strategy for those unable to exercise? Exerc. Immunol. Rev. 2020, 26, 42–55.
4. Lanneau, D.; Brunet, M.; Frisan, E.; Solary, E.; Fontenay, M.; Garrido, C. Heat shock proteins: Essential proteins for apoptosis regulation: Apoptosis Review Series. J. Cell. Mol. Med. 2008, 12, 743–761.
5. Tukaj, S.; Węgrzyn, G. Anti-Hsp90 therapy in autoimmune and inflammatory diseases: A review of preclinical studies. Cell Stress Chaperones 2016, 21, 213–218.
6. Doberentz, E.; Madea, B. Supravital expression of heat-shock proteins. Forensic Sci. Int. 2019, 294, 10–14.
7. Liu, Q.; Liang, C.; Zhou, L. Structural and functional analysis of the Hsp70/Hsp40 chaperone system. Protein Sci. 2020, 29, 378–390.
8. Rosenzweig, R.; Nillegoda, N.B.; Mayer, M.P.; Bukau, B. The Hsp70 chaperone network. Nat. Rev. Mol. Cell Biol. 2019, 20, 665–680.
9. Karunanayake, C.; Page, R.C. Minireview Cytosolic protein quality control machinery: Interactions of Hsp70 with a network of co-chaperones and substrates. Exp. Biol. Med. 2021, 246, 1419–1434.
10. Mashaghi, A.; Bezrukavnikov, S.; Minde, D.P.; Wentink, A.S.; Kityk, R.; Zachmann-Brand, B.; Mayer, M.P.; Kramer, G.; Bukau, B.; Tans, S.J. Alternative modes of client binding enable functional plasticity of Hsp70. Nature 2016, 539, 448–451.
11. Mayer, M.P.; Gierasch, L.M. Recent advances in the structural and mechanistic aspects of Hsp70 molecular chaperones. J. Biol. Chem. 2019, 294, 2085–2097.
12. Wang, Z.; Li, Y.; Yang, X.; Zhao, J.; Cheng, Y.; Wang, J. Mechanism and Complex Roles of HSC70 in Viral Infections. Front. Microbiol. 2020, 11, 1577.
13. Nollen, E.A.A.; Brunsting, J.F.; Roelofsen, H.; Weber, L.A.; Kampinga, H.H. In Vivo Chaperone Activity of Heat Shock Protein 70 and Thermotolerance. Mol. Cell. Biol. 1999, 19, 2069–2079.
14. Mosser, D.D.; Caron, A.W.; Bourget, L.; Meriin, A.B.; Sherman, M.Y.; Morimoto, R.I.; Massie, B. The Chaperone Function of hsp70 Is Required for Protection against Stress-Induced Apoptosis. Mol. Cell. Biol. 2000, 20, 7146–7159.
15. Hut, H.M.J.; Kampinga, H.H.; Sibon, O.C.M. Hsp70 Protects Mitotic Cells against Heat-induced Centrosome Damage and Division Abnormalities. Mol. Biol. Cell 2005, 16, 3776.
16. Nylandsted, J.; Gyrd-Hansen, M.; Danielewicz, A.; Fehrenbacher, N.; Lademann, U.; Høyer-Hansen, M.; Weber, E.; Multhoff, G.; Rohde, M.; Jäättelä, M. Heat shock protein 70 promotes cell survival by inhibiting lysosomal membrane permeabilization. J. Exp. Med. 2004, 200, 425–435.
17. Leist, M.; Jäättelä, M. Four deaths and a funeral: From caspases to alternative mechanisms. Nat. Rev. Mol. Cell Biol. 2001, 2, 589–598.
18. Kroemer, G.; Jäättelä, M. Lysosomes and autophagy in cell death control. Nat. Rev. Cancer 2005, 5, 886–897.
19. Zhu, D.; Dix, D.J.; Eddy, E.M. HSP70-2 is required for CDC2 kinase activity in meiosis I of mouse spermatocytes. Development 1997, 124, 3007–3014.
20. Dix, D.J.; Allen, J.W.; Collins, B.W.; Poorman-Allen, P.; Mori, C.; Blizard, D.R.; Brown, P.R.; Goulding, E.H.; Strong, B.D.; Eddy, E.M. HSP70-2 is required for desynapsis of synaptonemal complexes during meiotic prophase in juvenile and adult mouse spermatocytes. Development 1997, 124, 4595–4603.
21. Govin, J.; Caron, C.; Escoffier, E.; Ferro, M.; Kuhn, L.; Rousseaux, S.; Eddy, E.M.; Garin, J.; Khochbin, S. Post-meiotic shifts in HSPA2/HSP70.2 chaperone activity during mouse spermatogenesis. J. Biol. Chem. 2006, 281, 37888.
22. Munro, S.; Pelham, H.R.B. An hsp70-like protein in the ER: Identity with the 78 kd glucose-regulated protein and immunoglobulin heavy chain binding protein. Cell 1986, 46, 291–300.
23. Hendershot, L.M.; Valentine, V.A.; Lee, A.S.; Morris, S.W.; Shapiro, D.N. Localization of the gene encoding human bip/grp78, the endoplasmic reticulum cognate of the hsp70 family, to chromosome 9q34. Genomics 1994, 20, 281–284.
24. Gething, M.J. Role and regulation of the ER chaperone BiP. Semin. Cell Dev. Biol. 1999, 10, 465–472.
25. Lindquist, S.; Craig, E.A. The Heat-Shock Proteins. Annu. Rev. Genet. 1988, 22, 631–677.
26. Bukau, B.; Weissman, J.; Horwich, A. Molecular Chaperones and Protein Quality Control. Cell 2006, 125, 443–451.
27. Deocaris, C.C.; Kaul, S.C.; Wadhwa, R. On the brotherhood of the mitochondrial chaperones mortalin and heat shock protein 60. Cell Stress Chaperones 2006, 11, 116–128.

28. Mizzen, L.A.; Chang, C.; Garrels, J.I.; Welch, W.J. Identification, characterization, and purification of two mammalian stres proteins present in mitochondria, grp 75, a member of the hsp 70 family and hsp 58, a homolog of the bacterial groEL protein. J. Biol. Chem. 1989, 264, 20664–20675.

29. Panaretou, B.; Prodromou, C.; Roe, S.M.; O'Brien, R.; Ladbury, J.E.; Piper, P.W.; Pearl, L.H. ATP binding and hydrolysis are essential to the function of the Hsp90 molecular chaperone in vivo. EMBO J. 1998, 17, 4829–4836.

30. Dutta, R.; Inouye, M. GHKL, an emergent ATPase/kinase superfamily. Trends Biochem. Sci. 2000, 25, 24–28.

31. Meyer, P.; Prodromou, C.; Hu, B.; Vaughan, C.; Roe, S.M.; Panaretou, B.; Piper, P.W.; Pearl, L.H. Structural and functional analysis of the middle segment of Hsp90: Implications for ATP hydrolysis and client protein and cochaperone interactions. Mol. Cell 2003, 11, 647–658.

32. Minami, Y.; Kawasaki, H.; Suzuki, K.; Yahara, I. The calmodulin-binding domain of the mouse 90-kDa heat shock protein. J. Biol. Chem. 1993, 268, 9604–9610.

33. Meng, X.; Devin, J.; Sullivan, W.P.; Toft, D.; Baulieu, E.E.; Catelli, M.G. Mutational analysis of Hsp90 alpha dimerization and subcellular localization: Dimer disruption does not impede "in vivo'' interaction with estrogen receptor. J. Cell Sci. 1996, 109, 1677–1687.

34. Soti, C.; Vermes, Á.; Haystead, T.A.J.; Csermely, P. Comparative analysis of the ATP-binding sites of Hsp90 by nucleotide affinity cleavage: A distinct nucleotide specificity of the C-terminal ATP-binding site. Eur. J. Biochem. 2003, 270, 2421–2428.

35. Scroggins, B.T.; Robzyk, K.; Wang, D.; Marcu, M.G.; Tsutsumi, S.; Beebe, K.; Cotter, R.J.; Felts, S.; Toft, D.; Karnitz, L.; et al. An Acetylation Site in the Middle Domain of Hsp90 Regulates Chaperone Function. Mol. Cell 2007, 25, 151–159.

36. Kovacs, J.J.; Murphy, P.J.M.; Gaillard, S.; Zhao, X.; Wu, J.T.; Nicchitta, C.V.; Yoshida, M.; Toft, D.O.; Pratt, W.B.; Yao, T.P. HDAC6 regulates Hsp90 acetylation and chaperone-dependent activation of glucocorticoid receptor. Mol. Cell 2005, 18, 601–607.

37. Bali, P.; Pranpat, M.; Bradner, J.; Balasis, M.; Fiskus, W.; Guo, F.; Rocha, K.; Kumaraswamy, S.; Boyapalle, S.; Atadja, P.; et al. Inhibition of histone deacetylase 6 acetylates and disrupts the chaperone function of heat shock protein 90: A novel basis for antileukemia activity of histone deacetylase inhibitors. J. Biol. Chem. 2005, 280, 26729–26734.

38. Schopf, F.H.; Biebl, M.M.; Buchner, J. The HSP90 chaperone machinery. Nat. Rev. Mol. Cell Biol. 2017, 18, 345–360.

39. Wandinger, S.K.; Suhre, M.H.; Wegele, H.; Buchner, J. The phosphatase Ppt1 is a dedicated regulator of the molecular chaperone Hsp90. EMBO J. 2006, 25, 367–376.

40. Martínez-Ruiz, A.; Villanueva, L.; De Orduña, C.G.; López-Ferrer, D.; Ángeles Higueras, M.; Tarín, C.; Rodríguez-Crespo, I.; Vázquez, J.; Lamas, S. S-nitrosylation of Hsp90 promotes the inhibition of its ATPase and endothelial nitric oxide synthase regulatory activities. Proc. Natl. Acad. Sci. USA 2005, 102, 8525–8530.

41. Retzlaff, M.; Stahl, M.; Eberl, H.C.; Lagleder, S.; Beck, J.; Kessler, H.; Buchner, J. Hsp90 is regulated by a switch point in the C-terminal domain. EMBO Rep. 2009, 10, 1147–1153.

42. Miyata, Y.; Yahara, I. Interaction between Casein Kinase II and the 90-kDa Stress Protein, HSP90. Biochemistry 1995, 34, 8123–8129.

43. Daturpalli, S.; Waudby, C.A.; Meehan, S.; Jackson, S.E. Hsp90 inhibits α-synuclein aggregation by interacting with soluble oligomers. J. Mol. Biol. 2013, 425, 4614–4628.

44. Evans, C.G.; Wisén, S.; Gestwicki, J.E. Heat shock proteins 70 and 90 inhibit early stages of amyloid β-(1-42) aggregation in vitro. J. Biol. Chem. 2006, 281, 33182–33191.

45. Jakob, U.; Lilie, H.; Meyer, I.; Buchner, J. Transient interaction of Hsp90 with early unfolding intermediates of citrate synthase: Implications for heat shock in vivo. J. Biol. Chem. 1995, 270, 7288–7294.

46. Wiech, H.; Buchner, J.; Zimmermann, R.; Jakob, U. Hsp90 chaperones protein folding in vitro. Nature 1992, 358, 169–170.

47. Kazlauskas, A.; Sundström, S.; Poellinger, L.; Pongratz, I. The hsp90 Chaperone Complex Regulates Intracellular Localization of the Dioxin Receptor. Mol. Cell. Biol. 2001, 21, 2594–2607.

48. Csermely, P.; Schnaider, T.; Soti, C.; Prohászka, Z.; Nardai, G. The 90-kDa Molecular Chaperone Family: Structure, Function, and Clinical Applications. A Comprehensive Review. Pharmacol. Ther. 1998, 79, 129–168.

49. Koyasu, S.; Nishida, E.; Kadowaki, T.; Matsuzaki, F.; Iida, K.; Harada, F.; Kasuga, M.; Sakai, H.; Yahara, I. Two mammalian heat shock proteins, HSP90 and HSP100, are actin-binding proteins. Proc. Natl. Acad. Sci. USA 1986, 83, 8054–8058.

50. Sato, S.; Fujita, N.; Tsuruo, T. Modulation of Akt kinase activity by binding to Hsp90. Proc. Natl. Acad. Sci. USA 2000, 97, 10832–10837.

51. Weis, F.; Moullintraffort, L.; Heichette, C.; Chrétien, D.; Garnier, C. The 90-kDa heat shock protein Hsp90 protects tubulin against thermal denaturation. J. Biol. Chem. 2010, 285, 9525–9534.
52. Etard, C.; Roostalu, U.; Strähle, U. Shuttling of the chaperones Unc45b and Hsp90a between the A band and the Z line of the myofibril. J. Cell Biol. 2008, 180, 1163–1175.
53. Marzec, M.; Eletto, D.; Argon, Y. GRP94: An HSP90-like protein specialized for protein folding and quality control in the endoplasmic reticulum. Biochim. Biophys. Acta-Mol. Cell Res. 2012, 1823, 774–787.
54. Koch, G.; Smith, M.; Macer, D.; Webster, P.; Mortara, R. Endoplasmic reticulum contains a common, abundant calcium-binding glycoprotein, endoplasmin. J. Cell Sci. 1986, 86, 217–232.
55. Yang, Y.; Liu, B.; Dai, J.; Srivastava, P.K.; Zammit, D.J.; Lefrançois, L.; Li, Z. Heat Shock Protein gp96 Is a Master Chaperone for Toll-like Receptors and Is Important in the Innate Function of Macrophages. Immunity 2007, 26, 215–226.
56. Morales, C.; Wu, S.; Yang, Y.; Hao, B.; Li, Z. Drosophila Glycoprotein 93 Is an Ortholog of Mammalian Heat Shock Protein gp96 (grp94, HSP90b1, HSPC4) and Retains Disulfide Bond-Independent Chaperone Function for TLRs and Integrins. J. Immunol. 2009, 183, 5121–5128.
57. Altieri, D.C.; Stein, G.S.; Lian, J.B.; Languino, L.R. TRAP-1, the mitochondrial Hsp90. Biochim. Biophys. Acta-Mol. Cell Res. 2012, 1823, 767–773.
58. Gesualdi, N.M.; Chirico, G.; Pirozzi, G.; Costantino, E.; Landriscina, M.; Esposito, F. Tumor necrosis factor-associated protein 1 (TRAP-1) protects cells from oxidative stress and apoptosis. Stress 2007, 10, 342–350.
59. Masuda, Y.; Shima, G.; Aiuchi, T.; Horie, B.; Hori, K.; Nakajo, S.; Kajimoto, S.; Shibayama-Imazu, T.; Nakaya, K. Involvement of tumor necrosis factor receptor-associated protein 1 (TRAP1) in apoptosis induced by β-hydroxyisovalerylshikonin. J. Biol. Chem. 2004, 279, 42503–42515.
60. Siegelin, M.D.; Dohi, T.; Raskett, C.M.; Orlowski, G.M.; Powers, C.M.; Gilbert, C.A.; Ross, A.H.; Plescia, J.; Altieri, D.C. Exploiting the mitochondrial unfolded protein response for cancer therapy in mice and human cells. J. Clin. Investig. 2011, 121, 1349–1360.
61. Chavez-Salinas, S.; Ceballos-Olvera, I.; Reyes-del Valle, J.; Medina, F.; del Angel, R.M. Heat shock effect upon dengue virus replication into U937 cells. Virus Res. 2008, 138, 111–118.
62. Ali, M.M.U.; Mark Roe, S.; Vaughan, C.K.; Meyer, P.; Panaretou, B.; Piper, P.W.; Prodromou, C.; Pearl, L.H. Crystal structure of an Hsp90-nucleotide-p23/Sba1 closed chaperone complex. Nature 2006, 440, 1013–1017.
63. Prodromou, C. The ATPase cycle of Hsp90 drives a molecular clamp' via transient dimerization of the N-terminal domains. EMBO J. 2000, 19, 4383–4392.
64. Cunningham, C.N.; Krukenberg, K.A.; Agard, D.A. Intra- and intermonomer interactions are required to synergistically facilitate ATP hydrolysis in Hsp90. J. Biol. Chem. 2008, 283, 21170–21178.
65. Hessling, M.; Richter, K.; Buchner, J. Dissection of the ATP-induced conformational cycle of the molecular chaperone Hsp90. Nat. Struct. Mol. Biol. 2009, 16, 287–293.
66. Åkerfelt, M.; Morimoto, R.I.; Sistonen, L. Heat shock factors: Integrators of cell stress, development and lifespan. Nat. Rev. Mol. Cell Biol. 2010, 11, 545–555.
67. Richter, K.; Haslbeck, M.; Buchner, J. The Heat Shock Response: Life on the Verge of Death. Mol. Cell 2010, 40, 253–266.
68. Lamut, A.; Gjorgjieva, M.; Naesens, L.; Liekens, S.; Lillsunde, K.E.; Tammela, P.; Kikelj, D.; Tomašič, T. Anti-influenza virus activity of benzo[d]thiazoles that target heat shock protein 90. Bioorg. Chem. 2020, 98, 103733.
69. Li, G.; Zhang, J.; Tong, X.; Liu, W.; Ye, X. Heat shock protein 70 inhibits the activity of influenza a virus ribonucleoprotein and blocks the replication of virus In Vitro and In Vivo. PLoS ONE 2011, 6, e16546.
70. Hirayama, E.; Atagi, H.; Hiraki, A.; Kim, J. Heat Shock Protein 70 Is Related to Thermal Inhibition of Nuclear Export of the Influenza Virus Ribonucleoprotein Complex. J. Virol. 2004, 78, 1263–1270.
71. Seo, H.W.; Seo, J.P.; Jung, G. Heat shock protein 70 and heat shock protein 90 synergistically increase hepatitis B viral capsid assembly. Biochem. Biophys. Res. Commun. 2018, 503, 2892–2898.
72. Shim, H.Y.; Quan, X.; Yi, Y.S.; Jung, G. Heat shock protein 90 facilitates formation of the HBV capsid via interacting with the HBV core protein dimers. Virology 2011, 410, 161–169.