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REVIEW

Progress in Molecular Chaperone Regulation of Heat Shock Protein 90 and Cancer

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Abstract: Heat shock protein 90 (HSP90) is a member of genetically conserved heat shock protein family. As an important molecular chaperone in eukaryotic cells, HSP90 plays a key regulatory role in maintaining cellular protein homeostasis. HSP90 clients encompass a wide range of proteins, thus HSP90 is involved in diverse biological process. With the deeper study, it is found that HSP90 takes an important part in the development and metastasis of cancer, and has become a promising target for the study of anticancer biology. In this review, the progress of HSP90 as molecular chaperone and its relationship with cancer are discussed.

Key Words: Heat shock protein 90; Molecular chaperone; Cancer; Review

1 Introduction

Cancer with high mortality has become a serious threat to human health. It is estimated that in 2015, there were 4292,000 new cancer cases and 2814,000 cancer and 200 deaths in China, of which lung cancer was the highest mortality cancer, followed by gastric cancer, esophageal cancer and liver cancer in turn[1]. The study of the molecular mechanism of the occurrence and metastasis of cancer is still a significant scientific problem to be solved in the field of biomedical research. Heat shock protein (HSP), also known as stress protein, is a rapidly synthesized protein after being stimulated by external adverse factors (high temperature, hypoxia, cytokine release, etc.). HSP was found in the study of the salivary gland chromosome of Drosophila larvae in 1962 by the Italy geneticist Ferruccio Ritossa[2]. When the temperature of the environment increases, the salivary gland of the Drosophila became swelling, which is called heat shock response (HSR). There are six members of HSP family. According to molecular weight difference, they are divided into HSP110, HSP90, HSP70, HSP60, HSP40 and small molecule heat shock protein (small Heat Shock Proteins, sHSPs). As a class of glycoproteins, heat shock proteins are highly conserved in heredity. The nucleotide sequences and amino acid sequences of HSP of different species are highly homologous. In cells, one of the most important functions of HSP is as a molecular chaperone to participate in the correct folding of new synthetic proteins, to help proteins to renature after stress damage, and to maintain the conformation and stability of proteins. With the further research on molecular mechanism of tumor occurrence and development, it has been found that HSP90 plays an important role in regulating proteins in multiple signaling pathways during tumor carcinogenesis. HSP90 has become a hot topic in the field of anti-tumor biology. This article reviews the progress of the molecular chaperone regulation of HSP90 and its relationship with tumor development and metastasis.

2 Heat shock protein 90 and its structure

The heat shock protein 90 family is a class of ATP-dependent molecular chaperones with molecular weight of 90 kDa. HSP90 exists in the form of dimer in cells, and the dimerization of HSP90 is necessary for its intracellular function[3]. In non-stressed state, the expression of HSP90 accounts for about 1%–2% of the cellular protein, which is thousands times of the average protein content. Under stress state, the content of HSP90 can increase to 4%–6%[4–6]. In

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human cells, HSP90 protein is divided into HSP90α (inducible form) and HSP90β (constitutive form). After thermal induction, the expression of HSP90α increased. HSP90α is not necessary in mammals, which is related to maintain cell homeostasis under stress. HSP90β expresses insistently and is necessary in mammals. HSP90β is related with life activity of mammals[7,8]. In addition, the subtypes of HSP90 include Gr994 in endoplasmic reticulum, TRAP1 in mitochondria and HSP90 C in chloroplast[9]. As an important molecular chaperone, HSP90 can activate different types of proteins and participate in the regulation of a variety of life activities.

HSP90 monomer includes three domains[10]: N-terminal domain (NTD), middle domain (MD) and C-terminal domain (CTD)[10], as shown in Fig.1. Each domain has different functions. HSP90 stayed as open "V"-shape conformation without ATP binding[11]. The N-terminal domain of HSP90 has dimer structure containing ATP binding site. HSP90 and its co-chaperones regulate the hydrolysis process of ATP[12], which promotes the beginning of HSP90 chaperone cycle and provides the energy for the process. The middle domain is the binding region of the substrate proteins and the co-chaperones[13,14]. The part of the N-terminal domain between middle domain is a variable and charged connector. Owing to the unstable structure, it is difficult to identify the full-length structure of HSP90. When the catalytic ring of middle domain converted into an active state, HSP90 has ATPase activity. The ring-shaped structure of middle domain contains a conservative arginine residue, which interacts with ATP's γ-phosphate to promote ATP hydrolysis by HSP90. The C-terminal domain is another region for the co-chaperones binding, which is responsible for the dimerization of HSP90[15,16]. The C-terminal has a MEEVD consensus sequence[17], which interacts with the co-chaperones containing the tetratricopeptide repeat (TPR) structure. After the substrate proteins binding with middle domain, the conformation of N-terminal domain rearranged through the interactions between HSP90 and its co-chaperones and the energy from ATP hydrolysis. The HSP90 converts to "closed" state, which exercises the function of molecular chaperone[18,19].

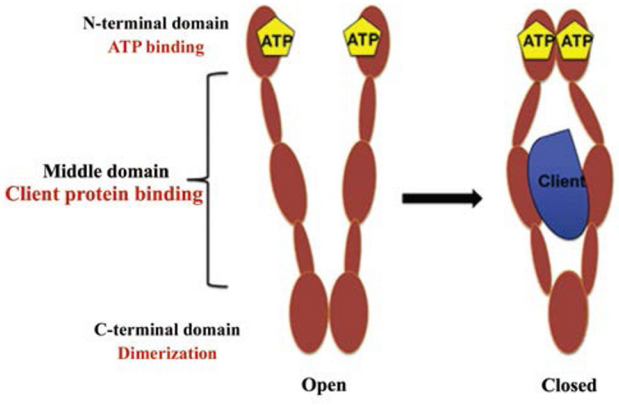

Fig.1 Schematic diagram of structure of HSP90[10]

3 HSP90 as a molecular chaperone

In mammalian cells, there are about 300 mg of protein per milliliter of cytoplasm[20]. The newly synthesized peptides and unstable proteins will expose the hydrophobic surface, which increases the risk of abnormal folding and degradation of proteins. These abnormal proteins will cause various kinds of diseases. To exercise normal biological function, the molecular chaperones can activate newly synthesized proteins, assembly and disassembly of molecular complexes, help misfolded proteins refold and regulate the degradation of HSP90 by ubiquitin proteasome degradation system. HSP90 is a class of important molecular chaperones, and it is reported that HSP90α and HSP90β can interact with nearly 2000 proteins from eukaryote[21]. Thus, HSP90 is widely involved in diverse life activities, such as steroid signal transduction, protein transport, cell cycle regulation, apoptosis, immune response and cancer development, etc.

3.1 Regulation of HSP90 function

3.1.1 Regulation of HSP90 expression

The heat shock reaction is initiated when high temperature, virus/bacterial infection or hypoxia, which is regulated by heat shock factor 1 (HSF1) at the transcriptional level. Besides, HSF1 is also a substrate protein of HSP90[22]. Under normal state, HSF1 with inactive form binds with HSP90. Otherwise, under stress state, HSF1 and HSP90 protein complexes depolymerize, and inactive HSF1 is released. HSF1 with monomer form is converted to trimers form and transferred to the nucleus followed by combining with heat stress element (heat shock element, HSE). Subsequently, HSF1 trimer is transformed into an active transcription factor by phosphorylation. Thus, HSF1 promotes the expression of HSP90 at the transcriptional level. Meanwhile, the expression of other molecular chaperones (such as HSP70 and HSP40) and co-chaperones are also increased rapidly. When the external stress stimulation ends or the expression of HSP90 reaches a certain level, the activated HSF1 is suppressed again[23–25].

3.1.2 Regulation of co-chaperones to HSP90's function

Similar to other molecular chaperones, HSP90 usually regulates the substrate proteins in the form of molecular chaperone complexes. HSP90 molecular chaperone complexes mainly include other molecular chaperones (HSP70, HSP40), co-chaperones (HOP/Sti1, Cdc37, PP5/Ppt1, p23/Sba1 and Aha1)[3,26] and other factors (as shown in Table 1). HSP90 can recruit different co-chaperones according to the different tissues, cells and substrate proteins. Each co-chaperone has unique role in protein refolding and refolding process. Among the identified HSP90 co-chaperones, some proteins containing