In S. cerevisiae, the molecular chaperone HSP90 exists as two isoforms, encoded by the genes HSC82 and HSP82. HSP90 family member activity is required for folding a specific set of difficult-to-fold proteins from nascent polypeptides into biologically active structures as well as for the refolding of denatured proteins back into native conformations. Although most cellular proteins do not require Hsp82p/Hsc82p chaperone activity for correct folding under normal conditions, Hsp82p and Hsc82p are required for the activation of many key cellular regulatory and signaling proteins, like kinases and transcription factors, such as Swe1p, Gcn2p, and Hap1p.HSP82 and HSC82 share ~97% sequence identity and together, the encoded proteins comprise 1-2% of all the protein in the cytosol. While HSC82 is expressed constitutively at high levels and only slightly induced by heat shock, HSP82 transcription is strongly induced by both heat and stress. Increased HSP82 expression is mediated by the transcription factor Hsf1p, which binds cooperatively to three heat shock elementsin the HSP82 promoter. It has been shown that Hsp1p-HSE interaction is also required for stimulating HSP82 basal transcription..All members of the HSP90 family function as dimers and protein folding is driven by the ATPase activity of the chaperone. Binding of ATP to the Hsp82p/Hsc82p N-terminus induces conformational changes in the protein as well as transient dimerization of the N-terminal nucleotide-binding domain. Studies of the mammalian homolog show that Hsp82p and Hsc82p also contain a second ATP-binding site in the C-terminus that only forms after a conformational change is induced by occupancy of the N-terminal ATP binding site. Hsp82p and Hsc82p associate with many co-chaperones which both positively and negatively regulate Hsp82p/Hsc82p function. Hsp82p/Hsc82p co-chaperones include Sti1p, Cdc37p, Cns1p, Sba1p, Cpr6p, Cpr7p, Sse1p, Hch1p, and Aha1p. One common method by which these partner proteins regulate Hsp82p/Hsc82p activity is through the inhibition/enhancement of ATP hydrolysis. Mechanistically, this can occur through direct interference of ATP binding or by alteration of Hsp82p/Hsc82p protein conformation such that ATP binding is affected. HSP82 and HSC82 are highly conserved among eukaryotes and the presence of at least one of the HSP90 gene product family members is essential for viability in yeast, Drosophila, and humans. Overexpression of HSP82 in S. cerevisiae has been shown to increase the virulence of the yeast in mice. Human HSP90is being explored as a target for cancer therapeutics due to its role in folding oncogenic protein kinases and because inhibition of chaperone activity by ATP analogs has been shown to promote substrate protein degradation via the ubiquitin-dependent proteasomal pathway.