SSA1, SSA2, SSA3, and SSA4 encode chaperone proteins that comprise the S. cerevisiae SSA subfamily of cytosolic HSP70 proteins. HSP70 is a large family of proteins that has been evolutionarily conserved from bacteriato humans. HSP70 proteins were originally classified based upon their induction by heat shock and their size of ~70kDa. The main function of these proteins is to serve as molecular chaperones, binding newly-translated proteins to assist in proper folding and prevent aggregation/misfolding. In yeast, HSP70s are also involved in disassembling aggregates of misfolded proteins, translocating select proteins into the mitochondria and ER, degrading aberrant proteins, and regulating the expression of other heat shock proteins. S. cerevisiae has at least 9 cytosolic forms of HSP70, 2 HSP70s which are found in the endoplasmic reticulum, and 3 mitochondrial HSP70s.The 4 genes of the SSA subfamily are closely related, with Ssa2p sharing 99%, 84%, and 85% amino acid identity with Ssa1p, Ssa3p, and Ssa4p, respectively. SSA2 is the only member of the SSA subfamily whose transcription is not inducible by heat or stress; the SSA2 gene is constitutively expressed at high levels. Although the majority of Ssa protein is found in the cytosol, Ssa1p and Ssa2p can also be detected in the cell wall. An Ssa2p-GFPfusion protein was observed to relocate from the cytosol to the mitochondrial outer surface upon oxidative stress. Additionally, Ssa1p and Ssa2p have been implicated in DNA-damage as they have been identified as members of Rad9 DNA-checkpoint complexes.Most of the structural knowledge of the S. cerevisiae HSP70 proteins is based on experimental evidence from bacterial DnaK, mammalian HSP70, and Ssa1p. All Hsp70s contain an N-terminal ATPase domain and a C-terminal peptide binding domain. ATPase activity of HSP70s is intrinsically weak but can be enhanced by interaction with DnaJ/HSP40 proteins. It has been shown for Ssa1p, and based on similarity is implicated for the remaining Ssa subfamily, that activity is stimulated by interaction with the DnaJ/HSP40 co-chaperones Ydj1p, Sis1p, Sti1p, and Cns1p. Substrate binding is regulated by ATP turnover; in the presence of ATP, peptide exchange is rapid and the binding constant is low while when ADP is bound, peptide exchange is slower and the substrate affinity higher. The rate of Ssa protein ATP/ADP exchange is stimulated by the nucleotide exchange factors Fes1p and Snl1p.The effect of SSA2 expression has also been studied in yeast models of human prion disease such as Creutzfeldt-Jakob disease. For the [PSI+] prion, overexpression of any one of the Ssa proteins promotes prion formation and suppresses the ability of Hsp104p to cure prion propagation. In contrast, a mutant allele of SSA2 has been shown to destabilize and prevent propagation of the yeast prion [URE3]. In cells carrying the [PIN+] prion, ssa1ssa2 double null mutations result in the loss of polyglutamine aggregate expansion and toxicity, which are two hallmarks of Huntington disease.