Role of molecular chaperones in ubiquitin-dependent protein degradation

Abstract

Molecular chaperones Hsp70 and Hsp90 are essential regulators of protein degradation. In a highly crowded population of native and folding-deficient proteins, the molecular chaperones discriminate between native and non-native states of proteins and target the folding-deficient proteins for proteasomal degradation by the protein quality control (PQC) pathway. Hsp70 is a general protein-folding chaperone that helps in the folding of newly synthesized polypeptides as well as in the refolding of non-native proteins. If folding cannot be achieved, Hsp70 targets the non-native proteins for degradation. Nevertheless the cellular factor that links Hsp70 to the protein degradation pathway has remained uncertain. In the present work, it is shown that Fes1, one of several Hsp70 nucleotide exchange factors, specifically releases misfolded proteins from Hsp70 thereby promoting their transfer to the ubiquitin ligase Ubr1 and degradation by the proteasome.

In contrast to the more general role of Hsp70, the *de novo* folding function of Hsp90 is restricted to several classes of proteins, so called client proteins. Previous work in the Dohmen laboratory, in addition, identified Hsp90 as a factor specifically required for the degradation of several ubiquitin-dependent proteasomal substrates, but it is dispensable for the degradation of ubiquitin-independent proteasomal substrates (Fröhlich, 2005). The present work identifies Hsp90 as a protein that is required to keep intracellular ubiquitylated proteins in a soluble state suitable for degradation by the proteasome. Genetic interaction studies revealed that Hsp90 has functional redundancy with ubiquitin receptors in delivering ubiquitin conjugates to proteasome.