localization close to the microtubule-organizing centre, but not the bio-
genesis of aggresomes itself, is de-
pendent on intact microtubules. Furthermore, the intermediate fila-
ment protein vimentin redistributes upon formation of aggresomes, form-
ing a cage-like structure around the aggregated proteins.

It is proposed that the appearance of aggresomes is a general cellular
response to overexpression of pro-
teins, when intracellular folding and degradation machineries are exhausted. Even though the proteins
trapped in aggresomes seem to be rather stable, it will be interesting to
learn about the dynamic nature of this novel structure, and about other
components participating in its for-

mation and/or present in the aggre-
gates. Clearly, the importance of the
new findings is underscored by the
role that protein aggregation is
known to play in the pathogenesis of
several diseases, including those char-
acterized by neurodegeneration.

Getting in is easy, but how to get out?

In yeast, the heat-shock proteins Kar2p (BiP) and Ssa1p play essential roles in
the import of nascent proteins into the
ER by working together as ratchets or motors in the endoplasmic reticulum
(ER) lumen and the cytosol, respec-
tively. Defective imported proteins are
scouted out by other ER chaperones
such as calnexin (Cne1p) and prepared
for export back into the cytosol, where they are degraded in proteasomes.

Both the import of nascent proteins into the ER as well as the export of mis-
folded proteins from the ER require
Kar2p and the Sec61p translocation
complex, suggesting a mechanistic
link between these two processes.

To investigate this hypothesis, Brodsky et al.1 generated mutant alleles
of some of the major players involved,
namely Cne1p, Kar2p and Ssa1p. By
following the degradation of green
fluorescent protein in vivo and in vitro,
they could show that mutations in Kar2p inhibit
this degradation and that Kar2p is required for export and for the recog-
nition of degradation substrates. By
contrast, mutations in Ssa1p had no
effect on export or degradation,
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import into the ER both in vivo and
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nature of the role for Ssa1p for protein
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export. Finally, they observed a syn-
thetic interaction between kar2 and
cne1 at elevated temperatures.

The authors suggest that misfolded
proteins are captured by Cne1p in the
ER lumen but must be handed over to
Kar2p for proper re-translocation.

Mutations in either chaperone might
compromise the release of the sub-
strate and therefore abolish this hand-
over. Taken together, the mechanisms
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The expression of genes in response to
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Investigators usually focused on the
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