Autophagy ›
Volume 7, 2011 - Issue 9

Free access

1,433 Views | 45 CrossRef citations to date | 0 Altmetric

Listen

Autophagic Punctum

Development of p97 AAA ATPase inhibitors

Tsui-Fen Chou & Raymond J. Deshaies

Pages 1091-1092 | Received 28 Apr 2011, Accepted 13 May 2011, Published online: 01 Sep 2011

Cite this article https://doi.org/10.4161/auto.7.9.16489

Abstra

Specific and cellular
investiga rone that
has mult hat require
long s are likely
to gene se upon
slow dep nhibitor,
N^2,N^4-di on blocking
autopha pendent
ubiquitir m
conventi utophagic
protein c eQ activates
autophagic and/or apoptotic cell death will require further work to evaluate its detailed

mechanism of action. An exciting goal for the future will be to generate p97 inhibitors that affect one or the other pathway. We propose that generation of ‘separation of function’ inhibitors will be a challenging adventure for chemical biologists but will yield extremely powerful tools to study p97 and enable evaluation of the therapeutic potential of targeting distinct p97 complexes.

This article refers to:

p97 AAA (ATPase associated with diverse cellular activities) ATPase is known as valosin-containing protein (VCP) and translational endoplasmic reticulum ATPase (TERA). p97 plays critical roles in a broad range of cellular activities, which is thought to derive from its ability to associate with different cofactors and interacting partners. Various cofactors link p97 to specific functions in many different cellular processes. In general, it is thought that p97 unfolds proteins or remodels/disassembles protein complexes, but the detailed mechanism of how p97 works and is linked to specific cellular processes remains unknown. Recent proteomic network analysis of the human autophagy systems reveals interaction of p97 with 17 autophagy-related proteins. This finding hints at multiple unidentified functions of p97 within the autophagy pathway.

p97 is m ed proteins
via the e which
misfolde ately
degrade gradation of
aggrega t a key
mechani to be their
ability t chanism in
resp night be an
effective ys may
cause ra onse. This
may hav l, and
therefor xes.

A high-t e NIH
Molecula rs of p97
ATPase activity. Among them, N^2,N^4-dibenzylquinazoline-2,4-diamine was identified as a

selective, reversible and ATP-competitive p97 inhibitor. Importantly, DBeQ exhibits 20-fold selectivity for stabilizing p97-dependent vs. independent UPS reporter substrates in HeLa cells. Some examples of previously known p97 substrates in mammalian cells are grouped into 4 categories in Figure 1. DBeQ impairs degradation of substrates within the ERAD and autophagy pathways. A lot of questions remain to be addressed. Does DBeQ target all p97-dependent processes or only a subset of them? Evaluation of the effects of DBeQ on other p97 functions will provide more insight into the full spectrum of its activity.

We now focus our effort on determining how DBeQ activates caspase 3/7 and induces cell death so rapidly. An important question is, does induction of cell death by DBeQ occur through autophagic and/or apoptotic machineries? DBeQ completely inhibits autophagic degradation within 30 min. By contrast, caspase 3/7 activation is prominent after 4 h treatment. These kinetics are consistent with the possibility that inhibition of autophagy underlies the cell-killing activity of DBeQ. An alternative possibility for why DBeQ induces rapid caspase activation is that DBeQ may impinge on maintenance of inhibited caspase-IAP (inhibitor of apoptosis) complexes. It is possible that the caspase activation and cell death induced by DBeQ are ‘off-target’ effects mediated by unknown factors. However, p97 knockdown also induces caspases 3 and 7 and cell death.

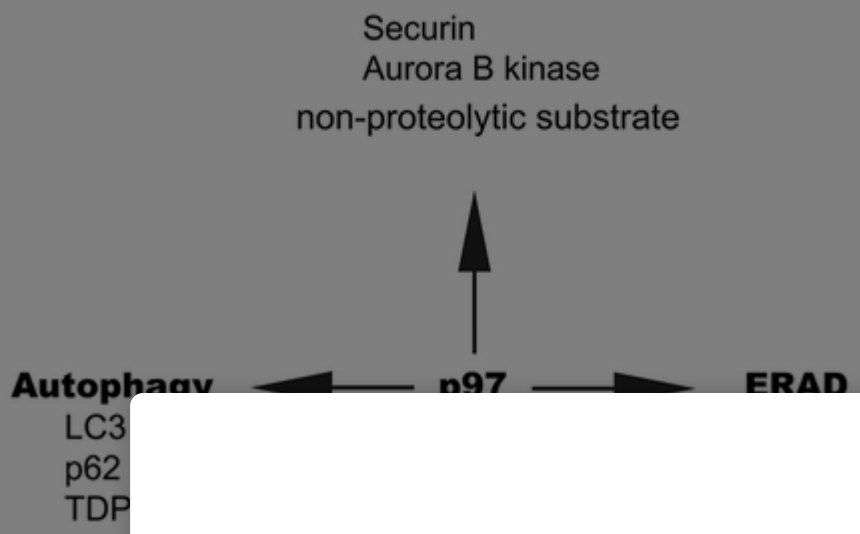
Currently, an extensive structure-activity relationships (SAR) study is underway to discover g the effect of novel pendent UPS reporter bstrates will enable u tic that this effort wi ds that selective le evaluati such as canc

Abb

LC3	
ERAD	endoplasmic reticulum associated degradation

Figures and Tables

Figure 1 Examples of p97 substrates. Most known p97 substrates belong to the ERAD pathway. Emerging data suggests that p97 is involved in degradation of many other non-ERAD UPS substrates and autophagic substrates, as well as in disassembling and maintaining protein complexes (non-proteolytic function). DBeQ blocks the autophagy and ERAD functions of p97. More experiments are needed to determine whether DBeQ acts on other p97 pathways. Blockade of multiple pathways at the same time is likely to result in pleiotropic effects that resist molecular dissection. Therefore, development of ‘separation of function’ p97 inhibitors would provide more powerful tools to study individual p97 functions in cells.



Acknow

We than vas
supporte ma Research
Foundation, the Howard Hughes Medical Institute (HHMI) and the Weston Havens

Foundation. R.J.D. is an HHMI Investigator, and this work was funded in part by HHMI and in part by a National Institutes of Health R03 grant (MH085687).

Punctum to: Chou TF, Brown SJ, Minond D, Nordin BE, Li K, Jones AC, et al. Reversible inhibitor of p97, DBeQ, impairs both ubiquitin-dependent and autophagic protein clearance pathways. Proc Natl Acad Sci USA 2011; 108:4834 - 4839; PMID: 21383145; http://dx.doi.org/10.1073/pnas.1015312108