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# Development of p97 AAA ATPase inhibitors

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## Abstract

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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 most well-studied for its role in mediating degradation of ubiquitinated proteins via the endoplasmic reticulum-associated degradation (ERAD) pathway, in which misfolded proteins are extracted from the endoplasmic reticulum and ultimately

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Molecula rs of p97  
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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 more potent and specific p97 inhibitors. Simultaneously monitoring the effect of novel p97 inhibitors on purified p97, cell-based p97-dependent and independent UPS reporters, autophagic markers, caspase activation and other unexplored substrates will enable us to determine the mechanism of action of these inhibitors. Our ongoing effort will focus on identifying more potent and specific p97 inhibitors. Selective p97 inhibitors will be evaluated in cell-based assays for their ability to induce cell death in cancer, particularly in those cancers that are dependent on p97 for survival.

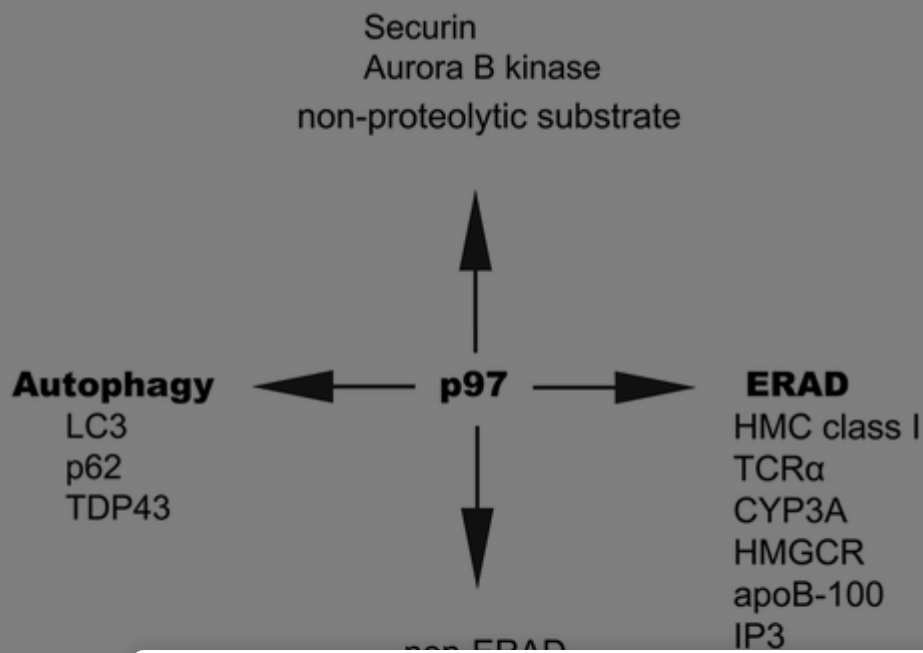
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Figure 1 Examples of p97 substrates. Most known p97 substrates belong to the ERAD pathway. Emerging data suggests that p97 is involved in degradation of many other non-ERAD UPS substrates and autophagic substrates, as well as in disassembling and maintaining 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.



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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>

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