

Many of our proteins need to be shaped, folded and trimmed after they are made, to coax them into their proper functional form. A variety of specialized chaperones and proteases perform these tasks. Occasionally, however, these chaperones and proteases make mistakes that can have life-threatening consequences.

Trimming Proteins

Beta-secretase, also known as BACE1 or memapsin-2, is a protease that makes specific cuts during the maturation of some protein chains. It is normally found in the endoplasmic reticulum and the Golgi, where it trims a few proteins that are particularly important in neural function. These include neuregulin, a protein that helps control the formation of myelin sheaths around nerve axons, and voltage-gated sodium channels, which are important for the transmission of nerve signals.

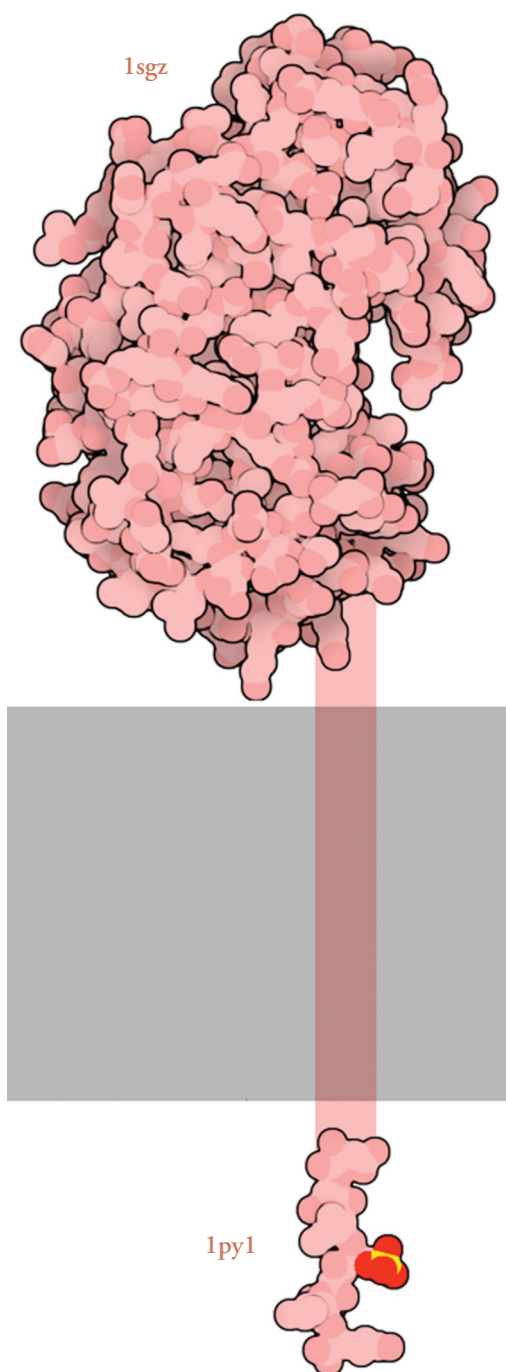
Tethered Trimmer

Beta-secretase is very similar to the digestive protease pepsin. Like pepsin, it has a deep active site cleft that grips protein chains, and a pair of aspartate amino acids that make the cut. Beta-secretase is different, however, in that it has a long tail that tethers the enzyme to the membrane surface. This tail localizes the enzyme in the proper place, so that it doesn't float freely through the cell and wreak havoc on other proteins. Two structures in the PDB show two portions of the enzyme: **1sgz** (at the top) is the catalytic domain that cleaves proteins, and **1py1** contains a small portion of the chain on the other side of the membrane (at the bottom) which is important for regulating the activity of the enzyme and directing it towards the proper site in the cell.

Performing a Job Too Well

Unfortunately, beta-secretase has a dark side as well. It makes a specific cut in the amyloid-beta precursor protein, breaking the protein chain and releasing a large portion of it. Then, a second protease makes another cut, and a tiny but dangerous peptide is formed. In small amounts, this peptide is important for normal synaptic function. However, if beta-secretase is overactive, the peptide builds up and can aggregate into tangled fibers. If these fibers form in nerve cells, they block nerve transmission and may lead to Alzheimer's disease. This connection to

Alzheimer's disease has made beta-secretase into one of the most studied enzymes in the fight against the disease.



About the RCSB PDB Molecule of the Month

Using selected molecules from the PDB archive, each feature includes an introduction to the structure and function of the molecule, a discussion of its relevance to human health and welfare, and suggestions for viewing and accessing further details.

The RCSB PDB Molecule of the Month is read by students, teachers, and scientists worldwide at www.pdb.org.

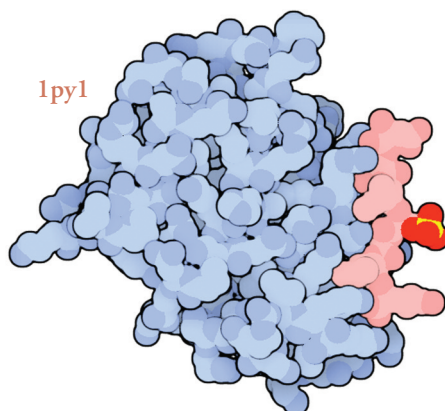
This July 2009 edition was written and illustrated by David S. Goodsell (RCSB PDB and The Scripps Research Institute).

RCSB Protein Data Bank

The Protein Data Bank (PDB) is the single worldwide repository for the processing and distribution of 3D structure data of large molecules of proteins and nucleic acids. The RCSB PDB is operated by Rutgers, The State University of New Jersey and the San Diego Supercomputer Center and the Skaggs School of Pharmacy and Pharmaceutical Sciences at the University of California, San Diego—two members of the Research Collaboratory for Structural Bioinformatics (RCSB).

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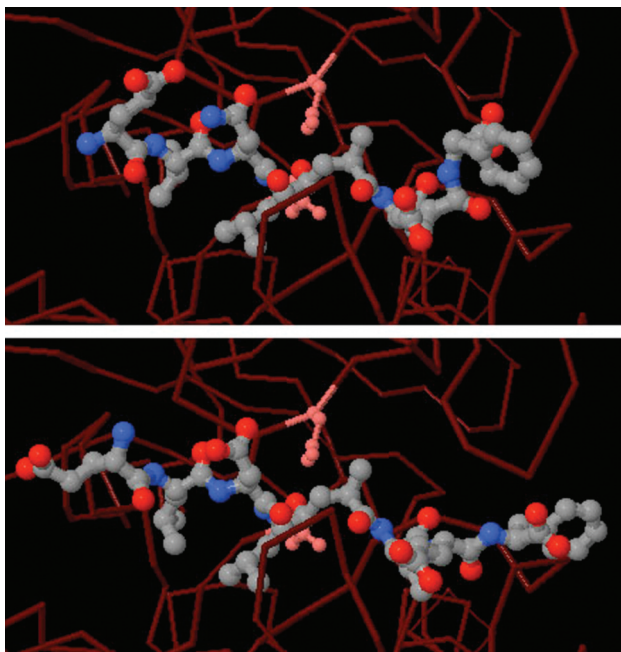
The RCSB PDB is a member of the worldwide PDB (www.pdb.org).



Getting to the Right Place

The tail of beta-secretase (shown in pink) controls the location of the enzyme inside the cell. It binds to proteins that control the traffic of proteins between the endoplasmic reticulum, Golgi, and cell surface, such as GGA, shown here in blue from PDB entry **1py1**. This short tail is phosphorylated (bright red and yellow atoms) to help control its association with the proteins that orchestrate this motion through the cell.

Exploring the Structure



Since beta-secretase is so important for the development of Alzheimer's disease, many laboratories have been working hard to find inhibitors to block it. The first success is

shown at the top here from PDB entry **1fkn**, and an improved compound that binds much more tightly is shown at the bottom from PDB entry **1m4h**. Structures of many other drug candidates may be found in the PDB. Unfortunately, these compounds are not efficiently transported from the blood to the brain, so they have not been particularly useful as drugs to fight Alzheimer's disease. But the search continues in the fight against this debilitating disease.

Topics for Further Exploration

1. Several proteases use a pair of aspartate amino acids to cleave protein chains. Can you find other examples in the PDB?
2. Many structures of inhibitors bound to beta-secretase are available in the PDB. Can you find examples of peptide-like inhibitors that are very similar to the protein chains that are cleaved by beta-secretase, and other inhibitors that are significantly different than peptides? What are the advantages and disadvantages of each?

Additional Information on beta-Secretase

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- 1py1:** X. He, G. Zhu, G. Koelsch, K. Rodgers, X. C. Zhang, J. Tang (2003) Biochemical and structural characterization of the interaction of memapsin 2 (beta-secretase) cytosolic domain with the VHS domain of GGA proteins. *Biochemistry* 42, 12174-12180
- 1fkn:** L. Hong, G. Koelsch, X. Lin, S. Wu, S. Terzyan, A. K. Ghosh, X. C. Zhang, J. Tang (2000) Structure of the protease domain of memapsin 2 (beta-secretase) complexed with inhibitor. *Science* 290, 150-153
- 1m4h:** L. Hong, R. T. Turner, G. Koelsch, D. Shin, A. K. Ghosh, J. Tang (2002) Crystal structure of memapsin 2 (beta-secretase) in complex with an inhibitor OM00-3. *Biochemistry* 41, 10963-10967