The 26S proteasome, comprised of a 19S regulatory particle and a 20S catalytic core particle, is a protease that is the responsible for the non-vacuolar degradation of cellular proteins. Classic substrates of the proteasome are polyubiquitinated proteins, including damaged proteins, aberrant or misfolded proteins, and proteins that are essential to the regulation of a pathway. In addition, non-ubiquitinated proteins and proteins with unconventional polyubiquitin linkages have been identified as substrates of the 26S proteasome. The 19S regulatory particle recognizes, unfolds, and translocates ubiquitinated proteins into the catalytic core particle. The 20S catalytic core degrades the protein into fragments ranging from 3 to 25 amino acids.The 20S catalytic core contains 7 alpha-type and 7 beta-type subunits. The 7 alpha-type subunits form a ring, as do the 7 beta-type subunits. The 20S catalytic core is a cylinder of four stacked rings: two beta-type rings in the center and two alpha-type rings at the ends. Each beta-type ring contains 3 catalytically active subunits: Pre3p, Pup1p, and Pre2p, which provide the postacidic/post-glutamic-like, the trypsin-like, and the chymotrypsin-like activities, respectively. Five of the beta-type subunits are synthesized with N-terminal propeptides that are removed. The three catalytically active subunits are activated by autocatalytic removal of their propeptides during assembly and maturation of the proteasome.The 20S catalytic core is first assembled to form \"half-proteasome precursor complexes\" containing an alpha-type ring, a beta-type ring, and the maturation factor Ump1p. The dimerization of these two halves results in the degradation of Ump1p and activation of the catalytic subunits. In addition to Ump1p, the propeptides of Pre2p and Pup1p and proteasomal subunits Pre1p and Pre4p contribute to efficient assembly of the 20S proteasome core. Additional 20S proteasome assembly factors include the Poc1p-Poc2p, Poc3p-Poc4p, and Pba3p-Pba4p heterodimers. Once assembled, the catalytic core is opened and stabilized by the 19S regulatory particle and Blm10p.Transcription of proteasomal subunit genes is regulated by Rpn4p. The catalytic activity of the proteasome can be inactivated by N-acetylation of Pre1p, Pre2p, and Pup1p as well as S-glutathionylation. Additional post-translational modification of the proteasomal subunits have been identified.The subunit composition and structure of the proteasome are conserved in various organisms, including Archaea, plants, and mammals. In mammals, the protein fragments resulting from degradation are loaded onto MHC class I molecules for antigen presentation. Because the 20S proteasome is essential in the proper regulation of multiple cellular process and antigen generation, it is a target for many drugs.