

A6 Regulation of meprins at the cell surface

J.S. Bond

Department of Biochemistry and Molecular Biology, Penn State University, Hershey PA 17033 USA

Meprins are membrane-bound and secreted multidomain, oligomeric zinc metalloendopeptidases composed of α and/or β subunits. The α and β subunits (each ~80 kDa) form disulfide-linked dimers, and have different substrate specificities (peptides such as gastrin and bradykinin, as well as matrix proteins). They are abundantly expressed in brush border membranes of epithelial cells of intestine and kidney in the embryo and adults, and in leukocytes and cancer cells. Oligomerization and concentration of meprin proteins are important for activity of these proteases. Meprin α homodimers are secreted as latent proteins and self-associate to form heterogeneous multimers (ring, spiral and barrel-like structures) of up to 100 subunits with molecular masses up to 6MDa. The latent proteins are activated at sites containing trypsin-like proteases. The meprin β subunits are integral membrane proteins and form homodimers or heterotetramers with meprin α . The homo- and heterophilic propensities of the subunits are determined by the MAM (meprin, A5 protein and protein-tyrosine phosphatase μ) and TRAF (tumor necrosis factor receptor-associated factor) domains and are being studied by size exclusion chromatography-light scattering, electron microscopy, crosslinking, and site-directed mutagenesis. Gene disruption studies indicate that meprins are important for embryonic survival and immune system functions.