FUNCTIONAL RELEVANCE OF A SLYX MOTIF IN NON-CONVENTIONAL SECRETION OF INSULIN-DEGRADING ENZYME

K. Glebov, S. Schütze, J. Walter

Neurology, University Hospital Bonn, Bonn, Germany

Insulin-degrading enzyme (IDE) is a Zn2+ metalloprotease with a characteristic inverted catalytic motif. IDE is ubiquitously expressed and it degrades peptide substrates including insulin, endorphin and the amyloid-beta peptide. While IDE is mainly expressed in the cytosol, it can also be found on the cell surface and in secreted forms in extracellular fluids. As IDE lacks a classical signal sequence that targets the protein to the classical secretory pathway, release of the enzyme involves non-conventional mechanisms. However, functional domains of IDE involved in its secretion remain elusive. By bioinformatics, biochemical and cell biological methods, we identified a new domain close to the C-terminus of IDE and characterized its function in the non-conventional secretion of the protein. Because its close homology to a motif also found in bacterial Slyx proteins, we propose to call it SlyX domain. Mutagenesis revealed that deletion of this domain strongly decreased the release of IDE, while deletion of a potential microbody targeting sequence at the extreme C-terminus had no effect on secretion. The combined data indicate that non-conventional secretion of IDE is regulated by newly identified SlyX domain.