Cleavage of Amyloid-β Precursor Protein (APP) by Membrane-Type Matrix Metalloproteinases.

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Amyloid-β precursor protein (APP) was identified by the expression cloning from a human placenta cDNA library as a gene product which modulates the activity of membrane-type matrix metalloproteinase-1 (MT1-MMP). Co-expression of MT1-MMP with APP in HEK293T cells induced cleavage and shedding of APP ectodomain when co-expressed with APP adaptor protein Fe65. Among MT-MMPs tested, MT3-MMP and MT5-MMP also caused efficient APP shedding. Recombinant APP protein was cleaved by MT3-MMP *in vitro* at the A^{463}-M^{464}, N^{579}-M^{580}, H^{622}-S^{623} and H^{685}-Q^{686} peptide bonds, which included a cleavage site within the amyloid β peptide region known to produce a C-terminal fragment. The Swedish-type mutant of APP, which produces a high level of amyloid β peptide, was more effectively cleaved by MT3-MMP than wild-type APP either in the presence or absence of Fe65; however, amyloid β peptide production was not affected by MT3-MMP expression. Expression of MT3-MMP enhanced Fe65-dependent transactivation by APP fused to the Gal4 DNA-binding and transactivation domains. These results suggest that MT1-MMP, MT3-MMP and MT5-MMP should play an important role in regulation of APP functions in tissues including central nervous system.

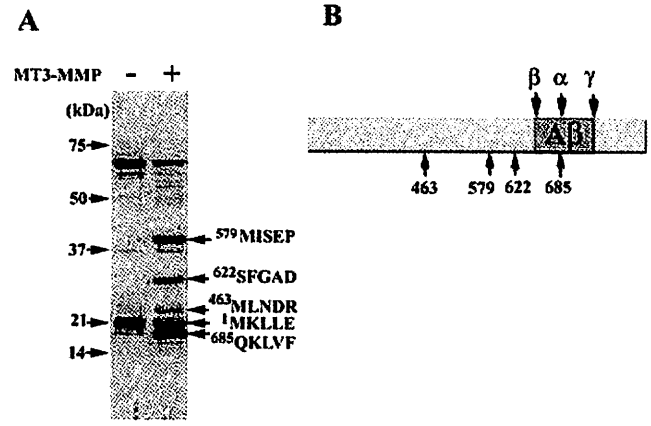

Fig. 1 (A) Recombinant APP protein (5 μg) was incubated with or without recombinant MT3-MMP catalytic domain, separated by 12% SDS-PAGE and stained with Coomassie Brilliant Blue. The N-terminal amino acid sequence of each fragment was determined. (B) MT3-MMP cleavage sites are marked on full length APP in relation to the cleavage sites for α-, β and γ-secretases.

Reference: M. Ahmad et al. J. Biochem., 139, 517-526 (2006).