A novel processing of β-amyloid precursor protein catalyzed by MT1-MMP abrogates its metalloproteinase inhibitor activity

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In various mammalian cell lines, β-amyloid precursor protein (APP) is proteolytically processed to release its NH₂-terminal extracellular domain as a soluble APP (sAPP). To investigate roles of matrix metalloproteinases (MMPs) in the processing of APP, we examined the correlation between the activity of cell-associated MMPs and processing of APP. We found that stimulation of HT1080 fibrosarcoma cells with concanavalin A led to activation of endogenous progelatinase A and to a novel processing of APP which releases a low molecular weight fragment named truncated sAPP (sAPPtrc, 95 kDa) into the culture medium. Structural analysis of the fragment showed that sAPPtrc was a COOH-terminally truncated form of sAPP. Both the production of sAPPtrc and the activation of progelatinase A were inhibited in the presence of a hydroxamate-based synthetic inhibitor or tissue inhibitor of metalloproteinases-2 (TIMP-2). On the other hand, the chemically modified TIMP-2, of which the reactive site had been destroyed by carbamylation, could prevent the activation of progelatinase A, but it failed to inhibit the production of sAPPtrc. Because the reactive site-modified TIMP-2 does not inhibit the catalytic activity of membrane type 1-MMP (MT1-MMP), this MMP was thought to be responsible for the production of sAPPtrc. Recombinant MT1-MMP converted purified sAPP to an sAPPtrc-like molecule. Reverse zymographic analysis showed that sAPP had an ability to inhibit the gelatinolytic activity of gelatinase A, but sAPPtrc did not. Taken together, these data support a model in which MT1-MMP destroys the metalloproteinase inhibitor domain of APP, thus making it feasible for activated gelatinase A to degrade components of extracellular matrix.