Matrix metalloproteinase-9 degrades amyloid-beta fibrils in vitro and compact plaques in situ.

許重義

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Abstract

The pathological hallmark of Alzheimer disease is the senile plaque principally composed of tightly aggregated amyloid-beta fibrils (fAbeta), which are thought to be resistant to degradation and clearance. In this study, we explored whether proteases capable of degrading soluble Abeta (sAbeta) could degrade fAbeta as well. We demonstrate that matrix metalloproteinase-9 (MMP-9) can degrade fAbeta and that this ability is not shared by other sAbeta-degrading enzymes examined, including endothelin-converting enzyme, insulin-degrading enzyme, and neprilysin. fAbeta was decreased in samples incubated with MMP-9 compared with other proteases, assessed using thioflavin-T. Furthermore, fAbeta breakdown with MMP-9 but not with other proteases was demonstrated by transmission electron microscopy. Proteolytic digests of purified fAbeta were analyzed with matrix-assisted laser desorption ionization time-of-flight mass spectrometry to identify sites of Abeta that are cleaved during its degradation. Only MMP-9 digests contained fragments (Abeta(1-20) and Abeta(1-30)) from fAbeta(1-42) substrate; the corresponding cleavage sites are thought to be important for beta-pleated sheet formation. To determine whether MMP-9 can degrade plaques formed in vivo, fresh brain slices from aged APP/PS1 mice were incubated with proteases. MMP-9 digestion resulted in a decrease in thioflavin-S (ThS) staining. Consistent with a role for endogenous MMP-9 in this process in vivo, MMP-9 immunoreactivity was detected in astrocytes surrounding amyloid plaques in the brains of aged APP/PS1 and APPsw mice, and increased MMP activity was selectively observed in compact ThS-positive plaques. These findings suggest that MMP-9 can degrade fAbeta and may contribute to ongoing clearance of plaques from amyloid-laden brains.