

Matrix metalloproteinases expressed by astrocytes mediate extracellular A-beta catabolism.

許重義

**Yin KJ;Cirrito JR;Yan P;Hu X;Xiao Q;Pan X;Bateman R;Song H;Hsu
FF;Turk J;Xu J;Hs**

Abstract

It has been postulated that the development of amyloid plaques in Alzheimer's disease (AD) may result from an imbalance between the generation and clearance of the amyloid-beta peptide (Abeta). Although familial AD appears to be caused by Abeta overproduction, sporadic AD (the most prevalent form) may result from impairment in clearance. Recent evidence suggests that several proteases may contribute to the degradation of Abeta. Furthermore, astrocytes have recently been implicated as a potential cellular mediator of Abeta degradation. In this study, we examined the possibility that matrix metalloproteinases (MMPs), proteases known to be expressed and secreted by astrocytes, could play a role in extracellular Abeta degradation. We found that astrocytes surrounding amyloid plaques showed enhanced expression of MMP-2 and MMP-9 in aged amyloid precursor protein (APP)/presenilin 1 mice. Moreover, astrocyte-conditioned medium (ACM) degraded Abeta, lowering levels and producing several fragments after incubation with synthetic human Abeta(1-40) and Abeta(1-42). This activity was attenuated with specific inhibitors of MMP-2 and -9, as well as in ACM derived from mmp-2 or -9 knock-out (KO) mice. In vivo, significant increases in the steady-state levels of Abeta were found in the brains of mmp-2 and -9 KO mice compared with wild-type controls. Furthermore, pharmacological inhibition of the MMPs with N-[(2R)-2-(hydroxamidocarbonylmethyl)-4-methylpentanoyl]-L-tryptophan methylamide (GM 6001) increased brain interstitial fluid Abeta levels and elimination of half-life in APPsw mice. These results suggest that MMP-2 and -9 may contribute to extracellular brain Abeta clearance by promoting Abeta catabolism.