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COMMENTARY

Matrix metalloproteinase 13, a new target for therapy in Alzheimer's disease

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Alzheimer's disease (AD), the most common neurodegenerative disorder, affects millions of people worldwide. In a recent publication, Guo-Jun Chen and colleagues highlight the role of matrix metalloproteinase (MMP) 13 (also called Collagenase 3) in AD pathogenesis through regulating BACE1,[1] a rate-limiting enzyme for β-amyloid (Aβ) peptide production.[2] Proteolytic processing of amyloid precursor protein (APP) by BACE1 and γ-secretase generates Aβ, which accumulate in brain senile plaques in AD.[3] MMPs are a group of enzymes that degrade extracellular matrix and cleave proteins involved in signal transduction. MMPs have central roles in a myriad of biological processes including cancer invasion and neuroinflammation but their role in AD pathophysiology remains elusive.[4] Initial reports highlighted the beneficial effects of MMP2 and MMP9 in attenuating Aβ levels.[5] Subsequent studies revealed that MT1-and MT5-MMP, two membrane-type MMPs, stimulate Aβ production and AD pathogenesis[6–8] and further, MT5-MMP5 releases a neurotoxic APP fragment that inhibits neuronal synaptic transmission.[9] Previously, MMP13 was recognized for its role in extracellular matrix remodeling, bone and cartilage metabolism, as well as in tumor invasion and metastasis.[10] Microglial cells were known to upregulate MMP13 in response to Aβ, suggesting a likely involvement of this MMP in AD.[5]

Zhu et al[1] report an increase of MMP13 in human AD brains as well as in a transgenic AD mouse model. A series *in vitro* studies demonstrate that the overexpression of MMP13 stimulates phosphatidylinositide kinase-3 (PI3K) signaling, promoting eukaryotic translation initiation factor 4B (eIF4B) phosphorylation, which in turn facilitates the 5′UTR-dependant BACE1 mRNA translation. Selectively targeting MMP13 using the inhibitor CL82198 decreases eIF4B phosphorylation at Serine residue 422 and led to

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reduced BACE1 synthesis. In a transgenic AD mouse model, shRNA silencing of MMP13 expression or its inhibition by CL82198 attenuated cerebral amyloid pathology. Finally, MMP13 inhibition rescued learning and memory deficits in the AD mouse model. Overall, the report describes a novel mechanism for MMPs to influence Aβ production through BACE1 mRNA translational mechanism involving eIF4B phosphorylation downstream of PI3K. It is interesting to consider how MMP13 activates PI3K signaling. Since CL82198 targets the catalytic activity of MMP13, it is likely that MMP13 cleaves PI3K and/or protein partners that control its activity. It might be possible to identify new substrates of MMP13 responsible for PI3K/Akt signaling through proteomics approaches. Progress in this front is essential for developing strategies to selectively inhibit MMP13 activation of PI3K signaling without interfering with MMP13's other physiological roles. Similarly, limiting the translational inhibition mechanism-based adverse effects associated with compromising eIF4B phosphorylation could be equally challenging. Nevertheless, the discovery is exciting because it provides compelling *in vitro* and *in vivo* evidence highlighting MMP13 and PI3K/Akt signaling as new therapeutic targets in AD and opens up new research directions.

Conflict of interest

The authors declare no conflicts of interest.

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