# Matrix metallopeptidase 9

Matrix metallopeptidase 9 (MMP-9), also known as 92 kDa type IV collagenase, 92 kDa gelatinase or gelatinase B (GELB), is a matrixin, a class of enzymes that belong to the zinc-metalloproteinases family involved in the degradation of the extracellular matrix. In humans the MMP9 gene encodes for a signal peptide, a propeptide, a catalytic domain with inserted three repeats of fibronectin type II domain followed by a C-terminal hemopexin-like domain.

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Although brain metastases are 10-fold more prevalent than primary brain cancers, relatively little is understood about the genes and pathways that promote metastatic cell entry, growth, and survival in the brain. Hence, determining how metastatic tumors colonize the brain and thrive within the neural microenvironment is a topic of both fundamental importance and direct clinical relevance. In this issue, a report by Karreman and colleagues explores pathways that are exploited by metastatic tumor cells to arrest in the circulation, cross the endothelial blood-brain barrier (BBB), and thrive in the brain microenvironment. The authors used elegant imaging tools including intravital fluorescence microcopy and serial reconstruction of ultrastructural sections to analyze BBB breach and subsequent colonization of the brain. They show that matrix metalloprotease 9 (MMP9) plays a central role in these events. Pharmacologic or genetic targeting of MMP9 significantly reduced penetration across the BBB and limited micrometastasis formation. Surprisingly, extravasation and brain colonization does not involve significant degradation of canonical MMP9 protein targets such as collagen and laminin in vascular basement membranes, indicating the requirement for other extracellular matrix (ECM) or non-ECM substrates for MMP9. Collectively, these new and important findings reveal cell-cell adhesion and signaling events between cerebral endothelial and metastatic cancer cells as well as identify potential therapeutic targets to prevent metastatic tumor cell dissemination in the brain [1)]

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Rashad et al., from Sendai, Japan showed the intense activation of immune cells, particularly the microglia, along with the increase in macrophage activity and NLRP3 inflammasome activation that is indicated by NLRP3, Interleukin 1 beta (IL-1β), and Interleukin 18 gene and caspase 1 upregulation and cleavage as well as pyroptosis.

Leukocytes were observed in the brain parenchyma, indicating a role in cerebral venous thrombosis (CVT)-induced inflammation. In addition, astrocytes were activated, and they induced glial scar leading to parenchymal contraction during the subacute stage and tissue loss. MMP9 was responsible primarily for the BBB breakdown after CVT and it is mainly produced by pericytes. MMP9 activation was observed before inflammatory changes, indicating that BBB breakdown is the initial driver of the pathology of CVT. These results show an inflammation driven pathophysiology of CVT that follows MMP9-mediated BBB breakdown, and identified several targets that can be targeted by pharmaceutical agents to improve the neuroinflammation that follows CVT, such as MMP9, NLRP3, and IL-1β. Some of these pharmaceutical agents are already in clinical practice or under clinical trials indicating a good potential for translating this work into patient care [2)].

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McCarty JH. MMP9 Clears the Way for Metastatic Cell Penetration Across the Blood-Brain Barrier. Cancer Res. 2023 Apr 14;83(8):1167-1169. doi: 10.1158/0008-5472.CAN-23-0151. PMID: 37057598.
2)
Rashad S, Niizuma K, Sato-Maeda M, Fujimura M, Mansour A, Endo H, Ikawa S, Tominaga T. Early BBB

breakdown and subacute inflammasome activation and pyroptosis as a result of cerebral venous thrombosis. Brain Res. 2018 Jul 4. pii: S0006-8993(18)30362-7. doi: 10.1016/j.brainres.2018.06.029. [Epub ahead of print] PubMed PMID: 29981290.