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High levels of MMP-cleaved mimecan is associated to carotid plaque stability and less future cardiovascular events

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Introduction: The clinical consequences of atherosclerosis, myocardial infarction and stroke are the most common causes of death globally. Mimecan, a small leucine rich-repeat proteoglycan (SLRP), is cleaved by matrix metalloproteinases (MMPs) and known to be involved in collagen fibrillogenesis and angiogenesis. Circulating levels of MMP-cleaved mimecan (cMIM) has previously been identified as a marker of extracellular matrix remodelling in ApoE^{-/-} knockout mice. The role of mimecan and its degradation in human atherosclerotic plaques has not been explored.

Purpose: We explored whether full-length mimecan and cleaved mimecan (cMIM) are associated to plaque composition and evaluated if they can predict future cardiovascular events.

Methods: Two hundred and eighteen human atherosclerotic plaques were stained for mimecan using immunohistochemistry. cMIM was measured in 202 plaque tissue homogenates using a competitive ELISA assay. Histological components (α -actin, CD68 and glycophorin A) were assessed using immunohistochemistry, neutral lipids were measured using Oil Red O and visible areas of calcium deposits were quantified. Matrix metalloproteinases (MMP-1, -2, -3, -9, -10 and -12), tissue inhibitors of matrix metalloproteinases (TIMP-1 and -2) were analysed in plaque tissue homogenates using ELISA assays and a proximity extension assay. ECM components

(glycosaminoglycans, collagen and elastin) were detected with colorimetric assays and the TGF- β 1, β 2 and β 3 were measured by a multiplex assay. Cardiovascular events were registered using national registers, patient records and telephone calls during a follow-up period of 59 months IQR (34–73).

Results: Mimecan was expressed in human atherosclerotic plaques. The expression correlated positively with neutral lipids and intraplaque hemorrhage and inversely with α -actin. In contrast cMIM correlated with α -actin and inversely with neutral lipids. cMIM correlated also with stabilizing extracellular matrix proteins elastin, collagen as well as TGF- β 1, β 2 and β 3. Mimecan correlated to MMP-9 and cMIM correlated to MMP-2 and TIMP-2. Patient with high levels of cMIM had a lower risk of future cardiovascular events which remained significant after adjusting for risk factors (age, gender, diabetes and symptoms) in a multivariate Cox regression

Conclusion(s): Mimecan was associated with vulnerable plaque features, whereas cMIM was related to stable plaque features. Low levels of cMIM predicted future cardiovascular events, independently of known risk factors. Taken together this suggests a possible role for mimecan and its cleavage in atherosclerosis that needs to be further explored.