Inhibiting extracellular matrix metalloproteinase inducer maybe beneficial for diminishing the atherosclerotic plaque instability

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ABSTRACT

Atherosclerotic plaque rupture and local thrombosis activation in the artery cause acute serious incidents such as acute coronary syndrome (ACS) and stroke. The exact mechanism of plaque rupture remains unclear but excessive degradation of the extracellular matrix scaffold by matrix-degrading metalloproteinases (MMPs) has been implicated as one of the major molecular mechanisms in this process. Convincing evidence is available to prove that extracellular matrix metalloproteinase inducer (EMMPRIN) induces MMP expression and is involved in the inflammatory responses in the artery wall. The inflammation and MMPs have been shown to play a critical role for atherosclerotic lesion development and progression. More recent data showed that increased EMMPRIN expression was associated with vulnerable atherosclerotic lesions. Therefore, we speculate that EMMPRIN may be pivotal for atherosclerotic plaque instability, and hence inhibition of EMMPRIN expression could be a promising approach for the prevention or treatment of atheroma instability.

Hypothesis

The evidence cited above provides us a hypothesis that EMMPRIN is an important factor in the pathology of atherosclerotic plaque instability. Most probably, blocking the expression of EMMPRIN may serve as a novel therapeutic strategy for diminishing atherosclerotic lesion development and atheroma instability.

Discussion

Atherosclerosis is a chronic inflammatory disease and immune system plays a key role in atherogenesis. Pro-inflammatory cytokines, such as IL-6 and TNF-α, potently stimulate MMP expression in monocytes and vascular smooth muscle cells; and these pro-inflammatory cytokines control stability of plaques and cause clinical acute vascular events through the regulation of tissue MMPs. EMMPRIN as a tumor-derived protein has been found to induce MMP production from stromal fibroblasts and is related to tumor invasion. However, recent findings indicate that EMMPRIN plays a pivotal role in the progression of molecules on endothelial cells, proliferation of smooth-muscle cells, activation of immune cells, and stimulation of the acute-phase response.

KEY WORDS: Atherosclerosis, acute coronary syndrome, extracellular matrix metalloproteinase inducer, stroke
atherosclerosis and in many ways, which might include induction of MMP and pro-inflammatory cytokines.\textsuperscript{13,14,15,16} EMMPRIN activates NF-κB, which is a critical regulator of innate and adaptive immunity and regulates many key inflammatory genes such as those of IL-6 and TNF-α. As these are linked to atherosclerosis, EMMPRIN’s activation of NF-κB constitutes an important step.\textsuperscript{[1]} This might suggest that EMMPRIN-NF-κB pathway is activated in the lesion. Furthermore, evidence shows that \textit{Chlamydia pneumoniae} induces MMP activity directly in monocytes through an EMMPRIN-dependent pathway in the human atherosclerosis.\textsuperscript{[12,13]} Some other studies have shown that oxidized low-density lipoproteins can upregulate the EMMPRIN expression of human coronary artery smooth muscle cells,\textsuperscript{[14]} macrophages and foam cells, which suggest a potential mechanism for the synergistic effects of hypercholesterolemia and infection in acceleration of atherosclerosis observed in experimental models\textsuperscript{[14,15,16]} and human epidemiological observations.\textsuperscript{[10,17]} Moreover, recent reports show that the expression of EMMPRIN on monocyte/macrophage differentiation suggests that EMMPRIN may be an important protein in the early phases of directed cell migration and differentiation in atherosclerosis.\textsuperscript{[1,8,9]} EMMPRIN may induce a vicious circle in the progress of promoting plaque progression and destabilization by the cellular interactions with monocytes/macrophages, SMCs and platelets stimulating a cascade of MMP activation.\textsuperscript{[1]} In aggregate, these findings indicate that EMMPRIN might be the link among lipid, infection/inflammation, atherosclerosis and plaque rupture.

Schmidt \textit{et al}.\textsuperscript{[8]} have reported that EMMPRIN expression is upregulated on monocytes in human acute myocardial infarction compared with that in chronic stable angina. After successful therapy, EMMPRIN surface expression on monocytes normalizes.\textsuperscript{[9]} Available evidence also proves that CRP increases EMMPRIN and MMP-9 activity in macrophages resulting in plaque destabilization, and statin can inhibit these effects by inhibiting EMMPRIN expression.\textsuperscript{[9,10]} Moreover, other experiments have proved that reducing EMMPRIN expression such as by small-interfering RNA, PPAR-α or PPAR-γ agonists can hinder monocyte or macrophage secretion of MMPs.\textsuperscript{[1,8,9]} Overall, these findings raise the possibility that EMMPRIN could serve as a novel target of therapy in the management of plaque destabilization. It must, however, be conceded that till date no definite in vivo evidence has proved that inhibiting the expression of EMMPRIN \textit{in vivo} to diminish atherosclerotic lesion development and atheroma instability. This is the new vista for future clinical research.

\textbf{Conclusions}

As EMMPRIN plays a critical role not only in immune reactions linking among lipid, infection/inflammation and atherosclerosis, but also in directly inducing MMP secretion and attenuating the fibrous cap of plaques, we hypothesize that EMMPRIN is a key element in the pathology of atherosclerotic plaque instability. The hypothesis provides a new perspective in the study of mechanisms of the EMMPRIN-related progression of atherosclerosis and vascular remodeling. Intervention with the expression of EMMPRIN would be effective in preventing the plaque rupture, and thereby decreasing the incidence of acute coronary syndrome or stroke. However, more experiments \textit{in vivo} are needed to undertake to prove this hypothesis in the future.

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