Monocytes M(*MP*)aking Way for T-Cell Vascular Infiltration

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Giant cell arteritis (GCA) is a chronic inflammatory vasculopathy of the medium and large-sized arteries including the external carotid branches, the ophthalmic, vertebral, subclavian, and axillary arteries, as well as thoracic aorta.[1] Severe granulomatous vasculitis, with profound T cell and macrophage activation and infiltration into the otherwise immunoprivileged vascular wall, results in occlusion of vascular lumen leading to ischemic symptoms, such as loss of vision in ca. 15% of patients.[1] Dissection and aneurysm formation, especially in the aorta also occur. Although very long-term high-dose glucocorticosteroid treatments are used in controlling the inflammation to alleviate symptoms, they are associated with complications, and when glucocorticoids are gradually reduced, disease flares occur frequently.[1] Thus, glucocorticoid sparing regimens including methotrexate as well as biologics such as tocilizimab or abatacept have been tested to further reduce risk of relapse and lower serious systemic side effects.[2] A need for additional potentially safer therapies is very evident.

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Although our understanding of immunopathology of advanced disease has significantly improved over the years, researchers know less about the early stages of the disease enabling the breakdown of immunoprivilege. As with many vascular disorders linked to vascular remodeling, a possible focus lies in MMPs (matrix metalloproteinases) and their tissue inhibitors (TIMPs [tissue inhibitors of metalloproteinases]), as final effectors of pathological vascular remodeling and neovascularization. Accumulating evidence suggest that MMPs can also regulate vascular inflammation,[3] making them a particularly interesting therapeutic target in vasculitis. Indeed, in GCA high gelatinase expression and activity occurs at the granulomatous areas surrounding the internal elastic lamina.[4]

In the present issue of *Circulation Research*, the Weyand group present a pathogenetic role of monocyte and macrophage-derived MMP-9 in facilitating T-cell infiltration into the vessel wall.[5] In a series of elegant in vitro mechanistic experiments, using an artificial collagen I and IV basement membrane model, they show that GCA patient monocytes show an increased ability to pass through the collagen barrier, but even more importantly, enable rapid T-cell invasion into the matrix, that without monocytes did not occur.[5] The ability to penetrate through the collagen layers was dependent on MMP-9 release from GCA monocytes. To verify the potential translational value of their finding, as in a number of their previous publications, the authors have used a humanized chimera model created by grafting human temporal or axillary arteries subcutaneously into the back of immunocompromised NOD *SCID* Gamma mice. Adoptive transfer of peripheral blood mononuclear cells from a GCA patient into the chimeras induces vasculitis.[6] Despite not being ideal for all purposes, this model addresses key questions linked to human vascular immunobiology. In this model, systemic blockade of MMP-9 prevented several vasculogenic mechanisms, reducing T-cell invasion into the vessel, and inhibiting neovascularization and intimal hyperplasia. At the same time, administration of recombinant MMP-9 led to increased vascular inflammation. These effects of MMP-9 were dependent on destruction of the basement membrane, induction of neoangiogenesis and vascular remodeling mediated by PDGF (platelet-derived growth factor) and FGF (fibroblast growth factor) and also, at least in part, through proinflammatory effects induced by the products of extracellular matrix degradation (matrikines), such as the acetylated tripeptide proline-glycine-proline (ac-PGP; Figure).

Researchers have known for some time that there is increased expression of gelatinases MMP-2 and MMP-9 in human GCA specimens in macrophages, vascular smooth muscle cells, and fibroblasts.[7] However, this study sheds new light on the potential contribution of MMPs to the early-onset of the pathology. Interestingly, in the present study, MMP-9 expression was found predominantly in monocytes and macrophages. One may postulate that at an early stage of disease, preceding T-cell invasion, this source predominates while at later stages of vascular destruction and remodeling other cell types may contribute as well. Moreover, although authors have focused on MMP-9, as the MMP which is most abundant in monocytes and macrophages, a very a significant overexpression of MMP-2 and MMP-7 was also observed in GCA. Future studies need to take this into account when trying to think about future strategies of metalloproteinase inhibition in vasculitis. Although providing important clues about the role of MMP-9 producing monocytes as critical checkpoints in the pathogenesis of vasculitis and associated leukocyte intramural infiltration, the translational diagnostic, prognostic, and therapeutic usefulness of these new findings has yet to be provided.

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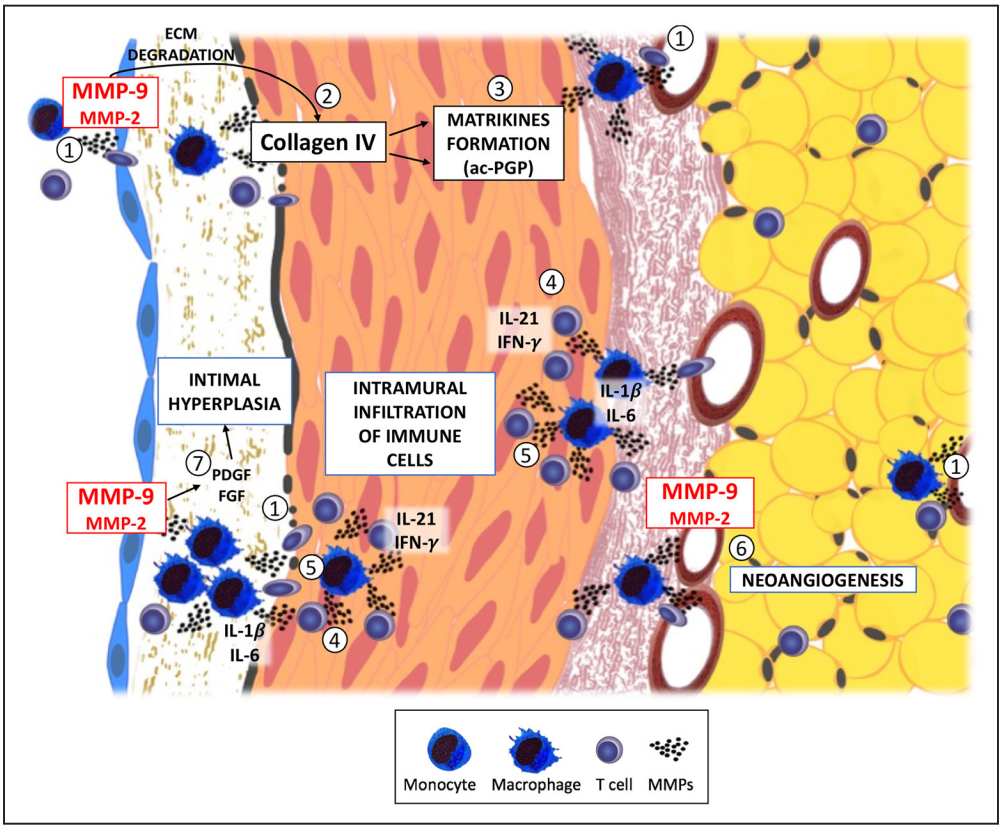

Figure. MMP (matrix metalloproteinase)-9 role in giant cell arteritis. MMP-9 producing monocytes/macrophages (1) degrade the extracellular matrix (ECM) enabling T-cells homing into the vascular wall (2). MMP-9 and collagen IV breakdown products such as matrikines (3) stimulate immune cells to produce proinflammatory cytokines (IL [interleukin]-1β, IL-6, IL-21, IFN [interferon]-γ); (4) leading to a further increase in intramural infiltration of leukocytes and their activation (5). In addition, MMP-9 promotes vascular angiogenesis (6) and intimal hyperplasia by inducing release of growth factors such as platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF) (7). ac-PGP indicates acetylated tripeptide proline-glycine-proline.

It is, however, important to point out that production of MMP-9 and MMP-2 by macrophages as well as synthetic vascular smooth muscle cells is increased in many other chronic vascular inflammatory diseases apart from vasculitis. Aortic abdominal aneurysms, atherosclerotic plaque rupture leading to myocardial infarction and stroke or hypertension are prime examples. In all of these pathologies, vascular and perivascular inflammation is a prominent pathognomonic feature.[8] Therefore, the data from Watanabe et al[5] could in principle shed light on key early mechanism(s) regulating immune cell trafficking in other forms of vascular[8] or cardiac[9] inflammation.

Several important questions arise from this work. For example, in the advanced stages of experimental atherosclerosis, researchers have shown that T cells can extravasate in the aortic adventitia mainly via high endothelial venules, to form structured artery tertiary lymphoid organs able to control vascular immune responses in situ.[10] Is MMP-9 produced by monocytes and macrophages pivotal in this process? In other words, is MMP-9 able to facilitate T-cell infiltration through high endothelial venules or are other pathways involved in this process but not addressed by Watanabe et al? Gelatinases are in fact known to cleave many different targets, for example, chemokines and cytokine receptors, which in turn may regulate cell migration, invasion and in result critically affect the development of vascular inflammation.[11] It would be also important to assess the net contribution of MMP-9 to intramural infiltration of other immune cell subsets.

Whatever the exact mechanism is, the study raises the possibility of therapeutic targeting of MMP-9 in the control of vascular inflammation. However, our enthusiasm may be somewhat dampened by the fact that various modalities of MMP targeting have failed in clinical trials to date, including cardiovascular risk outcome trials in human aortic aneurysms[12] or atherosclerotic disease.[13] One interpretation could be that MMP-inhibitors were tested in advanced stages of disease, while it might be more efficient to inhibit gelatinases at early stages of vascular inflammation. This prospect is interesting in the light of novel therapeutic approaches available to relatively safely target MMPs such as the inhibitor of elastolytic matrix metalloproteinases XL784.[14] Moreover, specific MMP-9 inhibitor andecaliximab/GS-5745 has entered phase 2/3 clinical trials showing good tolerability although low clinical efficacy in Crohn disease or ulcerative colitis.[15] Although we are unquestionably still far from successful translation, metalloproteinases seem to still have quite a lot to teach us about initiation and propagation of vascular inflammation.

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Disclosures

None.

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