

Matrix metalloproteinases and angiogenesis

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Angiogenesis is a prominent feature of numerous diseases, including cancer and arthritis, and appears to play an important role in kidney disease and hypertension. The matrix metalloproteinases, especially matrix metalloproteinase-2, play a vital role during angiogenesis by degrading the surrounding extracellular matrix and allowing endothelial cell invasion. Membrane type 1 matrix metalloproteinase directly degrades matrix components as well as activating matrix metalloproteinase-2 on the cell surface. The integrin receptors, particularly $\alpha_v\beta_3$, can recruit and possibly activate matrix metalloproteinases to localized microdomains on the cell membrane. This restricts matrix metalloproteinase activity to the pericellular region, preventing excessive matrix degradation which would otherwise impede endothelial invasion. Inhibitors of matrix metalloproteinase activity may actually promote cell invasion by preventing uncontrolled matrix degradation. In addition to degrading the matrix, matrix metalloproteinases produce protein fragments that impede their angiogenic action. These multiple regulatory pathways permit fine control over cell invasion during angiogenesis and provide new, precise strategies for targeting abnormal angiogenesis, through control of matrix metalloproteinase activity. *Curr Opin Nephrol Hypertens*

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Abbreviations

APC	activated protein C
MMP	matrix metalloproteinase
MT1	membrane type 1
TIMP	tissue inhibitor of metalloproteinase
VEGF	vascular endothelial growth factor

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Introduction

Physiological angiogenesis occurs during the female reproductive cycle and wound healing. Numerous diseases including solid tumour growth, metastases, arthritis and diabetic retinopathy are characterized by abnormal angiogenesis. Far less studied is the role of angiogenesis in nephrology, even though impaired angiogenesis appears to be a prominent feature of some kidney diseases, such as autosomal-dominant polycystic kidney disease, a genetic disorder responsible for approximately 10% of end-stage renal disease. In this disease, there is an extensive capillary network in the cyst wall of kidneys, vascular malformations, upregulation of the potent angiogenic factor, vascular endothelial growth factor (VEGF), in cyst cells and its receptor, VEGFR-2, in endothelial cells, and co-expression of matrix metalloproteinase (MMP)-2 and the integrin, $\alpha_v\beta_3$ in blood vessels [1•]. In contrast, impaired angiogenesis may play a pivotal role in causing age-related nephropathy. Decreased angiogenesis is associated with the progression of the remnant kidney model and can be reversed by treatment with VEGF, which reduces fibrosis and stabilizes renal function [2•,3•]. VEGF also enhances glomerular capillary repair in rats with severe glomerular injury in glomerulonephritis [4].

Angiogenesis may contribute to the pathogenesis of complications of hypertension. Elevated plasma levels of VEGF and its soluble receptor, Flt-1, are present in patients with uncomplicated hypertension and levels are reduced by treatment of the hypertension [5]. Endothelial cells in the plexiform lesions of patients with severe pulmonary hypertension which proliferate and occlude the arteries overexpress VEGF as well as its receptor, VEGFR-2, and inducers, hypoxia inducible factor-1 α and 1 β [6•].

The MMPs are a family of enzymes that play a central role in extracellular matrix turnover during angiogenesis. There are currently 25 known MMPs, which differ in their substrate specificity but share a number of common structural and functional similarities. The regulation of MMP activity occurs at various levels including synthesis, secretion, activation and inhibition. MMPs involved in angiogenesis include MMP-1, MMP-2, MMP-9, MMP-12, MMP-19, MMP-26 and the membrane type MMPs (see Table 1). This review highlights some recent exciting findings on the role of MMPs in angiogenesis. For more comprehensive reviews on MMPs and angiogenesis see [7•,8••,9,10••].

Table 1. Human matrix metalloproteinases implicated in angiogenesis

MMP	Common name	Possible mode of action
MMP-1	Collagenase 1	Degrades interstitial collagen
MMP-2	Gelatinase A	Degrades vascular basement membrane collagens. Degrades interstitial collagen Cleaves plasminogen to produce angiostatin (inhibitory)
MMP-9	Gelatinase B	Degrades vascular basement membrane collagens. Cleaves plasminogen to produce angiostatin (inhibitory)
MMP-12	Metalloelastase	Cleaves u-PAR receptor (inhibitory) Cleaves plasminogen to produce angiostatin (inhibitory)
MMP-14	MT1-MMP	Activates latent MMP-2. Degrades fibrin, type I collagen
MMP-19		Strongly expressed in blood vessels
MMP-26	Matrilysin 2	Degrades fibrin

MMP, matrix metalloproteinase; MT1, membrane type 1; u-PAR, urokinase-plasminogen activator.

Matrix metalloproteinases involved in angiogenesis

The importance of membrane type 1 (MT1)-MMP during angiogenesis is highlighted by the severe defects in skeletal development and angiogenesis leading to growth retardation and early death in MT1-MMP-deficient mice [11]. As well as activating MMP-2 (see below), MT1-MMP directly degrades numerous matrix components, including type I collagen and fibrin, and may play a key direct role during angiogenesis, possibly by activating the extracellular signal-regulated protein kinase cascade [12]. MMP-26, or matrilysin 2, is expressed in cancer cells of epithelial origin and appears to be active during fibrinolysis, indicating that this enzyme, like MT1-MMP, may participate in angiogenesis [13*]. MMP-19 is strongly expressed in smooth muscle cells and blood vessels. Progression towards an invasive phenotype and neoplastic dedifferentiation, however, leads to the disappearance of MMP-19 and a concomitant rise in the levels of MMP-2, suggesting that this enzyme may not be crucial for tumour angiogenesis [14]. MMP-12, or metalloelastase, appears to inhibit angiogenesis, by cleaving the cellular receptor for urokinase-plasminogen activator, which renders the receptor non-functional and reduces vascular structures in a fibrin matrix [15*].

The gelatinases, MMP-2 and MMP-9, which degrade collagens present in the vascular basement membrane and the interstitium [16], appear to be the most important MMPs during angiogenesis. Knockout mouse models clearly demonstrate that the gelatinases play a vital role during tumour angiogenesis [17,18]. Their role during physiological angiogenesis is not as clear. Although the MMP-2 knockout mouse exhibits no phenotype when unchallenged, MMP-2 is required for an activity-induced angiogenesis model, induced by electrical stimulation of rat skeletal muscle [19*].

Matrix metalloproteinase-2 activation

MMP-2, the most abundant MMP, is constitutively secreted as a latent enzyme by most cells, including endothelial cells. Activation of MMP-2 represents a critical level of regulation. Unlike other MMPs, activation of MMP-2 occurs on the cell membrane via the transmembrane membrane type MMPs, MT1, MT2, MT3 and MT5-MMP, of which MT1-MMP is the most abundant. Tissue inhibitor of metalloproteinase (TIMP)-2 promotes activation by linking MT1-MMP to the hemopexin domain of MMP-2 and orientating the latter to be partially cleaved by a nearby free MT1-MMP molecule [20]. TIMP-4 can also bind to the same hemopexin moiety of MMP-2 but does not enhance MMP-2 activation [21]. In contrast to MT1-MMP, MT2-MMP does not require TIMP-2 to activate MMP-2 [22*]. The tight junction proteins, claudins, can mediate the full activation of latent MMP-2 by MT1-MMP, via a process which is independent of TIMP-2 [23**]. Interestingly, the endothelial-cell specific claudin-5 promotes the activation of pro-MMP-2, using any of the membrane type MMPs, including MT4-MMP which was not previously known to activate MMP-2.

Numerous physiological agents are now known to upregulate MT1-MMP and promote MMP-2 activation. Polymorphonuclear conditioned medium contains three enzymes, neutrophil elastase, cathepsin and proteinase-3, which activate MMP-2 via MT1-MMP [24]. Interstitial type I collagen matrix activates endothelial MMP-2 by upregulating MT1-MMP, a process which involves $\alpha_2\beta_1$ and may be mediated by Rac1, a member of Rho-related small GTPases [25,26]. Other soluble agents, including hydrogen peroxide, lipopolysaccharide, ulex europaeus 1 and hepatocyte growth factor also activate endothelial MMP-2 by utilizing MT1-MMP.

An alternative mechanism of MMP-2 activation occurs via the serine protease, activated protein C (APC), best known for its anticoagulant and anti-inflammatory activity [27]. Activation by APC does not require MT1-MMP and occurs in the absence of cells, indicating that it acts directly [28]. To date, APC is the most potent soluble agent able to directly and fully activate latent MMP-2, although its (patho)physiological relevance has not been tested. The procoagulant, thrombin, appears to activate MMP-2 by utilizing either MT1-MMP or APC [29*,30*].

Preventing excessive matrix degradation during angiogenesis

Uncontrolled proteolysis leads to impairment of endothelial cell adhesion and the disruption of the cell-matrix interactions that are required for cell migration. How is excessive matrix degradation by active MMPs prevented during angiogenesis? This may be achieved by strictly

controlling the inhibition of MMP activity via one of four endogenous MMP inhibitors, TIMPs. In this way, the TIMPs, regarded as inhibitors of angiogenesis, may assist in promoting invasion. Such an action, in combination with their growth promoting and anti-apoptotic activity, may, at least partly, explain why increased TIMP-1 levels contribute to certain malignancies [31].

Excessive matrix proteolysis may also be prevented by spatially controlling MMP activity, for example, by restricting enzyme activity to the pericellular region. To serve this purpose, the membrane-bound MT1-MMP concentrates at discrete membrane sites on the migrating front of endothelial cells [32]. Interestingly, MT1-MMP activity can be further controlled by rapid internalization via dynamin-dependent endocytosis in clathrin-coated vesicles [33•]. The α_2 chain domain of $\alpha_2\beta_1$ integrin, which is present on endothelial cells, can bind and anchor MMP-1 to the cell surface during cell invasion [34••]. A number of recent studies provide strong evidence that MMP-2 activity is also restricted to the membrane microdomains. Collaboration between MT1-MMP and the integrin, $\alpha_v\beta_3$, which binds MMP-2, promotes efficient activation and transient docking of active MMP-2 at discrete regions of cells [35•]. Moreover, whereas MT1-MMP alone produces partially active MMP-2, the co-expression of MT1-MMP and $\alpha_v\beta_3$ in MCF-7 breast carcinoma cells promotes full maturation of the enzyme [35•]. Puyraimond *et al.* [36•] found that MMP-2 and $\alpha_v\beta_3$, but not MMP-9 or TIMP-1, are colocalized to microdomains on the endothelial cell membrane, known as caveolae. Activation of MMP-2 by concanavalin A coincides with the appearance and localization of MT1-MMP and TIMP-2 at the same membrane regions [36•]. Caveolae may serve to cluster the necessary components to activate MMP-2 and limit matrix degradation to within finite surrounds of the cell, providing an efficient means to restrict proteolysis of the matrix.

Some of the cryptic sites derived from physiological proteins may inhibit angiogenesis by interfering with integrin-mediated endothelial cell invasion. The anti-angiogenic action of angiostatin, a fragment generated by MMP cleavage of plasminogen, appears to be mediated through $\alpha_v\beta_3$, [37•]. In addition, the potent angiogenic inhibitory activity of the Tum-5 domain of tumstatin, a fragment of type IV collagen, works via $\alpha_v\beta_3$ [38]. Overall, these findings raise the possibility that $\alpha_v\beta_3$ may provide finely tuned control of angiogenesis by functioning both as a positive and negative regulator.

Targeting matrix metalloproteinases in angiogenic disorders

The role of thrombospondins as naturally occurring angiogenesis inhibitors has been confirmed in transgenic mice. Thrombospondin-1 overproducing mice suppress spontaneous mammary tumour growth, possibly by

inhibiting the activation of MMP-9 [39•]. Thrombospondin-2 null mice display improved wound healing which is attributed to increased angiogenesis and a coinciding increase in the extracellular distribution of MMP-2 [40]. Other naturally occurring angiogenic inhibitors may act by regulating MMPs/TIMPs. Quercetin, a bioflavonoid present in fruits and vegetables, which has a chemoprotective role in cancer, inhibits TIMP-1 gene transcription and plasma protein levels [41]. Interestingly, a major component of green tea, epigallocatechin gallate, a potent inhibitor of angiogenesis [42], inhibits MMP-2 activation at concentrations (10–50 $\mu\text{g/ml}$) which are physiologically relevant to avid tea drinkers [43].

The generic MMP inhibitor, BB-94, prevents interleukin-10-induced angiogenesis in mice, as indicated by a decrease in blood vessel density and blood perfusion [44]. The results from clinical trials using generic MMP inhibitors in angiogenic disorders, however, have been disappointing [45]. There are a number of reasons for the failure of these drugs, but the use of more specific inhibitors that target only MMPs involved in angiogenesis are likely to improve outcome [30•]. Recent attention has been directed to the gelatinases. A new class of MMP inhibitors, the pyrimidine-2,4,6-triones, appear to be relatively specific for the gelatinases. A small molecule inhibitor, SB-3CT, selectively inhibits gelatinases by slowly binding and using a novel mechanism-based inhibition [46]. This inhibitor directly binds to the zinc ion that reconstructs the active site of the enzyme to the conformation of the latent form. MMI-166, another selective inhibitor of MMP-2 and MMP-9, limits both cancer spread and angiogenesis in a hamster pancreatic cancer model [47]. Whether these drugs will be therapeutically effective in angiogenic disorders is yet to be determined. Preventing the activation of gelatinase A is an alternative approach to blocking the active site of the enzyme and may be achieved by inhibiting MT1-MMP or APC [30•].

It is unclear whether targeting angiogenesis in kidney diseases or hypertension will be beneficial. Interestingly, in the ischaemic limb of spontaneously hypertensive rats, an angiotensin-converting enzyme inhibitor, perindopril, reverses the reduction in angiogenesis, suggesting that the drug may benefit patients with essential hypertension presenting with lower limb vascular insufficiency [48•].

Conclusion

The role of MMPs, particularly MMP-2 and MT1-MMP, during angiogenesis is well established, however this role appears more complex than originally envisaged. In addition to their ability to degrade the matrix, MMPs produce protein fragments which impede this action.

Inhibitors of MMP activity may actually promote cell invasion by preventing uncontrolled matrix degradation. Docking of either MMPs or angiogenic inhibitors to specific integrin receptors can enhance their activity. These regulatory pathways permit fine control over cell invasion during angiogenesis. In addition, they provide new strategies for targeting abnormal angiogenesis, through precise control of MMP activity.

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