Biochimica et Biophysica Acta 1843 (2014) 603–617

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbamcr

Review

Nitric oxide-matrix metaloproteinase-9 interactions: Biological and pharmacological significance
NO and MMP-9 interactions

Shane O'Sullivan [a], Carlos Medina [a,*], Mark Ledwidge [b], Marek W. Radomski [a], John F. Gilmer [a]

[a] School of Pharmacy and Pharmaceutical Sciences, Trinity College Dublin, Ireland
[b] School of Medicine and Medical Science, University College Dublin, Ireland

ARTICLE INFO

Article history:
Received 2 September 2013
Received in revised form 2 December 2013
Accepted 5 December 2013
Available online 12 December 2013

Keywords:
Matrix metalloproteinase-9
MMP-9
Nitric oxide
Expression
Activation
Regulation

ABSTRACT

Nitric oxide (NO) and matrix metalloproteinase 9 (MMP-9) levels are found to increase in inflammation states and in cancer, and their levels may be reciprocally modulated. Understanding interactions between NO and MMP-9 is of biological and pharmacological relevance and may prove crucial in designing new therapeutics. The reciprocal interaction between NO and MMP-9 have been studied for nearly twenty years but to our knowledge, are yet to be the subject of a review. This review provides a summary of published data regarding the complex and sometimes contradictory effects of NO on MMP-9. We also analyse molecular mechanisms modulating and mediating NO-MMP-9 interactions. Finally, a potential therapeutic relevance of these interactions is presented.

1. Introduction

1.1. Matrix metalloproteinases

Matrix metalloproteinases (MMPs) are a group of structurally similar endopeptidases with a zinc ion in the active site. All are capable of digesting components of the extracellular matrix including collagens, laminins, fibronectin, elastin, and proteoglycans. MMPs play a key role in controlling homeostasis of all extracellular matrix (ECM) proteins. The MMPs regulate cell function, growth and division, host defences, ECM synthesis, morphogenesis, wound healing, tissue repair, skeletal formation, apoptosis, as well as cleavage of transmembrane proteins and bioactive molecules. Dysregulation of the MMPs has been implicated in tumour angiogenesis, invasion and metastasis, inflammatory bowel disease, arthritis, atherosclerosis, respiratory and heart disease and may also play other diverse pathological roles [1–6].

1.1.1. Matrix metalloproteinase-9 and cardiovascular disease

Of MMPs, MMP-9 can be upregulated and it has been implicated in a variety of pathological conditions. A selective inhibition of MMP-9 may have a significant therapeutic relevance for the treatment of various inflammatory diseases. Cardiovascular (CV) disease, diabetes and cancer are responsible for the majority of human deaths in the developed world and have all been associated with MMP-9 abnormalities. For example, changes in the CV extracellular matrix (ECM) are regulated by the gelatinases and their tissue inhibitors and, as key components of CV remodelling, are associated with inflammation and reactive, rather than reparative, fibrosis [7,8]. MMP-2 and MMP-9 knockout models are associated with reduced aortic elastin degradation [9] and protection from pressure overload myocardial hypertrophy, fibrosis and dysfunction [10]. Post-infarction models and models of left ventricular arrythmogenesis have shown that MMP-9 gene promoters are temporally activated specifically in the region of myocardial injury [11,12]. The gene promoter region of MMP-9 includes a proximal activator protein-1 (AP-1) site which mediates an enhanced transcriptional response to a wide variety of cytokine and cellular stimuli [13]. In the clinic, independent associations between myocardial remodelling post-MI, left ventricular dysfunction and heart failure, have been identified with markers of inflammation, fibrosis and MMP-9 [8,14–17].

1.1.2. Matrix metalloproteinase-9 and diabetes

Microvascular and macrovascular complications of diabetes are associated with MMP-9 dysregulation. In an animal model of diabetic retinopathy, increased MMP-9 activity was observed in retinal microvessels and MMP-9 knockout was protective [18]. In patients, increased urinary excretion of MMP-9 supports a role for MMP-9 dysregulation in diabetic renal dysfunction [19] and aortic and coronary arteries of diabetic patients taken at autopsy had higher expression of MMP-9 compared

* Corresponding author at: School of Pharmacy and Pharmaceutical Sciences, Trinity College Dublin, Dublin 2, Ireland. Tel.: +353 1 8962824.
E-mail address: carlos.medina@tcd.ie (C. Medina).

0167-4889/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.bbamcr.2013.12.006

to non-diabetics and were correlated with HbA1c as well as apoptosis [20]. Elevated MMP-9 has also been associated with arterial stiffness in patients with diabetes [21]. Furthermore, human genetic polymorphisms associated with MMP-9 elevation support a role for this enzyme in the pathophysiology of vascular disease. The 1562C > T single neucleotide polymorphism (SNP), which affects the promoter region of MMP-9 gene and increases circulating levels of MMP-9, is significantly associated with vascular disease in type 2 diabetes mellitus [22]. In age and sex matched controls, patients with type 2 diabetes, without and with microangiopathy, T allele frequencies were 11.9%, 13.1% and 24.4% respectively ($p < 0.05$).

1.1.3. Matrix metalloproteinase-9 and cancer

Matrix metalloproteinases (MMPs) play a central role in cancer cell intravasation and extravasation and their plasma levels are known biomarkers of breast, ovarian, colorectal, renal, pancreas, bladder and lung cancers [23]. MMP-9, in particular, regulates vascular endothelial growth factors, which, in turn, promote tumour growth and angiogenesis [24]. MMP-9 also modulates tumour-associated inflammation via cytokines and their receptors [25] and is involved in endothelial–mesenchymal-transition (EMT) whereby cells acquire migratory characteristics [26]. While, numerous preclinical studies demonstrate the ability of MMP inhibitors to delay primary tumour growth and block metastasis [27], MMP inhibition in the clinic has been limited by toxicity, including dose-limiting musculoskeletal pain and inflammation [28], while recent research on the development of MMP inhibitors has been focused on selective inhibition of MMPs [29].

1.1.4. Matrix metalloproteinase-9 and other diseases

MMP-9 abnormalities have been associated with disease progression in many other key organs. In the liver, MMP-9 has been associated with the fibrotic response to hepatitis C [30] and in models of fulminant liver failure where MMP-9 expression is increased, inhibition of MMP-9 was associated with improvement outcome when used early in the natural history of the disease [31]. In patients with kidney disease, interstitial fibrosis correlated with MMP-9 expression in the atrophic tubular nuclei [32] and elevated MMP-9 is also associated with the vascular complications of chronic kidney disease associated with diabetes [33]. In children with aggressive chronic renal dysfunction, focal segmental glomeruloscloerosis is associated with elevated MMP-9, which may represent an early diagnostic biomarker as well as a therapeutic target [21]. In the gastrointestinal tract, elevated expression of MMP-9 is a feature of inflammatory bowel diseases such as Crohn's disease [34–36] and MMP-9 expressed in epithelial colonic tissue mediates inflammation in colitis with simultaneous increase in proinflammatory mediators [37].

The above paragraphs highlight the need for an MMP-9 inhibitor; however, to date, clinical trials of MMP inhibitors have been largely unsuccessful. Misguided outcome expectations combined with poor fundamental understanding of the complex role of MMPs in cancer and inflammation are seen as the main contributors to these failures. Several excellent reviews have examined the outcomes and postulate that a greater understanding of the role of MMPs in a given disease setting may yet offer hope for a clinically relevant MMP inhibitor in the future [1,38,39]. Improved selectivity for MMP-9 over constitutive MMPs would certainly be of benefit [40] and also an ability to target the dysregulation of the enzyme that leads to its pathophysiological role. Understanding the interactions of NO and MMP-9 may offer insights into novel mechanisms to inhibit the enzyme in disease states.

1.1.5. Structure and regulation of MMP-9

MMP-9 and MMP-2 are classified as gelatinases, owing to their ability to process synthetic gelatine. This designation may be considered a little arbitrary as they can digest a variety of the matrix proteins and have ability to cleave a growing list of bioactive molecules including transmembrane proteins [41]. Structurally, MMP-9 is composed of several domains, including the pre, pro, and catalytic domains which connect to the C-terminal hemopexin-like domain via a hinge or linker region [42]. The hemopexin domain not only acts as a stubstrate binding domain [43] but can also interact with integrins on the cell surface to anchor MMP-9 and has been shown to trigger anti-apoptotic signalling pathways in B-cell chronic lymphocytic leukaemia [44]. All MMPs possess a catalytic domain of 165–170 amino acids which is essential for proteolysis [42,45]. The catalytic domain varies slightly in groove depth and the accessibility and depth of six side pockets that flank the defining zinc ion which is coordinated at the centre of the cleft by three histidine residues [46]. The S1′ pocket has the greatest variation amongst the MMPs in both depth and amino acid composition. These features have made it an attractive target for small molecule inhibitor development. The gelatinases also have three fibronectin-like inserts in the catalytic domain and these differences account, in part for their differing substrate specificities [47,48].

MMP-9 is principally regulated at the level of transcription by various inflammatory factors but also through post-transcriptional events; secretion of the protein, activation, endogenous inhibitors and cell surface interactions [3]. De novo synthesis of large amounts MMP-9 can be rapidly induced by cytokines, growth factors or changes in cell–cell or cell–ECM interactions [3,49]. Like many other proteases, MMP-9 is secreted in the "pro" form as an inactive zymogen. Latency is conferred by the prodomain which masks the active-site cleft and prevents hydration of the catalytic zinc ion. An interaction between a sulfydryl group on a conserved cysteine residue in the prodomain and the zinc ion constitutes this "cysteine switch" [50–52]. Activation of the enzyme, therefore, requires either proteolytic removal of the propeptide or disruption of the Zn^{2+}-cysteine bond. MMP-9 is most commonly activated by other proteases such as serine proteases, trypsin, plasmin, chymase and other MMPs [38,48] but it can also be activated by conformational perturbants such as heat, substrate binding, heavy metals and organomercury compounds such as aminophenylmercuric acetate, as well as oxidants and alkylating agents [52–56]. It has therefore been agreed that the pro-MMP-9 has to be secreted to the ECM in order to get activated; however other mechanisms can be also involved. Indeed, it has been proposed that pro-MMP-9 activation could take place at the plasma membrane. The interactions of the MT1-MMP/MMP-2 axis with pro-MMP-9 on the plasma membrane induced a full activation of MMP-9 in vitro, and under the same conditions, MMP-3 was also able to activate MMP-9 [57]. In addition, thrombin has been shown to induce pro-MMP-9 activation and association with β1-integrin in a human osteosarcoma cell line through a PI 3-kinase-dependent pathway, a key step in thrombin-induced tumour invasion [58].

1.1.6. Endogenous inhibitors of MMPs

A large number of endogenous inhibitors of MMPs exist, which serve to regulate activity and prevent uncontrolled proteolysis (Table 1). Of these inhibitors, the tissue inhibitors of metalloproteinase (TIMPs) are the most specific for the MMPs. The TIMPs are a family of secreted proteins which can bind all the MMPs in a 1:1 stoichiometry with varying efficiencies; TIMP-1 binds to MMP-9 with high affinity whereas TIMP-2 is a more effective inhibitor of MMP-2 [59,60]. TIMPs (21 to 29 kDa) have an N- and C-terminal domain of ≈125 and 65 amino acids, respectively, with each containing three conserved disulfide bonds. The N-terminal domain folds as a separate unit and is capable of inhibiting MMPs. The main inhibitor of MMPs in tissue fluids is α2-macrogobulin [61]. Limited proteolysis of a bait region of the plasma protein by an MMP induces a conformational change in the macroglobulin which then encloses the enzyme [62]. It is a general proteinase inhibitor but may only bind to activated MMPs which are then irreversible cleared by endocytosis following binding to a scavenger receptor [63].

Other proteins with MMP inhibiting properties, albeit less potent than the TIMPs, include the C-terminal fragment of the procollagen C-terminal proteinase enhancer protein (PCPE) [64]. The noncollagenous NC1

Table 1
Endogenous inhibitors of MMP-9.

Inhibitor	Method of inhibition	Targets	Reference
TIMP-1	Catalytic activity	Most MMPs, ADAM-10, ADAMTS-4	[1]
TIMP-2	Catalytic activity	Most MMPs, ADAMTS-4	[1]
TIMP-3	Catalytic activity	Most MMPs, ADAM-10, -12, -17, ADAMTS-4, -5	[1]
TIMP-4	Catalytic activity	Most MMPs	[1]
α2-macroglobulin	Catalytic activity, clearance	Most proteases	[61]
C-terminal of PCPE	Catalytic activity		[64]
Tissue factor pathway inhibitor-2	Catalytic activity, activation	Serine proteases, other MMPs	[66]
NC1 domain of type IV collagen	Catalytic activity		[65]
Endostatin	Catalytic activity, activation	MT1-MMP	[67]
TSP-1	Inhibition of activation		[1]
TSP-2	Facilitates clearance		[1]
RECK proteins	Catalytic activity	MT1-MMP	[72]

domain of type IV collagen also shares structural similarities with TIMPs and has been shown to have MMP inhibiting properties [65]. A serine protease inhibitor named tissue factor pathway inhibitor-2 [66], and a collagen XVIII derived proteolytic fragment named endostatin can block the activation of MMP-2, MMP-9 and MMP-13 as well as the catalytic activity of MMP-2 and MT1-MMP [67,68]. Thrombospodin-1 (TSP-1) is an extracellular 450 kDa glycoprotein that directly binds pro-MMP-2 and -9 and inhibits their activation [69,70]. Thrombospondin-2 (TSP-2) is thought to bind MMP-2 and MMP-9 and facilitate a low density lipoprotein receptor-related protein (LRP)-mediated endocytosis and clearance in a manner similar to α2-macroglobulin [69,71]. Reversion-inducing cysteine-rich protein with Kazal motifs (RECK) protein is a 110-kDa glycoprotein expressed in many normal tissues and is the only known membrane bound MMP inhibitor [72,73]. Finally, fatty acids have been shown to inhibit gelatinase activity but only weakly other MMPs. Activity was dependent on carbon chain length and presence of unsaturation, and inhibition involved binding to the fibronectin type II module of these gelatinases [74]. Other excellent reviews discuss endogenous inhibitors of MMPs in more detail [5,75].

1.2. Nitric oxide

NO is a ubiquitous gaseous and diatomic mediator, transducer and modulator from the conversion of L-arginine to L-citrulline by nitric oxide synthase (NOS). Three NOS isoforms have been discovered and are classified as neuronal NOS (nNOS, NOS1), endothelial NOS (eNOS, NOS3), which are both constitutively expressed calcium-dependent enzymes producing physiological levels of NO, and inducible NOS (iNOS, NOS2) which produces high levels of NO in a sustained manner. This inducible isoform is transcriptionally upregulated in inflammation in response to bacterial lipopolysaccharide or endotoxin, pro-inflammatory cytokines and other immune complexes, some of which also lead to the upregulation of MMP-9. The diverse roles of NO include smooth muscle relaxation, inhibition of platelet aggregation, neurotransmission [76], and immune and inflammatory modulation [77,78]. The NO involvement in diverse physiological processes is mostly mediated though its activation of the heme iron in the soluble guanylate cyclase (sGC). NO can also react directly with signalling proteins and when generated in high amounts such as during inflammation, it can react with superoxide anion to produce peroxynitrite, a much stronger oxidant, with significant pathophysiological/inflammatory contributions. Although NO has a half-life in the range of seconds, properties such as charge neutrality, a small molecular radius and hydrophobicity, allow for free diffusion through cell membranes. As NO reacts with oxygen and with oxygen-derived radicals as well as metal centres in proteins, such properties make it a key signal transducer [79].

The net effect of NO in a given setting depends on its environment and concentration. The iNOS generates the highest local flux. Following transcriptional upregulation of the enzyme, there is a delay of 6–8 h before NO production begins but this production is then sustained for hours to days and is 1000 fold greater than those produced by the constitutive NOS isoforms [80]. The presence of molecular oxygen and its derived free radicals in the local environment affect NO concentration because these react at diffusion limited rates. Interestingly, vascular relaxation and vasodilator tone caused by NO are inhibited by superoxide and inhibition of superoxide production may enhance the effects of NO [81]. Therefore, scavengers of superoxide such as superoxide dismutase and oxyhaemoglobin influence NO bioavailability.

The observed effects of NO, especially those that lead to cytotoxicity have been also attributed to the generation of peroxynitrite from NO and superoxide [82–87]. In addition, NO not only can react directly with sulfhydryls [88,89], metal centres including iron/sulfur and Zn^{2+}-thiolate groups [82,90,91] but also can react via metal independent mechanisms through generation of hydroxyl or carboxyl radicals formed from different decomposition reactions [92–94]. Some excellent reviews deal comprehensively with the chemistry and biochemistry of NO [79,95,96].

2. Effects of NO on activation of pro-MMP-9

Inflammation leads to concurrent up regulation of NO and MMP-9 [97–99], however, the biological outcome of the crosstalk between these two enzymes is not clear (see Table 2). For a detailed review of pro-MMP-9 activation, see Fridman et al. [100]. It is also worth noting the difficulties in measuring MMP-9 activity. While relative abundance or concentration of the enzyme can be measured using techniques such as western blot or ELISA, this data does not reveal the activity of the enzyme. Gelatin zymography is a commonly used technique which can separate the pro and active forms of the enzyme but a recent review has highlighted its limitations in providing true activity information [101]. Incomplete refolding of the enzyme following electrophoresis and dissociation of endogenous inhibitors mean that activity data can only be obtained from gelatin zymography when it is combined with a complimentary substrate degradation assay. Let's first review evidence for NO-mediated activation of MMP-9.

2.1. NO activates pro-MMP-9

NO could disrupt the Zn-thiolate bond in pro-MMP-9 leading to its activation. For example, there is also evidence showing that NO activates TNF-α converting enzyme, another metalloproteinase [102]. Furthermore, peroxynitrite has been shown to activate other MMPs [83,103–105]; the free radical can modulate the protein activity through S-nitrosylation of cysteine thiols [106–109], and it may also release Zn^{2+} from other Zn-thiolate centres [110,111].

The effect of NO on MMP-9 activation in rat retinal neurons was investigated by comparing wild-type with nNOS null animals. Increased MMP-9 activation was observed in the wild-type rats which was attributed to S-nitrosylation of the pro-enzyme [112]. Co-localization of MMP-9 activity and nNOS was also observed in the cortex. The study went on to demonstrate that transfected recombinant MMP-9

Table 2
Reported effects of NO on MMP-9.

Cell line/strain	Stimulating factor	Incubation time	NO conc.	NO donor/iNOS inhibitor	Observed effect	Reference
$nNOS^{-/-}$ and wild type rats	Focal cereberal ischemia and reperfusion		NA	$nNOS^{-/-}$ or 3-bromo-7-nitroindazole	↓MMP-9 compared to controls	[55]
Purified MMP-9		0–25 h	NA	S-nitrosocystein	↑activation compared to controls	[55]
$nNOS^{-/-}$ and wild type rats	intravitreal injections of NMDA and glycine	0–12 h	NA	$nNOS^{-/-}$ vs wild type rats	↓MMP-9 compared to controls	[112]
Rat Brain Astrocyte cells RBA1.	Endothelin-1	16 h	≈50% reduction in NO, relative to ET-1 induced levels with L-NAME 100nM	L-NAME (1, 10, 100nM) and iNOS siRNA	Dose dependent reduction (up to 10 fold) in MMP 9 activity	[113]
ANA-1 macrophage	INF-γ, LPS, L-arginine	4 h	50nM	NO/sper	↑ at ≤50nM and ↓ at higher concs	[114]
Lewis and Brown–Norway rats	Allogenic (Brown Norway to Lewis) heterotopic cardiac transplantation	24 h		1400 W (N-(3-(Aminomethyl) benzyl) acetamidine (selective iNOS inhibitor))	↓ MMP-9 activity	[118]
HUVEC, NCI-H157, squamous carcinoma; NCI-H125, adenosquamous; and NCI-H522, adenocarcinoma	AMPA	16 h		Aminoguainidine 100 μM	↑ activity following incubation with aminoguanidine.	[124]
Purified r MMP-9	AMPA	6 h	5 or 10 nmol/min (for 0.5 and 1 μM spermin-NONOate). 30 μM NO from 100 μM SIN-1	spermine-NONOate (0.5 and 1 μM) or SIN-1 (20 μM, 200 μM, and 2 mM)	Dose dependent inhibition following incubation with the NO donors.	[124]
Purified rMMP-9		0–2 h		GSNO, SPER- NO, DETA NONOate, DEA-NONOate,SNOC	DETA NONOate or Sper-NO—↓activity at high concentration. SNOC—↑ activity	[125]
Rat glomerular mesangial cells	IL-1β	36 h		SNAP (up to 1mMol/L)	Conc dependent ↓ inhibition (up to 90%)	[175]
MDA-MB-231, MCF-7	TPA	24 h	?	DETA-NO, SNAP or Spermine-NO (500 μM)	Conc dependent inhibition. (max at 500 μM)	[177]
Rat primary astrocytes	LPS	48 h	Donors of 100 μM (max inhibition)	SNAP or SNP	↓ MMP 9 expression	[176]
NHBE, HBE1, CFT1, A549	IL-1β, INF-γ, TNF-α	24 h		spermine NONOate, DETA NONOate, SIN-1, SNAP, GSNO	Dose dependent ↓ with SNAP and GSNO.	[178]
RA-SMCs of Sprague Dawley rats	IL-1β (2 ng/ml)	24 h	2 to sixfold increase in NO.	DETA NONOate (0.1–500 μM)	Dose dependent ↓in MMP-9 activity and expression	[179]
NIH/3T3 cells	Thapsigargin-induced store-operated Ca^{2+} entry			SNAP (200 μM)	↓in MMP-9 activity	[180]
VSM from male Wistar rats	IL-1β (5 ng/ml)	24 h		DETA NONOate (500 μM)	↓in MMP-9 activity and expression	[181]
Rat glomerular mesangial cells	IL-1β (2 nmol)	48 h		L-NMMA (0.3–5 mM)	Conc dependent ↑ in expression and activity.	[175]
Rat primary astrocytes	LPS	48 h	7 μM of nitrite	L-NAME (100 μM)	↑ MMP 9 expression	[176]
Rat aortic SMC	IL-1β	48 h	approximately 50 ng NO_x/mg protein	L-NMMA (50nM)	5 fold ↑ in pro MMP-9 mRNA	[182]
Rat aortic smooth muscle cells from Sprague Dawley rats	IL-1β (2 ng/ml)	48 h	↓ to 8.2 NO_x (ng/mg of protein)	Aminoguanidine (0–5 mM)	Conc dependent. Up to 155%↑ in mRNA	[183]
Rat infrarenal aorta tissue	IL-1β	72 h	Approximately 1250 ng/mg protein (at max increase)	L-NMMA	↑ at ≤0.5 mM and ↓ at higher concs	[184]
NHBE, HBE1	Linear scratch in the cells	24 h	Approximately 14.1–389.1 μM NO_x	DETA NONOate (10–500 μM)	↑ expression at ≤10 μM and ↓ at higher concs	[123]
C57BL/6 $iNOS^{-/-}$. Murine neutrophils and macrophages	Hepatic I/R injury. IL-6, or INF- γ	24 h		$iNOS^{-/-}$, ONO-1714	iNOS inhibition ↓ MMP-9 activity.	[189]
Rat aortic vascular SMC (A7r5)	INF-γ, LPS, PMA	12 h		L-NAME (300 μM)	Inhibition to near control	[190]
WiDR		8 h		SNAP	↑ expression	[191]

undergoes S-nitrosylation, and thus activation, following incubation with the NO donor S-nitrosocysteine [55]. Another group working with rat brain astrocytes demonstrated an increase in tyrosine nitration of the MMP-9 enzyme by co-immunoprecipitation, corresponding to an increase in enzyme activity following iNOS induction. Inhibition of iNOS using siRNA or L-NAME significantly reduced nitrate accumulation and potential MMP-9 activity as measured by gelatin zymography [113]. A biphasic regulation of MMP-9 activity has been demonstrated in ANA-1 cells and the trend replicated in purified pro-MMP-9 enzyme where lower concentrations of Sper/NO result in activation of the enzyme and higher concentrations of NO cause inhibition [114].

2.2. NO indirectly activates MMP-9

It is argued that these experiments do not provide direct evidence for NO S-nitrosylation of the prodomain or direct activation of the cysteine switch in vivo. During periods of prolonged inflammation, where large amounts of NO are produced by iNOS, there is a corresponding increase in oxidative species. The reaction of NO with superoxide anion to yield peroxynitrite is key in mediating many of the pro-oxidant and toxic effects of NO [115]. Peroxynitrite generation could be the mechanism through which NO may indirectly activate pro-MMP-9 as has been shown for other MMPs [83,116,117]. Inhibition of iNOS and superoxide generation resulted in an inhibition of potential MMP-9 activity as measured by zymography; however, no experiments were carried out to ascertain whether the observed activity was as a result of decreased protein synthesis or inhibition of protein activation [118]. A study on term placentas of type II diabetic patients showed that an increase in potential gelatinase B activity measured by zymography was associated with nitration of the enzyme by peroxynitrite [119]. Purified pro-MMP-9 was shown to be activated by peroxynitrite and to a much greater extent by $GSNO_2$, a product of the reaction of glutathione and peroxynitrite. As well as increased substrate digestion, evidence of S-glutatiolation of the pro-domain was shown using radiolabelling and MALDI-TOF MS [120]. A rat model of reperfusion injury showed that a peroxynitrite decomposition catalyst reduced MMP-9 activation as shown by gelatin and in situ zymography [121]. Although cell surface activation of MMP-9 is likely to be less frequent, another proposed mechanism of the indirect action of NO on MMP-9 enzyme activation is the upregulation of urokinase plasminogen activator (uPA), which has been shown to activate pro-MMP-9 [122]. While S-nitrosocysteine caused mild activation of recombinant pro-MMP-9, incubation of DETA NONOate with HBE1 or NHBE cell resulted in increased uPA mRNA and therefore increased pro-MMP-9 activation [123].

2.3. Nitric oxide-mediated inhibition of MMP-9

While the above studies provide evidence for NO activation of MMP-9, either directly or indirectly, there is substantial evidence for an inhibitory role of NO on MMP-9 activity. For example, endothelial and carcinoma co-cultures showed a marked increase in potential MMP-9 activity measured by gelatin zymography when incubated with the iNOS inhibitor aminoguanidine. To explain the result, purified MMP-9 enzyme was incubated with NO donor spermine-NONOate and the NO/superoxide donor SIN-1 which was expected to produce peroxynitrite. Both incubations resulted in a significant decrease in enzyme activity [124]. A very interesting study in this context, suggests that NO does not directly modulate pro MMP-9 activation. A range of NO donors; S-nitroso-glutathione (GSNO), spermine NONO-ate (SPERNO), DETA NONOate (DETA-NO), and DEA NONOate (DEA-NO) and S-nitrosocysteine (CSNO) were tested on purified pro-MMP-9 enzyme. Of these NO donors, only SNOC caused any increase in activity. At high concentrations, DETA-NO inhibited gelatinase activity measured using a fluorescent substrate. While the compounds produced different modifications to a synthetic pro domain, these alterations were deemed to be unrelated to enzyme activation. The NO donors were incubated with the active form of MMP-9 and again, DETA-NO was found to markedly inhibit enzyme activity which was unrelated to cysteine switch activation or other oxidative modifications to the enzyme [125] and presumably due to interactions at the active site.

While activation of pro-MMP-9 by NO seems plausible, it has not been conclusively proven in an in-vitro or in-vivo setting. Variation in observations may be accounted for by the use of different NO donors with differing release properties and NO flux and duration. The use of S-nitrosocysteine as a surrogate of endogenous NO has also been questioned [126]. The above studies show that direct activation of pro-MMP-9 by NO is possible. The effect on MMP-9 is concentration dependent with a trend of increased activity at low concentration and inhibition at higher concentrations. The biological relevance of this observation remains to be determined as the presence of other oxidants and known MMP-9 activators are likely to be more salient in-vivo. The actions of NO in regulation of MMP-9 distribution and expression are expected to provide a greater net contribution to MMP-9 activity.

3. Effect of NO on MMP-9 release and distribution

Following synthesis of pro-MMP-9 enzyme, activation is dependent on its release from the cell and availability of activating agents. Once activated, the effect that the enzyme will exert is dependent on its distribution at the cell surface, in the extracellular milieu or even within the cell. Its gelatinolytic activity is therefore affected by cell surface associations, internalisation or other protein interactions. As generalised proteolysis is seen as counterproductive for cell migration, interaction with receptors, adhesion sites and invasive protrusions may have developed to allow local effective concentrations of active MMP-9 and directed ECM degradation [124,127].

Following its release, surface associated MMP-9 has been identified in a variety of biological systems under both physiological and pathological conditions including neutrophils [128], endothelial cells [129–131], myocardium [98,132–134], keratinocytes [135], breast epithelial [129,136], breast cancer [137], pancreatic cancer [138], ovarian cancer [139], prostate cancer [140], fibrosarcoma [141,142], and mouse mammary carcinoma cells [143]. It has been proposed that the affinity of the gelatinases for collagen IV, specifically through the α2 (IV) chain may cause the ECM to act as a reservoir for the enzymes which become activated by inflammatory cells. Other interactions with CD44, RECK and LRP proteins have been shown to cause surface localisation, inhibition and internalisation respectively. These interactions have demonstrated an additional, complex layer of MMP-9 regulation which can direct the activity of the enzyme and are the subject of other reviews [100,144]. Here we will focus on interactions that NO is reported to influence.

Treatment of neonatal rats subjected to hyperoxia with L-NAME, an inhibitor of NOS, led to increased activity of MMP-2 and MMP-9 in lungs [97]. The latter effect could reflect the inhibitory effects of NO on the release of these gelatinases from leukocyte gelatinase granules [97,145], as well as from human platelets [146].

In a study investigating the effect of doxycycline on neutrophil degranulation and MMP-9 release, nitro-glycerine (GTN) caused a reduction in the MMP-9 activity in the cell supernatant, even though microscopy revealed that degranulation had occurred. Most of the MMP-9 activity was found to be associated with the cell pellet and so it was hypothesised that nitrate caused increased cell surface association of the enzyme [147].

Migrating trophoblasts have been shown to express MMP-9 in a manner regulated by NO [148]. The motile cells actively redistribute iNOS to the leading migrating edge of the cell. Interestingly, MMP-9 was found to be co-localised with iNOS at the lamellopodia and to be crucial for cell invasion. This group postulate that the co-localisation is either NO-mediated S-nitrosylation and activation of the pro-MMP-9 enzyme, or else a possible effect on the release or distribution of the

enzyme [149]. In either case, the directed generation of NO and thus MMP-9 activity establishes a further role of NO in the distribution of active MMP-9.

The activity of MMP-9 in colon cancer cell lines is inhibited by cGMP analogues as shown by immunoblotting and gelatin zymography. It was discovered that this inhibition is not caused by a decrease in mRNA levels but by a compartmental redistribution of the enzyme leading to a tenfold increase in intracellular MMP-9 shown by flow cytometry [150].

Caveolin-1 (Cav-1) is a scaffold protein believed to play a role in survival and invasion of certain cancer types. While its exact role is poorly understood, it seems to act as an oncogene in some cancers [151–153] while playing the role of a tumour suppressor in others [154–157]. In a model of hepatocellular carcinoma, overexpression of cav-1 resulted in an increased expression of MMP-9 [158]. Conversely, a breast cancer model shows that MMP-9 activity is reduced in cells expressing cav-1 while cell lysates showed no alteration in endogenous expression of the enzyme. It has been suggested that cav-1 mediates an alteration in the secretion of the gelatinase [159]. Interestingly, caveolin also plays an important role in regulation of NOS [160]. In this context, Philips and Birnby studied the interactions of NO with MMP-9 and cav-1 using an endothelial and lung carcinoma cell co-culture model studied the effects of NO on MMP-9 and cav-1. Treatment with an iNOS inhibitor resulted in strong co-localisation. This localisation is believed necessary for optimum activation of MMP-9 but is abolished in the presence of an NO donor [124].

Activation of pro-MMP-9 by other MMPs such as MMP-2, MMP-7 and MMP-13 is likely to be a cell surface event as these enzymes associate with the cell surface. One activation cascade described for MMP-9 involves the activation of plasmin from plasminogen following binding of the urokinase plasminogen activator (uPA) to the urokinase plasminogen activator receptor (uPAR) which is on the plasma membrane. Activated plasmin can activate pro-MMP-3 which can in turn activate pro-MMP-9 [161]. This cascade offers the cell an opportunity to control the distribution of activated MMP-9 and directed proteolysis. There is evidence that NO can increase expression of uPAR but inhibit the expression of uPA [123,162,163] and so the net effect on the distribution of active MMP-9 is not clear.

Localisation of MMP-9 has been demonstrated to represent another layer of regulation on its activity and NO is implicated in this regulation. Increasing concentration of NO will increase the internalisation or cell surface association of MMP-9 which may occur through interaction with CD44 or collagen IV. NO can also regulate the expression and activation of MMP-9 activating factors including other MMPs, cav-1 and uPA which will affect the distribution of the active enzyme.

4. Effect of NO on expression of MMP-9

The MMPs, with the exception of MMP-2, are inducible enzymes whose basal expression is low in most normal adult cells. De novo synthesis of large amounts of MMPs can be rapidly induced by cytokines, growth factors or changes in cell-cell or cell-ECM interactions [3,49]. Important inducers include tumour necrosis factor (TNF-α), interleukin (IL-1 α and β, 2, 8, 15, 17), interferon (IFN-α and γ), epidermal-growth factor (EGF), platelet-derived growth factor (PDGF), hepatocyte growth factor (HGF), basic fibroblast growth factor (bFGF), transforming growth factor (TGF-α and β), amphiregulin, CCL5, bacterial lipopolysaccharide (LPS) and phorbol esters (e.g. PMA) [48,164–166]. Physical interactions of certain cells with the ECM or other cells that have been shown to induce MMP expression include extracellular matrix metalloproteinase inducer (EMMPRIN or basigin or CD147) [167], various integrins [168], leukocyte function-associated antigen-1 (LFA-1) interaction with intercellular adhesion molecule-1 (ICAM-1) [169], very late antigen 4 (VLA-4), vascular cell adhesion molecule-1 (VCAM-1) [170], gp39 and CD40 interaction [171]. Mechanical stress and alterations in cell shape have also been reported to lead to the transcriptional upregulation of certain MMPs. The transcription of each MMP is independently controlled depending on the cell type, stimulating factors and therefore the signal transduction pathways that are activated, although several MMPs share common cis-acting elements in their promoter and are therefore co-expressed. Some of the main pathways implicated are those involving the MAP kinases which are composed of JNK 1/2, ERK 1/2, and p38. These kinases may lead to the induction or inhibition of protease synthesis depending on the cell type [172,173]. Many of these signalling pathways converge at Jun and Fos oncoprotein activation which heterodimerize to bind to an Activator Protein-1 (AP-1) binding site, causing MMP upregulation [38,75]. Variation in transcription may be accounted for by the other elements or the combination of factors binding to the MMP promoters. ETS oncoproteins bind to PEA3 sites [174], Nuclear Factor kappa B (NF-κB), SP-1, JAK/STAT, and Smad are some of the contributors to MMP transcriptional regulation [173].

Although the effects of NO on MMP-9 expression have been studied by a number of investigators there is no agreement if NO promotes or reduces the expression of MMP-9. The following chapters review this conundrum as well as molecular mechanisms that may contribute to the effects of NO.

4.1. NO inhibits MMP-9 expression

Several studies report an inhibitory effect of NO donors on MMP-9 mRNA compared with stimulated controls [175–181]. Consistent with these observations are reports that in similar cell culture models, NOS inhibitors, which reduce NO availability, increase MMP-9 expression [175,176,182,183]. The change in mRNA appears to be dependent on the concentration of the NOS inhibitor or NO donor used, however, a biphasic regulation has been demonstrated where the increase in MMP-9 expression following incubation with the NOS inhibitor L-NMMA peaked at 0.5 mM (approximately 1250 ng NO_x/mg protein). Further increase in concentration of the inhibitor resulted in a decrease in mRNA until it reached control levels at 5 mM (approximately 500 ng NO_x/mg protein) [184]. An indirect role of NO in MMP-9 expression is through its ability to inhibit platelet aggregation [185]. This inhibition will prevent platelet aggregate mediated increase in MMP-9 expression [186–188].

4.2. NO promotes MMP-9 expression

In several studies, incubation of cells with NOS inhibitors caused an inhibition of MMP-9 expression suggesting a promoter roll for NO [123,189–191]. In a rat model of atherosclerosis it was reported that MMP-9 was induced to a greater extent in $iNOS^{+/+}$ rather than $iNOS^{-/-}$ animals indicating that NO increases MMP-9 expression [192]. As discussed previously, the effects of NO donors on MMP-9 expression may also be concentration dependent, as seen with a biphasic response to DETA-NONOate [123]. In this study, low levels of the NO donor (10 μM) resulted in increased gene expression; however, higher concentrations (100–500 μM) had the opposite effect. The biphasic response may be attributed to peroxynitrite following reaction with superoxide. In an ischemic–reperfusion injury model, peroxynitrite was found to increase the expression of MMP-9, an effect that was inhibited by NOS inhibitor L-NAME [193,194]. A study on amyloid beta degradation in Alzheimer's disease found that NO increased MMP-9 expression both in vitro and in vivo [195]. Further evidence of the complex indirect role of NO on MMP-9 expression was shown in a similar model where Cav-1 inhibited MMP-9 activity. L-NAME and iNOS null mice showed that NO decreased Cav-1 expression and so increased MMP-9 activity [196,197].

4.3. The effect of NO on signal transduction pathways and nuclear factors that modulate MMP-9 transcription

MMP-9 expression is controlled by extracellular factors which trigger a network of signal transduction pathways resulting in transcriptional upregulation. The human MMP-9 gene lies on chromosome 20 and covers 13 exons spanning 7.7 kb [198]. Expression of the gene yields a 2.5 kb mRNA which is regulated by a 670 bp sequence within the promoter which contains binding sites for NF-κB, AP-1, PEA3, and SP-1 [198,199]. The complex transcriptional regulation of MMP-9 has been the subject of intense study [200–207]. NO may preferentially alter transcription factors that are sensitive to the cellular redox state including NF-κB, AP-1 and SP-1 [80] (Fig. 1).

4.3.1. NF-κB

NF-κB is a transcription factor known to upregulate the transcription of many pro-inflammatory mediators [208,209] and has been shown to be essential for MMP-9 upregulation [210–212]. The interaction between NO and NF-κB has been widely studied and previously reviewed [213,214], however the picture remains unclear. A significant complicating factor in the context of MMP-9 regulation is the NF-κB regulation of iNOS. Low concentrations of NO or presence of peroxynitrite will augment NF-κB activity whereas at high concentration, NO is likely to function in a negative feedback loop to reduce iNOS expression. Reductions in NF-κB activity following exposure to NO have been attributed to S-nitrosylation of a cysteine residue in the p50 subunit [215,216], inhibition of NF-κB DNA binding [217] or stabilization of IκB [218]. Increased activity has been observed at low concentration of NO [219] through stimulation of IKK-α which likely occurs following S-nitrosylation and activation of ras [220].

Regulation of the NF-κB pathway by NO is likely to be the same for MMP-9 as iNOS and will depend on NO concentration and presence of superoxide. The iNOS inhibitor aminoguanidine caused an upregulation of MMP-9 through increased IκB degradation and NF-κB binding [183]. S-nitrosothiols inhibited p50 nuclear translocation and NF-κB DNA binding, thus reducing TNF-α mediated MMP-9 expression [178]. Superoxide and peroxynitrite have an opposite role to NO and increase p65 nuclear translocation and NF-κB binding [210,221]. Reactive oxygen species (ROS) generated from NADPH oxidase also activated NF-κB resulting in an upregulation of MMP-9 [222]. The effects on MMP-9 expression are, however, cell specific and NF-κB has been reported to play no role in some cases [177,223].

4.3.2. AP-1

AP-1 consists of a mixture of dimeric basic region-leucine zipper proteins (bZIP) that belong to the Jun, Fos, Maf and ATF sub families. C-Jun is the most potent transcriptional activator whereas Fos proteins cannot homodimerise but form heterodimers with Jun proteins [224]. The AP-1 motif in the MMP-9 gene is considered by some to be the most important for its expression [201,211]. Indeed, a single mutation in the AP-1 binding site abolishes TNF-α or IL-1β induced MMP-9 expression [210,225]. NO can modulate AP-1 activity through modifications of a redox sensitive cysteine residue in c-Jun or c-Fos [226]. Oxidation or nitrosylation reduces DNA binding [227].

DETA-NO is reported to inhibit the MMP-9 transcriptional upregulation in response to TPA in breast cancer cells. This effect was attributed to inhibition of c-Jun using EMSA and TransAM assay [177]. NOS inhibitors increase AP-1 binding by approximately 200% compared with IL-1β stimulated cells [183]. Where NO caused the upregulation of MMP-9, AP-1 was shown to be critical by using AP-1 deletion mutants of MMP-9 luciferase promoter constructs [191]. Superoxide has been shown to increase AP-1 binding in MMP-9 upregulation [210].

4.3.3. cGMP/protein kinase G

Many of NO's diverse physiological actions are attributed to its ability to activate soluble guanylate cyclase (sGC) through binding of its heme group. Activation of sGC triggers formation of cyclic GMP, an important signalling molecule [80]. cGMP exerts its effects through

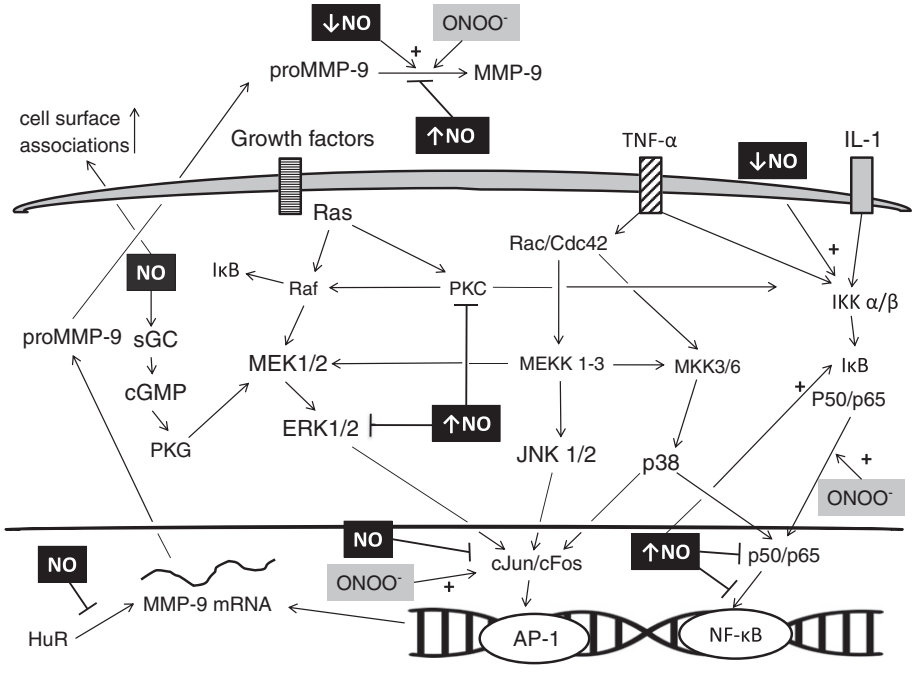

Fig. 1. Representation of some of the pathways involved in the transcriptional upregulation of MMP-9 and the possible impacts of NO and peroxynitrite ($ONOO^-$). ↑ indicates high concentration and ↓ indicates low concentration. + indicates a promoter role and − indicates an inhibitory role. The effect exerted by NO will depend on the concentration and presence of peroxynitrite. TNF-α, tumour necrosis factor-alpha; IL-1, interleukin-1 (alpha or beta); IκB, inhibitor of NF-κB; IKK (α or β), IκB (α or β) kinase; MEKK1-6, MEK1-6 kinase [mitogen-activated protein kinase kinase kinase (MAPKKK)-family]; MAPK, mitogen-activated protein kinase; MAPKAPK, MAPK-activated protein kinase; MAPKK, MAPK kinase; MAPKKK, MAPKK kinase; MEK/MKK, MAPK/ERK kinase; MEKK, MEK kinase; ERK, extracellular signal-regulated kinase; JNK/SAPK, c-jun N-terminal kinase/stress-activated protein kinase; sGC, soluble guanylate cyclase; cGMP, cyclic guanosine monophosphate; PKC/PKG, protein kinase C/G; NF-κB, nuclear factor-kappa B; AP-1, activating protein-1.

cyclic nucleotide-gated channels, phosphodiesterases, protein kinase A (PKA) and protein kinase G (PKG) [228], where change is effected through transcription factor phosphorylation and/or transcription. Interestingly, transcription factors, including AP-1, that are activated by cGMP are also regulated by NO through protein modification [229]. Several conflicting studies have used specific inhibitors of sCG, analogues of cGMP or PKG to determine whether observed effects of NO on MMP-9 expression are mediated through this pathway.

cGMP analogues can mimic the NO donor mediated down regulation of MMP-9 in MCF-7 cells. This down regulation was blocked following co-incubation with a PKG inhibitor, implicating the cGMP/PKG pathway [177]. Similar results were reported in smooth muscle cells where inhibition of MMP-9 activity by eNOS gene transfer was mimicked by DETA-NONOate or the cGMP analogue 8-bromo-cGMP [230].

Where MMP-9 expression was potentiated by NO, the addition of a sGC inhibitor returned MMP-9 mRNA to basal levels [191]. Similar results were reported when NO-donor mediated upregulation of MMP-9 was inhibited following co-incubation with sGC or PKG inhibitors. The role of the pathway was confirmed when the addition of a cGMP analogue reversed the effect [190].

Where a biphasic regulation of MMP-9 was observed, the stimulation observed at low NO level were attributed to cGMP, whereas the inhibition observed at higher concentrations was independent of sGC/cGMP [114]. In another study where MMP-9 was upregulated by NO, activation of a sGC/PKA pathway resulted in phosphorylation of Wilms tumour 1 (WT1). Phosphorylation caused a shuttling of WT1, a transcriptional repressor, from the nucleus to the cytosol causing upregulation of MMP-9 [231]. The NO sensitive cGMP/PKG pathway also negatively regulates store-operated Calcium entry (SOC) in fibroblasts. This inhibition has been reported to indirectly inhibit MMP-9 synthesis and release, where increased SOC increases MMP-9 release [180].

The influence of cGMP is likely cell specific, as NO-donor mediated inhibition of MMP-9 was found to be independent of cGMP in endothelial cells [223] and cGMP analogues were unable to replicate the effects of NO in IL-1β stimulated rat mesangial cells [175]. It is reported elsewhere that PKG had no effect on basal or NO modulated MMP-9 expression [123]. This suggests a PKG independent cGMP mediated pathway.

4.3.4. MAP kinases/protein kinase C

The mitogen activated protein kinases (MAPK) [232] and protein kinase C (PKC) [200] are two families of kinase signalling cascades involved in the activation of MMP-9 transcription factors. AP-1 and NF-κB are both regulated by MAP kinases which can in turn be activated by PKC-ζ, so interactions between the molecules in MMP-9 regulation seem likely [200].

Protein kinase C is a family of isoenzymes with differential distribution, substrate specificities and activation responsiveness. They are split into conventional (α, βI, βII, γ), novel (δ, ε, η/L, θ) and atypical (ζ, λ/L). Few studies have examined the specific isoenzyme involved in MMP-9 expression but PKC-α, β, and in particular ζ have been implicated [200,201]. NO donors have been shown to inhibit JNK through S-nitrosylation in several cell models [233–236]. Inhibitors of p38 and ERK MAP kinases showed an additive reduction though not complete inhibition of IL-1β or superoxide stimulated MMP-9 mRNA. Superoxide worked with IL-1β to increase phosphorylation of ERK, p38 and JNK to increase MMP-9 expression [210].

In one study where AP-1 was inhibited by an NO donor, the upstream MAPK, JNK was unaffected. The donor caused an inhibition of PKC-δ resulting in reduced MMP-9 expression [177]. ERK 1/2 stimulated by LPS was also shown to be inhibited by an NO donor. Interestingly, the inhibition was reversed with a cGMP analogue [176]. DETA-NONOate was found to attenuate superoxide mediated ERK activation and MMP-9 upregulation in vascular smooth muscle cells [181].

In a colon cancer cell line, NO caused the upregulation of MMP-9. The upregulation was abolished in the presence of inhibitors of sGC, PKG or ERK. The study showed that NO caused the upregulation in a cGMP/PKG/ERK dependent manner and can increase ERK 1/2 phosphorylation by 12 fold [191].

A careful analysis of reports on NO-stimulator or NO-inhibitor effects on the MMP-9 gene expression allows for the following conclusions. First, as MMP-9 is an inducible enzyme and basal expression levels are often low, the stimulating factor can strongly affect response. Nitric oxide does not appear to influence basal MMP-9 expression [175,177]. Second, reports describing opposing effects of NO on gene expression may be explained by the complexity of the regulation and the influence of cell type, NO source (physiological, pathological or pharmacological), its concentrations and duration of action, as well as timing of exposure of MMP-9-generating systems to NO.

5. Nitric oxide and its effects on MMP-9 mRNA stability

Post-transcriptional regulation is increasingly recognised as being critical for gene expression. Microarray studies have shown that over half of stress-response genes are regulated by changes in mRNA stability [237,238]. Regulation of the fate of mRNA is through its 3′ UTR (untranslated region) which contain cis-regulatory elements. The adenylate and uridylate-rich elements (AREs) constitute one class of these elements that regulate cytoplasmic mRNA [239] and target labile mRNA for degradation [240]. Several families of ARE-binding proteins (ARE-BP) regulate the fate of the mRNA. HuR is a ubiquitously expressed ARE-BP belonging to the ELAV family which stabilizes ARE containing mRNAs [241,242]. NO has been shown to regulate the expression of several genes including heme oxygenase 1 [243], transforming growth factor-β3 [244], endothelin-converting-enzyme-1 [245], IL-8, TNF-α and p21/Waf1 [246] by influencing the mRNA stability. Interestingly, binding of HuR is found to be essential for the stability of iNOS mRNA [247] and the inhibition of sGC induced by cAMP results from inhibition of HuR expression [248]. It has also been shown elsewhere that cGMP-elevating agents decrease the expression and RNA binding of HuR [249].

MMP-9 mRNA contains numerous AUUA motifs in its 3′UTR and the stabilizing effects of HuR have been reported [250,251]. The stability of existing mRNA can be measured using actinomycin to block de novo synthesis of mRNA. Nitric oxide donors were shown to inhibit the expression of HuR and thus reduce its binding to in the 3′UTR through a sGC-cGMP pathway [252]. The half-life of MMP-9 mRNA from rat mesangial cells was reduced from 8 h to 4 h following co-incubation with NO-donors [253]. This finding was consistent with the discovery that the stability of the MMP-9 mRNA is dependent on HuR binding to the ARE.

Where DETA-NONOate reduced the stability of MMP-9 mRNA in cultured astrocytes, AUF-1, and not HuR, was found to play a mediating role. Protein levels of the mRNA destabilising factor and its binding to theMMP-9 3′ UTR were found to be increased following addition of the NO donor [254]. Addition of AUF-1 siRNA was found to partially reverse the NO mediated inhibition of MMP-9 and thus confirming a further mechanism of NO mediated MMP-9 mRNA destabilisaiton.

Based on the available evidence, we conclude that increased concentrations of NO reduce the stability of MMP-9 mRNA, most likely, through downregulation of HuR and increased expression of AUF-1.

6. NO and MMP-9 in the tumour microenvironment

Our current understanding of the role of MMP-9 in cancer is incomplete but has been summarised elsewhere [1,5,38] and is seen as being a key agonist in the progression of several cancers including colorectal, lung, oral and pancreatic through increasing invasion, metastasis and angiogenesis [24,255]. While upregulation of MMPs by tumours has long been established, it is now known that stromal cells, such as fibroblasts, endothelial cells and leucocytes can play an equally important

role by releasing MMP-9 to the tumour microenvironment following activation of growth factors in the ECM by tumour cells, release of cytokines and growth factors, and through direct cell–cell contact with tumours [256,257]. Tumours and tumour associated stromal cell interactions are incompletely understood, but their recruitment serves to enhance the metastatic efficiency. An interesting study on skin squamous cell carcinoma found that increased expression of stroma-dervied MMP-9 occurred exclusively in enhanced malignant tumour transplants [258]. NO is believed to play a dual role in metastasis which may be linked to its concentration within the tumour microenvironment [259], where sources of NO include macrophages, neutrophils, fibroblasts, endothelial cells and in some cases, tumours themselves and all three NOS isoforms have been implicated in various cancer types [259]. An interesting study on the mechanism of IL-2/α-CD40 immunotherapy found that the inhibition of metastasis was as a result of induction of iNOS expression by stromal macrophages and therefore a reduction in MMP-9 expression and activity within the tumour. An NO donor JS-K was able to mimic these effects [260]. To our knowledge, this is the first example of an NO mediated cross-talk between the tumour and stroma resulting in the regulation of MMP-9 but it would seem likely to be more ubiquitous given the prevalence of NO and MMP-9 upregulation.

7. Using NO donors/mimetics as therapeutic agents

The quest for a clinically useful MMP inhibitor (MMPi) has been ongoing for several decades. The most common problems encountered during clinical development such as poor efficacy and side effects have been attributed to inadequate MMP subtype specificity. Over the past number of years, our knowledge of the role of individual MMPs in various processes and the regulation of these enzymes has greatly expanded. However, the emerging network and relationship between MMPs and their physiological and pathophysiological environments appear to be more complex than it had been originally anticipated. Therefore, the real challenge may not lie merely in the development of selective inhibitors of an MMP subtype (which might have multiple opposing roles in vivo), but rather in regulating the dysregulated enzymes activity that is specifically associated with pathobiology. This complex problem may require us to look at factors controlling MMP expression and aberrant activity. As more is being understood about the role of endogenous NO in various disease processes and more studies are being conducted on the influence of NO on MMP-9 regulation, nitrates and other NO donors may prove useful as therapeutic agents in inhibition of dysregulated MMPs.

NO has been incorporated into several established pharmacological agents as NO-drug hybrids in an effort to enhance efficacy and decrease side-effects of the resultant pharmacological agents. Of these, hybrids of NO with non-steroidal anti-inflammatory drugs (NO-NSAIDS) [261–264], NO-glucocorticoids [265–267], and NO-salbutamol [268–270] have been extensively studied for their anti-inflammatory properties but not specifically as MMP-9 inhibitors.

Glyceryl trinitrate (GTN) has long been used clinically for over 150 years and has a well-established toxicity profile [271]. Its potential use as an MMPi was demonstrated when it reduced plasma MMP-9 levels by increasing the enzyme membrane binding and inhibited release [147]. In contrast, GTN is reported to activate pro-MMP-9 [272], increasing potential MMP-9 activity through an increase in NF-κB activation [273] and increased MMP-9 expression [274].

Our group has reported an interesting family of barbiturate–nitrate hybrids. These compounds are able to inhibit MMP-9 catalytic activity and reduce MMP-9 secretion. The hybrids more potently inhibited tumour cell invasion than their non-nitrate analogues [275]. These promising results illustrate the potential for the use of NO donors or nitrate-hybrids in the treatment of conditions where MMP-9 plays a role in the pathophysiology.

Many of the issues relating to the use of NO donors as MMP-9 inhibitors overlap with their use as anti-cancer agents and are already the subject of review [276]. Understanding the endogenous role of NO in a given disease state, in particular the concentration threshold for any dual response, will be key in the effective use of these compounds as therapeutic agents.

8. Conclusion

The role of NO in the regulation of MMP-9 has been the subject of intense study over the previous two decades and the models used have spanned several cell types and disease states. This review presents these studies and the often conflicting results as a representation of the dual nature of the molecule at almost every level of MMP-9 regulation. In making sense of the apparent contradiction in the results, it is crucial to first understand the role of concentration in this biphasic nature of NO. NO effects are often separated into cGMP dependent, which tend to occur at lower NO flux, and cGMP independent, occurring at higher concentrations. These cGMP independent effects are often mediated by formation of peroxynitrite [86,87,277,278], leading to direct reaction with proteins to alter their function through S-nitrosylation, tyrosine nitration or oxidisation [279]. Indeed, peroxynitrite often opposes the biological effects of NO [86,87,280–282]. The balance of these reactions will often give rise to a threshold in concentration, beyond which the role of NO may change. To further complicate this concentration-dependent role of NO, effects will also be cell- and environment-specific depending on the presence of endogenous antioxidants [283] and other genes involved in regulating a given response. The dichotomy of protective and damaging effects of NO is evident in inflammation, where iNOS is generally considered pro-inflammatory, whereas eNOS and nNOS are considered anti-inflammatory [284] and also in the dual roles of NO in apoptosis [277,285].

Through studies with recombinant pro-MMP-9, activation of the zymogen by NO donors has been demonstrated. Other studies have shown that this effect is dependent on the donor used and that higher concentrations of NO may in fact inhibit enzyme activity through interaction with the active site. The overall relevance of these findings in an in-vivo setting remains to be determined. NO also directs proteolysis by MMP-9 by affecting local activity through increased cell surface association, directed distribution, internalisation or modulation of pro-MMP-9 activating factors. Regulation of MMP-9 expression by NO is a concentration dependent event with a trend of increased expression at low NO concentration and downregulation at higher concentrations of NO. This trend may not hold for all cells and will depend on the stimulating factors and so, the transcription factors involved in the expression. Activity of NF-κB and cGMP are both increased at low NO and inhibited at high NO concentration and so follow this observed trend. Increasing levels of NO will also reduce MMP-9 expression through a decrease in mRNA stability.

Despite intense work in the field over previous decades, and increased understanding of the role of MMP-9 in human pathology, clinically useful MMP inhibitors have proven elusive. This review highlights the complexity of NO-MMP-9 interactions and presents some of the challenges that have been encountered and need to be resolved. Further studies to separate the opposing roles of NO in MMP-9 regulation will clarify its part in a given disease process and will allow its inhibitory role to be exploited as a therapeutic agent.

Acknowledgements

This work was partially funded by a Science Foundation Ireland grant (SFI-RFP/BMT2781) awarded to CM and JFG. CM is an SFI Stokes lecturer.

References

[1] M. Egeblad, Z. Werb, New functions for the matrix metalloproteinases in cancer progression, Nat. Rev. Cancer 2 (2002) 161–174.
[2] Z.S. Galis, J.J. Khatri, Matrix metalloproteinases in vascular remodeling and atherogenesis: the good, the bad, and the ugly, Circ. Res. 90 (2002) 251–262.
[3] I. Stamenkovic, Matrix metalloproteinases in tumor invasion and metastasis, Semin. Cancer Biol. 10 (2000) 415–433.
[4] F.G. Spinale, Matrix metalloproteinases: regulation and dysregulation in the failing heart, Circ. Res. 90 (2002) 520–530.
[5] M. Bjorklund, E. Koivunen, Gelatinase-mediated migration and invasion of cancer cells, Biochim. Biophys. Acta 1755 (2005) 37–69.
[6] W.C. Parks, S.D. Shapiro, Matrix metalloproteinases in lung biology, Respir. Res. 2 (2001) 10–19.
[7] F. Kuwahara, H. Kai, K. Tokuda, M. Takeya, A. Takeshita, K. Egashira, T. Imaizumi, Hypertensive myocardial fibrosis and diastolic dysfunction: another model of inflammation? Hypertension 43 (2004) 739–745.
[8] P. Collier, C.J. Watson, V. Voon, D. Phelan, A. Jan, G. Mak, R. Martos, J.A. Baugh, M.T. Ledwidge, K.M. McDonald, Can emerging biomarkers of myocardial remodelling identify asymptomatic hypertensive patients at risk for diastolic dysfunction and diastolic heart failure? Eur. J. Heart Fail. 13 (2011) 1087–1095.
[9] D.M. Basalyga, D.T. Simionescu, W. Xiong, B.T. Baxter, B.C. Starcher, N.R. Vyavahare, Elastin degradation and calcification in an abdominal aorta injury model: role of matrix metalloproteinases, Circulation 110 (2004) 3480–3487.
[10] S. Heymans, F. Lupu, S. Terclavers, B. Vanwetswinkel, J.-M. Herbert, A. Baker, D. Collen, P. Carmeliet, L. Moons, Loss or inhibition of uPA or MMP-9 attenuates LV remodeling and dysfunction after acute pressure overload in mice, Am. J. Pathol. 166 (2005) 15–25.
[11] R. Mukherjee, G.P. Colbath, C.D. Justus, J.A. Bruce, C.M. Allen, K.W. Hewett, J.P. Saul, R.G. Gourdie, F.G. Spinale, Spatiotemporal induction of matrix metalloproteinase-9 transcription after discrete myocardial injury, FASEB J. 24 (2010) 3819–3828.
[12] R. Mukherjee, J.M. Snipes, S.M. Saunders, J.A. Zavadzkas, F.G. Spinale, Discordant activation of gene promoters for matrix metalloproteinases and tissue inhibitors of the metalloproteinases following myocardial infarction, J. Surg. Res. 172 (2012) 59–67.
[13] R. Mukherjee, J.T. Mingoia, J.A. Bruce, J.S. Austin, R.E. Stroud, G.P. Escobar, D.M. McClister Jr., C.M. Allen, M.A. Alfonso-Jaume, M.E. Fini, D.H. Lovett, F.G. Spinale, Selective spatiotemporal induction of matrix metalloproteinase-2 and matrix metalloproteinase-9 transcription after myocardial infarction, Am. J. Physiol. Heart Circ. Physiol. 291 (2006) H2216–H2228.
[14] R. Martos, J. Baugh, M. Ledwidge, C. O'Loughlin, C. Conlon, A. Patle, S.C. Donnelly, K. McDonald, Diastolic heart failure: evidence of increased myocardial collagen turnover linked to diastolic dysfunction, Circulation 115 (2007) 888–895.
[15] R. Martos, J. Baugh, M. Ledwidge, C. O'Loughlin, N.F. Murphy, C. Conlon, A. Patle, S.C. Donnelly, K. McDonald, Diagnosis of heart failure with preserved ejection fraction: improved accuracy with the use of markers of collagen turnover, Eur. J. Heart Fail. 11 (2009) 191–197.
[16] M.R. Zile, S.M. Desantis, C.F. Baicu, R.E. Stroud, S.B. Thompson, C.D. McClure, S.M. Mehurg, F.G. Spinale, Plasma biomarkers that reflect determinants of matrix composition identify the presence of left ventricular hypertrophy and diastolic heart failure, Circ. Heart Fail. 4 (2011) 246–256.
[17] W. Kuliczkowski, J. Urbaniak, J. Hallen, M. Wozniak, L. Polonski, A. Mysiak, D. Atar, M. Zembala, V. Serebruany, Matrix metalloproteinases and the activity of their tissue inhibitors in patients with ST-elevation myocardial infarction treated with primary angioplasty, Kardiol. Pol. 71 (2013) 453–463.
[18] R.A. Kowluru, G. Mohammad, J.M. dos Santos, Q. Zhong, Abrogation of MMP-9 gene protects against the development of retinopathy in diabetic mice by preventing mitochondrial damage, Diabetes 60 (2011) 3023–3033.
[19] K.M. Thrailkill, C.S. Moreau, G.E. Cockrell, C.H. Jo, R.C. Bunn, A.E. Morales-Pozzo, C.K. Lumpkin, J.L. Fowlkes, Disease and gender-specific dysregulation of NGAL and MMP-9 in type 1 diabetes mellitus, Endocrine 37 (2010) 336–343.
[20] T. Ishibashi, M. Kawaguchi, K. Sugimoto, H. Uekita, N. Sakamoto, K. Yokoyama, Y. Maruyama, Y. Takeishi, Advanced glycation end product-mediated matrix metallo-proteinase-9 and apoptosis via renin-angiotensin system in type 2 diabetes, J. Atheroscler. Thromb. 17 (2010) 578–589.
[21] A.W. Chung, H.H. Yang, M.K. Sigrist, G. Brin, E. Chum, W.A. Gourlay, A. Levin, Matrix metalloproteinase-2 and -9 exacerbate arterial stiffening and angiogenesis in diabetes and chronic kidney disease, Cardiovasc. Res. 84 (2009) 494–504.
[22] Y. Wang, Y. Su, Y. Xu, S.H. Pan, G.D. Liu, Genetic polymorphism c.1562C > T of the MMP-9 is associated with macroangiopathy in type 2 diabetes mellitus, Biochem. Biophys. Res. Commun. 391 (2010) 113–117.
[23] R. Roy, J. Yang, M.A. Moses, Matrix metalloproteinases as novel biomarkers and potential therapeutic targets in human cancer, J. Clin. Oncol. 27 (2009) 5287–5297.
[24] G. Bergers, R. Brekken, G. McMahon, T.H. Vu, T. Itoh, K. Tamaki, K. Tanzawa, P. Thorpe, S. Itohara, Z. Werb, D. Hanahan, Matrix metalloproteinase-9 triggers the angiogenic switch during carcinogenesis, Nat. Cell Biol. 2 (2000) 737–744.
[25] A. Noel, M. Jost, E. Maquoi, Matrix metalloproteinases at cancer tumor-host interface, Semin. Cell Dev. Biol. 19 (2008) 52–60.
[26] R. Kalluri, R.A. Weinberg, The basics of epithelial–mesenchymal transition, J. Clin. Invest. 119 (2009) 1420–1428.
[27] A. Kruger, M.J. Arlt, M. Gerg, C. Kopitz, M.M. Bernardo, M. Chang, S. Mobashery, R. Fridman, Antimetastatic activity of a novel mechanism-based gelatinase inhibitor, Cancer Res. 65 (2005) 3523–3526.
[28] G. Batist, F. Patenaude, P. Champagne, D. Croteau, C. Levinton, C. Hariton, B. Escudier, E. Dupont, Neovastat (AE-941) in refractory renal cell carcinoma patients: report of a phase II trial with two dose levels, Ann. Oncol. 13 (2002) 1259–1263.
[29] X. Li, J.F. Wu, Recent developments in patent anti-cancer agents targeting the matrix metalloproteinases (MMPs), Recent Pat. Anticancer Drug Discov. 5 (2010) 109–141.
[30] V.L. Gadd, M. Melino, S. Roy, L. Horsfall, P. O'Rourke, M.R. Williams, K.M. Irvine, M.J. Sweet, J.R. Jonsson, A.D. Clouston, E.E. Powell, Portal, but not lobular, macrophages express matrix metalloproteinase-9: association with the ductular reaction and fibrosis in chronic hepatitis C, Liver Int. 33 (2013) 569–579.
[31] T. Hori, S. Uemoto, L.B. Walden, F. Chen, A.M. Baine, T. Hata, T. Kogure, J.H. Nguyen, Matrix metalloproteinase-9 as a therapeutic target for the progression of fulminant liver failure with hepatic encephalopathy: a pilot study in mice, Hepatol. Res. (2013), http://dx.doi.org/10.1111/hepr.12161.
[32] J.P. Tsai, J.H. Liou, W.T. Kao, S.C. Wang, J.D. Lian, H.R. Chang, Increased expression of intranuclear matrix metalloproteinase 9 in atrophic renal tubules is associated with renal fibrosis, PLoS One 7 (2012) e48164.
[33] K.A. Czech, M. Bennett, P. Devarajan, Distinct metalloproteinase excretion patterns in focal segmental glomerulosclerosis, Pediatr. Nephrol. 26 (2011) 2179–2184.
[34] A. Altadill, N. Eiro, L.O. Gonzalez, S. Junquera, J.M. Gonzalez-Quintana, M.R. Sanchez, A. Andicoechea, C. Saro, L. Rodrigo, F.J. Vizoso, Comparative analysis of the expression of metalloproteases and their inhibitors in resected crohn's disease and complicated diverticular disease, Inflamm. Bowel Dis. 18 (2012) 120–130.
[35] C. Medina, S. Videla, A. Radomski, M.W. Radomski, M. Antolin, F. Guarner, J. Vilaseca, A. Salas, J.R. Malagelada, Increased activity and expression of matrix metalloproteinase-9 in a rat model of distal colitis, Am. J. Physiol. Gastrointest. Liver Physiol. 284 (2003) G116–G122.
[36] C. Medina, A. Santana, M.C. Paz, F. Diaz-Gonzalez, E. Farre, A. Salas, M.W. Radomski, E. Quintero, Matrix metalloproteinase-9 modulates intestinal injury in rats with transmural colitis, J. Leukoc. Biol. 79 (2006) 954–962.
[37] H. Liu, N.R. Patel, L. Walter, S. Ingersoll, S.V. Sitaraman, P. Garg, Constitutive expression of MMP9 in intestinal epithelium worsens murine acute colitis and is associated with increased levels of proinflammatory cytokine Kc, Am. J. Physiol. Gastrointest. Liver Physiol. 304 (2013) G793–G803.
[38] C.M. Overall, C. Lopez-Otin, Strategies for MMP inhibition in cancer: innovations for the post-trial era, Nat. Rev. Cancer 2 (2002) 657–672.
[39] J. Hu, P.E. Van den Steen, Q.X. Sang, G. Opdenakker, Matrix metalloproteinase inhibitors as therapy for inflammatory and vascular diseases, Nat. Rev. Drug Discov. 6 (2007) 480–498.
[40] A. Kruger, R.E. Kates, D.R. Edwards, Avoiding spam in the proteolytic internet: future strategies for anti-metastatic MMP inhibition, Biochim. Biophys. Acta 1803 (2010) 95–102.
[41] B. Cauwe, P.E. Van den Steen, G. Opdenakker, The biochemical, biological, and pathological kaleidoscope of cell surface substrates processed by matrix metalloproteinases, Crit. Rev. Biochem. Mol. Biol. 42 (2007) 113–185.
[42] G. Murphy, V. Knauper, Relating matrix metalloproteinase structure to function: why the "hemopexin" domain? Matrix Biol. 15 (1997) 511–518.
[43] E. Roeb, K. Schleinkofer, T. Kernebeck, S. Potsch, B. Jansen, I. Behrmann, S. Matern, J. Grotzinger, The matrix metalloproteinase 9 (mmp-9) hemopexin domain is a novel gelatin binding domain and acts as an antagonist, J. Biol. Chem. 277 (2002) 50326–50332.
[44] J. Redondo-Munoz, E. Ugarte-Berzal, M.J. Terol, P.E. Van den Steen, M. Hernandez del Cerro, M. Roderfeld, E. Roeb, G. Opdenakker, J.A. Garcia-Marco, A. Garcia-Pardo, Matrix metalloproteinase-9 promotes chronic lymphocytic leukemia b cell survival through its hemopexin domain, Cancer Cell 17 (2010) 160–172.
[45] H. Nagase, J.F. Woessner Jr., Matrix metalloproteinases, J. Biol. Chem. 274 (1999) 21491–21494.
[46] W. Bode, F.X. Gomis-Ruth, W. Stockler, Astacins, serralysins, snake venom and matrix metalloproteinases exhibit identical zinc-binding environments (HEXXHXXGXXH and Met-turn) and topologies and should be grouped into a common family, the 'metzincins', FEBS Lett. 331 (1993) 134–140.
[47] M.F. Browner, W.W. Smith, A.L. Castelhano, Matrilysin-inhibitor complexes: common themes among metalloproteases, Biochemistry 34 (1995) 6602–6610.
[48] P.E. Van den Steen, B. Dubois, I. Nelissen, P.M. Rudd, R.A. Dwek, G. Opdenakker, Biochemistry and molecular biology of gelatinase B or matrix metalloproteinase-9 (MMP-9), Crit. Rev. Biochem. Mol. Biol. 37 (2002) 375–536.
[49] T.H. Vu, Z. Werb, Matrix metalloproteinases: effectors of development and normal physiology, Genes Dev. 14 (2000) 2123–2133.
[50] E.B. Springman, E.L. Angleton, H. Birkedal-Hansen, H.E. Van Wart, Multiple modes of activation of latent human fibroblast collagenase: evidence for the role of a Cys73 active-site zinc complex in latency and a "cysteine switch" mechanism for activation, Proc. Natl. Acad. Sci. U. S. A. 87 (1990) 364–368.
[51] J.W. Becker, A.I. Marcy, L.L. Rokosz, M.G. Axel, J.J. Burbaum, P.M. Fitzgerald, P.M. Cameron, C.K. Esser, W.K. Hagmann, J.D. Hermes, et al., Stromelysin-1: three-dimensional structure of the inhibited catalytic domain and of the C-truncated proenzyme, Protein Sci. 4 (1995) 1966–1976.
[52] H.E. Van Wart, H. Birkedal-Hansen, The cysteine switch: a principle of regulation of metalloproteinase activity with potential applicability to the entire matrix metalloproteinase gene family, Proc. Natl. Acad. Sci. U. S. A. 87 (1990) 5578–5582.
[53] G.A. Bannikov, T.V. Karelina, I.E. Collier, B.L. Marmer, G.I. Goldberg, Substrate binding of gelatinase B induces its enzymatic activity in the presence of intact propeptide, J. Biol. Chem. 277 (2002) 16022–16027.
[54] G.J. Peppin, S.J. Weiss, Activation of the endogenous metalloproteinase, gelatinase, by triggered human neutrophils, Proc. Natl. Acad. Sci. U. S. A. 83 (1986) 4322–4326.

[55] Z. Gu, M. Kaul, B. Yan, S.J. Kridel, J. Cui, A. Strongin, J.W. Smith, R.C. Liddington, S.A. Lipton, S-nitrosylation of matrix metalloproteinases: signaling pathway to neuronal cell death, Science 297 (2002) 1186–1190.
[56] B. Paquette, M. Bisson, H. Therriault, R. Lemay, M. Pare, P. Banville, A.M. Cantin, Activation of matrix metalloproteinase-2 and -9 by 2- and 4-hydroxyestradiol, J. Steroid Biochem. Mol. Biol. 87 (2003) 65–73.
[57] M. Toth, I. Chvyrkova, M.M. Bernardo, S. Hernandez-Barrantes, R. Fridman, Pro-MMP-9 activation by the MT1-MMP/MMP-2 axis and MMP-3: role of TIMP-2 and plasma membranes, Biochem. Biophys. Res. Commun. 308 (2003) 386–395.
[58] A.R. Radjabi, K. Sawada, S. Jagadeeswaran, A. Eichbichler, H.A. Kenny, A. Montag, K. Bruno, E. Lengyel, Thrombin induces tumor invasion through the induction and association of matrix metalloproteinase-9 and beta1-integrin on the cell surface, J. Biol. Chem. 283 (2008) 2822–2834.
[59] J.P. O'Connell, F. Willenbrock, A.J. Docherty, D. Eaton, G. Murphy, Analysis of the role of the COOH-terminal domain in the activation, proteolytic activity, and tissue inhibitor of metalloproteinase interactions of gelatinase B, J. Biol. Chem. 269 (1994) 14967–14973.
[60] M.W. Olson, D.C. Gervasi, S. Mobashery, R. Fridman, Kinetic analysis of the binding of human matrix metalloproteinase-2 and -9 to tissue inhibitor of metalloproteinase (TIMP)-1 and TIMP-2, J. Biol. Chem. 272 (1997) 29975–29983.
[61] L. Sottrup-Jensen, H. Birkedal-Hansen, Human fibroblast collagenase-alpha-macroglobulin interactions. Localization of cleavage sites in the bait regions of five mammalian alpha-macroglobulins, J. Biol. Chem. 264 (1989) 393–401.
[62] G.S. Salvesen, C.A. Sayers, A.J. Barrett, Further characterization of the covalent linking reaction of alpha 2-macroglobulin, Biochem. J. 195 (1981) 453–461.
[63] S.K. Moestrup, T.L. Holtet, M. Etzerodt, H.C. Thogersen, A. Nykjaer, P.A. Andreasen, H.H. Rasmussen, L. Sottrup-Jensen, J. Gliemann, Alpha 2-macroglobulin-proteinase complexes, plasminogen activator inhibitor type-1-plasminogen activator complexes, and receptor-associated protein bind to a region of the alpha 2-macroglobulin receptor containing a cluster of eight complement-type repeats, J. Biol. Chem. 268 (1993) 13691–13696.
[64] J.D. Mott, C.L. Thomas, M.T. Rosenbach, K. Takahara, D.S. Greenspan, M.J. Banda, Post-translational proteolytic processing of procollagen C-terminal proteinase enhancer releases a metalloproteinase inhibitor, J. Biol. Chem. 275 (2000) 1384–1390.
[65] K.O. Netzer, K. Suzuki, Y. Itoh, B.G. Hudson, R.G. Khalifah, Comparative analysis of the noncollagenous NC1 domain of type IV collagen: identification of structural features important for assembly, function, and pathogenesis, Protein Sci. 7 (1998) 1340–1351.
[66] M.P. Herman, G.K. Sukhova, W. Kisiel, D. Foster, M.R. Kehry, P. Libby, U. Schonbeck, Tissue factor pathway inhibitor-2 is a novel inhibitor of matrix metalloproteinases with implications for atherosclerosis, J. Clin. Invest. 107 (2001) 1117–1126.
[67] Y.M. Kim, J.W. Jang, O.H. Lee, J. Yeon, E.Y. Choi, K.W. Kim, S.T. Lee, Y.G. Kwon, Endostatin inhibits endothelial and tumor cellular invasion by blocking the activation and catalytic activity of matrix metalloproteinase, Cancer Res. 60 (2000) 5410–5413.
[68] P. Nyberg, P. Heikkila, T. Sorsa, J. Luostarinen, R. Heljasvaara, U.H. Stenman, T. Pihlajaniemi, T. Salo, Endostatin inhibits human tongue carcinoma cell invasion and intravasation and blocks the activation of matrix metalloprotease-2, -9, and -13, J. Biol. Chem. 278 (2003) 22404–22411.
[69] K. Bein, M. Simons, Thrombospondin type 1 repeats interact with matrix metalloproteinase 2. Regulation of metalloproteinase activity, J. Biol. Chem. 275 (2000) 32167–32173.
[70] J.C. Rodriguez-Manzaneque, T.F. Lane, M.A. Ortega, R.O. Hynes, J. Lawler, M.L. Iruela-Arispe, Thrombospondin-1 suppresses spontaneous tumor growth and inhibits activation of matrix metalloproteinase-9 and mobilization of vascular endothelial growth factor, Proc. Natl. Acad. Sci. U. S. A. 98 (2001) 12485–12490.
[71] Z. Yang, D.K. Strickland, P. Bornstein, Extracellular matrix metalloproteinase 2 levels are regulated by the low density lipoprotein-related scavenger receptor and thrombospondin 2, J. Biol. Chem. 276 (2001) 8403–8408.
[72] C. Takahashi, Z. Sheng, T.P. Horan, H. Kitayama, M. Maki, K. Hitomi, Y. Kitaura, S. Takai, R.M. Sasahara, A. Horimoto, Y. Ikawa, B.J. Ratzkin, T. Arakawa, M. Noda, Regulation of matrix metalloproteinase-9 and inhibition of tumor invasion by the membrane-anchored glycoprotein RECK, Proc. Natl. Acad. Sci. U. S. A. 95 (1998) 13221–13226.
[73] J. Oh, R. Takahashi, S. Kondo, A. Mizoguchi, E. Adachi, R.M. Sasahara, S. Nishimura, Y. Imamura, H. Kitayama, D.B. Alexander, C. Ide, T.P. Horan, T. Arakawa, H. Yoshida, S. Nishikawa, Y. Itoh, M. Seiki, S. Itohara, C. Takahashi, M. Noda, The membrane-anchored MMP inhibitor RECK is a key regulator of extracellular matrix integrity and angiogenesis, Cell 107 (2001) 789–800.
[74] A. Berton, V. Rigot, E. Huet, M. Decarme, Y. Eeckhout, L. Patthy, G. Godeau, W. Hornebeck, G. Bellon, H. Emonard, Involvement of fibronectin type II repeats in the efficient inhibition of gelatinases A and B by long-chain unsaturated fatty acids, J. Biol. Chem. 276 (2001) 20458–20465.
[75] M.D. Sternlicht, Z. Werb, How matrix metalloproteinases regulate cell behavior, Annu. Rev. Cell Dev. Biol. 17 (2001) 463–516.
[76] S.R. Vincent, Nitric oxide neurons and neurotransmission, Prog. Neurobiol. 90 (2010) 246–255.
[77] D. Chakravortty, M. Hensel, Inducible nitric oxide synthase and control of intracellular bacterial pathogens, Microbes Infect. 5 (2003) 621–627.
[78] J.R. Kanwar, R.K. Kanwar, H. Burrow, S. Baratchi, Recent advances on the roles of NO in cancer and chronic inflammatory disorders, Curr. Med. Chem. 16 (2009) 2373–2394.
[79] H. Rubbo, V. Darley-Usmar, B.A. Freeman, Nitric oxide regulation of tissue free radical injury, Chem. Res. Toxicol. 9 (1996) 809–820.
[80] J. Pfeilschifter, W. Eberhardt, K.F. Beck, Regulation of gene expression by nitric oxide, Pflugers Arch. 442 (2001) 479–486.
[81] R.J. Gryglewski, R.M. Palmer, S. Moncada, Superoxide anion is involved in the breakdown of endothelium-derived vascular relaxing factor, Nature 320 (1986) 454–456.
[82] L. Castro, M. Rodriguez, R. Radi, Aconitase is readily inactivated by peroxynitrite, but not by its precursor, nitric oxide, J. Biol. Chem. 269 (1994) 29409–29415.
[83] T. Okamoto, T. Akaike, T. Nagano, S. Miyajima, M. Suga, M. Ando, K. Ichimori, H. Maeda, Activation of human neutrophil procollagenase by nitrogen dioxide and peroxynitrite: a novel mechanism for procollagenase activation involving nitric oxide, Arch. Biochem. Biophys. 342 (1997) 261–274.
[84] J.B. Hibbs Jr., R.R. Taintor, Z. Vavrin, Macrophage cytotoxicity: role for L-arginine deiminase and imino nitrogen oxidation to nitrite, Science 235 (1987) 473–476.
[85] R. Radi, M. Rodriguez, L. Castro, R. Telleri, Inhibition of mitochondrial electron transport by peroxynitrite, Arch. Biochem. Biophys. 308 (1994) 89–95.
[86] M.A. Moro, V.M. Darley-Usmar, D.A. Goodwin, N.G. Read, R. Zamora-Pino, M. Feelisch, M.W. Radomski, S. Moncada, Paradoxical fate and biological action of peroxynitrite on human platelets, Proc. Natl. Acad. Sci. U. S. A. 91 (1994) 6702–6706.
[87] L.M. Villa, E. Salas, V.M. Darley-Usmar, M.W. Radomski, S. Moncada, Peroxynitrite induces both vasodilatation and impaired vascular relaxation in the isolated perfused rat heart, Proc. Natl. Acad. Sci. U. S. A. 91 (1994) 12383–12387.
[88] R. Radi, J.S. Beckman, K.M. Bush, B.A. Freeman, Peroxynitrite oxidation of sulfhydryls. The cytotoxic potential of superoxide and nitric oxide, J. Biol. Chem. 266 (1991) 4244–4250.
[89] H. Rubbo, A. Denicola, R. Radi, Peroxynitrite inactivates thiol-containing enzymes of Trypanosoma cruzi energetic metabolism and inhibits cell respiration, Arch. Biochem. Biophys. 308 (1994) 96–102.
[90] J.P. Crow, J.S. Beckman, J.M. McCord, Sensitivity of the essential zinc-thiolate moiety of yeast alcohol dehydrogenase to hypochlorite and peroxynitrite, Biochemistry 34 (1995) 3544–3552.
[91] H. Ischiropoulos, L. Zhu, J. Chen, M. Tsai, J.C. Martin, C.D. Smith, J.S. Beckman, Peroxynitrite-mediated tyrosine nitration catalyzed by superoxide dismutase, Arch. Biochem. Biophys. 298 (1992) 431–437.
[92] B. Alvarez, R. Radi, Peroxynitrite reactivity with amino acids and proteins, Amino Acids 25 (2003) 295–311.
[93] O. Augusto, M.G. Bonini, A.M. Amanso, E. Linares, C.C. Santos, S.L. De Menezes, Nitrogen dioxide and carbonate radical anion: two emerging radicals in biology, Free Radic. Biol. Med. 32 (2002) 841–859.
[94] R. Radi, Peroxynitrite reactions and diffusion in biology, Chem. Res. Toxicol. 11 (1998) 720–721.
[95] J.C. Toledo Jr., O. Augusto, Connecting the chemical and biological properties of nitric oxide, Chem. Res. Toxicol. 25 (2012) 975–989.
[96] J.S. Beckman, W.H. Koppenol, Nitric oxide, superoxide, and peroxynitrite: the good, the bad, and ugly, Am. J. Physiol. 271 (1996) C1424–C1437.
[97] A. Radomski, G. Sawicki, D.M. Olson, M.W. Radomski, The role of nitric oxide and metalloproteinases in the pathogenesis of hyperoxia-induced lung injury in newborn rats, Br. J. Pharmacol. 125 (1998) 1455–1462.
[98] I. Mayers, T. Hurst, L. Puttagunta, A. Radomski, T. Mycyk, G. Sawicki, D. Johnson, M.W. Radomski, Cardiac surgery increases the activity of matrix metalloproteinases and nitric oxide synthase in human hearts, J. Thorac. Cardiovasc. Surg. 122 (2001) 746–752.
[99] I. Mayers, T. Hurst, A. Radomski, D. Johnson, S. Fricker, G. Bridger, B. Cameron, M. Darkes, M.W. Radomski, Increased matrix metalloproteinase activity after canine cardiopulmonary bypass is suppressed by a nitric oxide scavenger, J. Thorac. Cardiovasc. Surg. 125 (2003) 661–668.
[100] R. Fridman, M. Toth, I. Chvyrkova, S.O. Meroueh, S. Mobashery, Cell surface association of matrix metalloproteinase-9 (gelatinase B), Cancer Metastasis Rev. 22 (2003) 153–166.
[101] J. Vandooren, N. Geurts, E. Martens, P.E. Van den Steen, G. Opdenakker, Zymography methods for visualizing hydrolytic enzymes, Nat. Methods 10 (2013) 211–220.
[102] Z. Zhang, J.K. Kolls, P. Oliver, D. Good, P.O. Schwarzenberger, M.S. Joshi, J.L. Ponthier, J.R. Lancaster Jr., Activation of tumor necrosis factor-alpha-converting enzyme-mediated ectodomain shedding by nitric oxide, J. Biol. Chem. 275 (2000) 15839–15844.
[103] S. Viappiani, A.C. Nicolescu, A. Holt, G. Sawicki, B.D. Crawford, H. Leon, T. van Mulligen, R. Schulz, Activation and modulation of 72 kDa matrix metalloproteinase-2 by peroxynitrite and glutathione, Biochem. Pharmacol. 77 (2009) 826–834.
[104] K. Migita, Y. Maeda, S. Abiru, A. Komori, T. Yokoyama, Y. Takii, M. Nakamura, H. Yatsuhashi, K. Eguchi, H. Ishibashi, Peroxynitrite-mediated matrix metalloproteinase-2 activation in human hepatic stellate cells, FEBS Lett. 579 (2005) 3119–3125.
[105] H. Saari, K. Suomalainen, O. Lindy, Y.T. Konttinen, T. Sorsa, Activation of latent human neutrophil collagenase by reactive oxygen species and serine proteases, Biochem. Biophys. Res. Commun. 171 (1990) 979–987.
[106] L. Jia, C. Bonaventura, J. Bonaventura, J.S. Stamler, S-nitrosohaemoglobin: a dynamic activity of blood involved in vascular control, Nature 380 (1996) 221–226.
[107] Y.B. Choi, L. Tenneti, D.A. Le, J. Ortiz, G. Bai, H.S. Chen, S.A. Lipton, Molecular basis of NMDA receptor-coupled ion channel modulation by S-nitrosylation, Nat. Neurosci. 3 (2000) 15–21.
[108] S.R. Jaffrey, H. Erdjument-Bromage, C.D. Ferris, P. Tempst, S.H. Snyder, Protein S-nitrosylation: a physiological signal for neuronal nitric oxide, Nat. Cell Biol. 3 (2001) 193–197.
[109] J.R. Matthews, C.H. Botting, M. Panico, H.R. Morris, R.T. Hay, Inhibition of NF-kappaB DNA binding by nitric oxide, Nucleic Acids Res. 24 (1996) 2236–2242.

[110] D. Berendji, V. Kolb-Bachofen, K.L. Meyer, O. Grapenthin, H. Weber, V. Wahn, K.D. Kroncke, Nitric oxide mediates intracytoplasmic and intranuclear zinc release, FEBS Lett. 405 (1997) 37–41.
[111] C.M. St Croix, K.J. Wasserloos, K.E. Dineley, I.J. Reynolds, E.S. Levitan, B.R. Pitt, Nitric oxide-induced changes in intracellular zinc homeostasis are mediated by metallothionein/thionein, Am. J. Physiol. Lung Cell. Mol. Physiol. 282 (2002) L185–L192.
[112] S. Manabe, Z. Gu, S.A. Lipton, Activation of matrix metalloproteinase-9 via neuronal nitric oxide synthase contributes to NMDA-induced retinal ganglion cell death, Invest. Ophthalmol. Vis. Sci. 46 (2005) 4747–4753.
[113] H.H. Wang, H.L. Hsieh, C.M. Yang, Nitric oxide production by endothelin-1 enhances astrocytic migration via the tyrosine nitration of matrix metalloproteinase-9, J. Cell. Physiol. 226 (2011) 2244–2256.
[114] L.A. Ridnour, A.N. Windhausen, J.S. Isenberg, N. Yeung, D.D. Thomas, M.P. Vitek, D.D. Roberts, D.A. Wink, Nitric oxide regulates matrix metalloproteinase-9 activity by guanylyl-cyclase-dependent and -independent pathways, Proc. Natl. Acad. Sci. U. S. A. 104 (2007) 16898–16903.
[115] P. Pacher, J.S. Beckman, L. Liaudet, Nitric oxide and peroxynitrite in health and disease, Physiol. Rev. 87 (2007) 315–424.
[116] S. Rajagopalan, X.P. Meng, S. Ramasamy, D.G. Harrison, Z.S. Galis, Reactive oxygen species produced by macrophage-derived foam cells regulate the activity of vascular matrix metalloproteinases in vitro. Implications for atherosclerotic plaque stability, J. Clin. Invest. 98 (1996) 2572–2579.
[117] M.W. Owens, S.A. Milligan, D. Jourd'heuil, M.B. Grisham, Effects of reactive metabolites of oxygen and nitrogen on gelatinase A activity, Am. J. Physiol. 273 (1997) L445–L450.
[118] K. Egi, N.E. Conrad, J. Kwan, C. Schulze, R. Schulz, S.M. Wildhirt, Inhibition of inducible nitric oxide synthase and superoxide production reduces matrix metalloproteinase-9 activity and restores coronary vasomotor function in rat cardiac allografts, Eur. J. Cardiothorac. Surg. 26 (2004) 262–269.
[119] E. Capobianco, V. White, M. Sosa, I. Di Marco, M.N. Basualdo, M.C. Faingold, A. Jawerbaum, Regulation of matrix metalloproteinases 2 and 9 activities by peroxynitrites in term placentas from type 2 diabetic patients, Reprod. Sci. 19 (2012) 814–822.
[120] T. Okamoto, T. Akaike, T. Sawa, Y. Miyamoto, A. van der Vliet, H. Maeda, Activation of matrix metalloproteinases by peroxynitrite-induced protein S-glutathiolation via disulfide S-oxide formation, J. Biol. Chem. 276 (2001) 29596–29602.
[121] Y. Suofu, J. Clark, J. Broderick, K.R. Wagner, T. Tomsick, Y. Sa, A. Lu, Peroxynitrite decomposition catalyst prevents matrix metalloproteinase activation and neurovascular injury after prolonged cerebral ischemia in rats, J. Neurochem. 115 (2010) 1266–1276.
[122] C. Legrand, M. Polette, J.M. Tournier, S. de Bentzmann, E. Huet, M. Monteau, P. Birembaut, uPA/plasmin system-mediated MMP-9 activation is implicated in bronchial epithelial cell migration, Exp. Cell Res. 264 (2001) 326–336.
[123] P.F. Bove, U.V. Wesley, A.K. Greul, M. Hristova, W.R. Dostmann, A. van der Vliet, Nitric oxide promotes airway epithelial wound repair through enhanced activation of MMP-9, Am. J. Respir. Cell Mol. Biol. 36 (2007) 138–146.
[124] P.G. Phillips, L.M. Birnby, Nitric oxide modulates caveolin-1 and matrix metalloproteinase-9 expression and distribution at the endothelial cell/tumor cell interface, Am. J. Physiol. Lung Cell. Mol. Physiol. 286 (2004) L1055–L1065.
[125] S.M. McCarthy, P.F. Bove, D.E. Matthews, T. Akaike, A. van der Vliet, Nitric oxide regulation of MMP-9 activation and its relationship to modifications of the cysteine switch, Biochemistry 47 (2008) 5832–5840.
[126] J.R. Hickok, D. Vasudevan, G.R. Thatcher, D.D. Thomas, Is S-nitrosocysteine a true surrogate for nitric oxide? Antioxid. Redox Signal. 17 (2012) 962–968.
[127] Z. Werb, ECM and cell surface proteolysis: regulating cellular ecology, Cell 91 (1997) 439–442.
[128] P. Gaudin, S. Berthier, C. Barro, P. Zaoui, F. Morel, Proteolytic potential of human neutrophil membranes, Eur. J. Cell Biol. 72 (1997) 345–351.
[129] M.W. Olson, M. Toth, D.C. Gervasi, Y. Sado, Y. Ninomiya, R. Fridman, High affinity binding of latent matrix metalloproteinase-9 to the alpha2(IV) chain of collagen IV, J. Biol. Chem. 273 (1998) 10672–10681.
[130] M. Nguyen, J. Arkell, C.J. Jackson, Active and tissue inhibitor of matrix metalloproteinase-free gelatinase B accumulates within human microvascular endothelial vesicles, J. Biol. Chem. 273 (1998) 5400–5404.
[131] G. Taraboletti, S. D'Ascenzo, P. Borsotti, R. Giavazzi, A. Pavan, V. Dolo, Shedding of the matrix metalloproteinases MMP-2, MMP-9, and MT1-MMP as membrane vesicle-associated components by endothelial cells, Am. J. Pathol. 160 (2002) 673–680.
[132] P. Rouet-Benzineb, J.M. Buhler, P. Dreyfus, A. Delcourt, R. Dorent, J. Perennec, B. Crozatier, A. Harf, C. Lafuma, Altered balance between matrix gelatinases (MMP-2 and MMP-9) and their tissue inhibitors in human dilated cardiomyopathy: potential role of MMP-9 in myosin-heavy chain degradation, Eur. J. Heart Fail. 1 (1999) 337–352.
[133] M.M. Lalu, C.Q. Gao, R. Schulz, Matrix metalloproteinase inhibitors attenuate endotoxemia induced cardiac dysfunction: a potential role for MMP-9, Mol. Cell. Biochem. 251 (2003) 61–66.
[134] N.L. Bautista-Lopez, C.A. Morillo, P. Lopez-Jaramillo, R. Quiroz, C. Luengas, S.Y. Silva, J. Galipeau, M.M. Lalu, R. Schulz, Matrix metalloproteinases 2 and 9 as diagnostic markers in the progression to Chagas cardiomyopathy, Am. Heart J. 165 (2013) 558–566.
[135] M. Makela, T. Salo, H. Larjava, MMP-9 from TNF alpha-stimulated keratinocytes binds to cell membranes and type I collagen: a cause for extended matrix degradation in inflammation? Biochem. Biophys. Res. Commun. 253 (1998) 325–335.
[136] M. Toth, D.C. Gervasi, R. Fridman, Phorbol ester-induced cell surface association of matrix metalloproteinase-9 in human MCF10A breast epithelial cells, Cancer Res. 57 (1997) 3159–3167.
[137] E. Mira, S. Manes, R.A. Lacalle, G. Marquez, A.C. Martinez, Insulin-like growth factor I-triggered cell migration and invasion are mediated by matrix metalloproteinase-9, Endocrinology 140 (1999) 1657–1664.
[138] S. Zucker, U.M. Moll, R.M. Lysik, E.I. DiMassimo, J.W. Schwedes, L.A. Liotta, Extraction of type IV collagenase/gelatinase from plasma membranes of human pancreatic cancer cells, Matrix Suppl. 1 (1992) 411.
[139] S.M. Ellerbroek, J.M. Halbleib, M. Benavidez, J.K. Warmka, E.V. Wattenberg, M.S. Stack, L.G. Hudson, Phosphatidylinositol 3-kinase activity in epidermal growth factor-stimulated matrix metalloproteinase-9 production and cell surface association, Cancer Res. 61 (2001) 1855–1861.
[140] C. Festuccia, A. Angelucci, G.L. Gravina, I. Villanova, A. Teti, A. Albini, M. Bologna, Osteoblast-derived TGF-beta1 modulates matrix degrading protease expression and activity in prostate cancer cells, Int. J. Cancer 85 (2000) 407–415.
[141] A. Ginestra, S. Monea, G. Seghezzi, V. Dolo, H. Nagase, P. Mignatti, M.L. Vittorelli, Urokinase plasminogen activator and gelatinases are associated with membrane vesicles shed by human HT1080 fibrosarcoma cells, J. Biol. Chem. 272 (1997) 17216–17222.
[142] R. Mazzieri, L. Masiero, L. Zanetta, S. Monea, M. Onisto, S. Garbisa, P. Mignatti, Control of type IV collagenase activity by components of the urokinase-plasmin system: a regulatory mechanism with cell-bound reactants, EMBO J. 16 (1997) 2319–2332.
[143] Q. Yu, I. Stamenkovic, Localization of matrix metalloproteinase 9 to the cell surface provides a mechanism for CD44-mediated tumor invasion, Genes Dev. 13 (1999) 35–48.
[144] G. Murphy, H. Nagase, Localizing matrix metalloproteinase activities in the pericellular environment, FEBS J. 278 (2011) 2–15.
[145] L. Kjeldsen, J.B. Cowland, N. Borregaard, Human neutrophil gelatinase-associated lipocalin and homologous proteins in rat and mouse, Biochim. Biophys. Acta 1482 (2000) 272–283.
[146] G. Sawicki, E. Salas, J. Murat, H. Miszta-Lane, M.W. Radomski, Release of gelatinase A during platelet activation mediates aggregation, Nature 386 (1997) 616–619.
[147] N. Fiotti, N. Altamura, M. Moretti, S. Wassermann, S. Zacchigna, R. Farra, B. Dapas, L. Consoloni, M. Giacca, G. Grassi, C. Giansante, Short term effects of doxycycline on matrix metalloproteinases 2 and 9, Cardiovasc. Drugs Ther. 23 (2009) 153–159.
[148] V. Novaro, A. Colman-Lerner, F.V. Ortega, A. Jawerbaum, D. Paz, F. Lo Nostro, C. Pustovrh, M.F. Gimeno, E. Gonzalez, Regulation of metalloproteinases by nitric oxide in human trophoblast cells in culture, Reprod. Fertil. Dev. 13 (2001) 411–420.
[149] L.K. Harris, J. McCormick, J.E. Cartwright, G.S. Whitley, P.R. Dash, S-nitrosylation of proteins at the leading edge of migrating trophoblasts by inducible nitric oxide synthase promotes trophoblast invasion, Exp. Cell Res. 314 (2008) 1765–1776.
[150] W.J. Lubbe, D.S. Zuzga, Z. Zhou, W. Fu, J. Pelta-Heller, R.J. Muschel, S.A. Waldman, G.M. Pitari, Guanylyl cyclase C prevents colon cancer metastasis by regulating tumor epithelial cell matrix metalloproteinase-9, Cancer Res. 69 (2009) 3529–3536.
[151] A.K. Witkiewicz, A. Dasgupta, F. Sotgia, I. Mercier, R.G. Pestell, M. Sabel, C.G. Kleer, J.R. Brody, M.P. Lisanti, An absence of stromal caveolin-1 expression predicts early tumor recurrence and poor clinical outcome in human breast cancers, Am. J. Pathol. 174 (2009) 2023–2034.
[152] K. Wiechen, C. Sers, A. Agoulnik, K. Arlt, M. Dietel, P.M. Schlag, U. Schneider, Down-regulation of caveolin-1, a candidate tumor suppressor gene, in sarcomas, Am. J. Pathol. 158 (2001) 833–839.
[153] H. Wikman, E. Kettunen, J.K. Seppanen, A. Karjalainen, J. Hollmen, S. Anttila, S. Knuutila, Identification of differentially expressed genes in pulmonary adenocarcinoma by using cDNA array, Oncogene 21 (2002) 5804–5813.
[154] H.J. Joo, D.K. Oh, Y.S. Kim, K.B. Lee, S.J. Kim, Increased expression of caveolin-1 and microvessel density correlates with metastasis and poor prognosis in clear cell renal cell carcinoma, BJU Int. 93 (2004) 291–296.
[155] V. Barresi, S. Cerasoli, G. Tuccari, Correlative evidence that tumor cell-derived caveolin-1 mediates angiogenesis in meningiomas, Neuropathology 28 (2008) 472–478.
[156] K.C. Moon, G.K. Lee, S.H. Yoo, Y.K. Jeon, J.H. Chung, J. Han, D.H. Chung, Expression of caveolin-1 in pleomorphic carcinoma of the lung is correlated with a poor prognosis, Anticancer Res 25 (2005) 4631–4637.
[157] H.N. Choi, K.R. Kim, H.S. Park, K.Y. Jang, M.J. Kang, D.G. Lee, Y.K. Kim, B.H. Cho, E.J. Cha, W.S. Moon, Expression of caveolin in hepatocellular carcinoma: association with unpaired artery formation and radiologic findings, Korean J. Hepatol. 13 (2007) 396–408.
[158] Y. Tang, X. Zeng, F. He, Y. Liao, N. Qian, M. Toi, Caveolin-1 is related to invasion, survival, and poor prognosis in hepatocellular cancer, Med. Oncol. 29 (2012) 977–984.
[159] T.M. Williams, F. Medina, I. Badano, R.B. Hazan, J. Hutchinson, W.J. Muller, N.G. Chopra, P.E. Scherer, R.G. Pestell, M.P. Lisanti, Caveolin-1 gene disruption promotes mammary tumorigenesis and dramatically enhances lung metastasis in vivo. Role of Cav-1 in cell invasiveness and matrix metalloproteinase (MMP-2/9) secretion, J. Biol. Chem. 279 (2004) 51630–51646.
[160] J.H. Chidlow Jr., W.C. Sessa, Caveolae, caveolins, and cavins: complex control of cellular signalling and inflammation, Cardiovasc. Res. 86 (2010) 219–225.
[161] N. Ramos-DeSimone, E. Hahn-Dantona, J. Sipley, H. Nagase, D.L. French, J.P. Quigley, Activation of matrix metalloproteinase-9 (MMP-9) via a converging plasmin/stromelysin-1 cascade enhances tumor cell invasion, J. Biol. Chem. 274 (1999) 13066–13076.
[162] S.Y. Yoon, Y.J. Lee, J.H. Seo, H.J. Sung, K.H. Park, I.K. Choi, S.J. Kim, S.C. Oh, C.W. Choi, B.S. Kim, S.W. Shin, Y.H. Kim, J.S. Kim, uPAR expression under hypoxic conditions

depends on iNOS modulated ERK phosphorylation in the MDA-MB-231 breast carcinoma cell line, Cell Res. 16 (2006) 75–81.
[163] S.A. ter Horst, F.J. Walther, B.J. Poorthuis, P.S. Hiemstra, G.T. Wagenaar, Inhaled nitric oxide attenuates pulmonary inflammation and fibrin deposition and prolongs survival in neonatal hyperoxic lung injury, Am. J. Physiol. Lung Cell. Mol. Physiol. 293 (2007) L35–L44.
[164] G. Opdenakker, P.E. Van den Steen, J. Van Damme, Gelatinase B: a tuner and amplifier of immune functions, Trends Immunol. 22 (2001) 571–579.
[165] R.N. Johnatty, D.D. Taub, S.P. Reeder, S.M. Turcovski-Corrales, D.W. Cottam, T.J. Stephenson, R.C. Rees, Cytokine and chemokine regulation of proMMP-9 and TIMP-1 production by human peripheral blood lymphocytes, J. Immunol. 158 (1997) 2327–2333.
[166] M. Chabaud, J.M. Durand, N. Buchs, F. Fossiez, G. Page, L. Frappart, P. Miossec, Human interleukin-17: a T cell-derived proinflammatory cytokine produced by the rheumatoid synovium, Arthritis Rheum. 42 (1999) 963–970.
[167] S. Caudroy, M. Polette, B. Nawrocki-Raby, J. Cao, B.P. Toole, S. Zucker, P. Birembaut, EMMPRIN-mediated MMP regulation in tumor and endothelial cells, Clin. Exp. Metastasis 19 (2002) 697–702.
[168] D.L. Crowe, C.F. Shuler, Regulation of tumor cell invasion by extracellular matrix, Histol. Histopathol. 14 (1999) 665–671.
[169] F. Aoudjit, E.F. Potworowski, Y. St-Pierre, Bi-directional induction of matrix metalloproteinase-9 and tissue inhibitor of matrix metalloproteinase-1 during T lymphoma/endothelial cell contact: implication of ICAM-1, J. Immunol. 160 (1998) 2967–2973.
[170] A.M. Romanic, J.A. Madri, The induction of 72-kD gelatinase in T cells upon adhesion to endothelial cells is VCAM-1 dependent, J. Cell Biol. 125 (1994) 1165–1178.
[171] N. Malik, B.W. Greenfield, A.F. Wahl, P.A. Kiener, Activation of human monocytes through CD40 induces matrix metalloproteinases, J. Immunol. 156 (1996) 3952–3960.
[172] M. Kajita, Y. Itoh, T. Chiba, H. Mori, A. Okada, H. Kinoh, M. Seiki, Membrane-type 1 matrix metalloproteinase cleaves CD44 and promotes cell migration, J. Cell Biol. 153 (2001) 893–904.
[173] M.P. Vincenti, C.E. Brinckerhoff, Signal transduction and cell-type specific regulation of matrix metalloproteinase gene expression: can MMPs be good for you? J. Cell. Physiol. 213 (2007) 355–364.
[174] L.G. Hudson, N.M. Moss, M.S. Stack, EGF-receptor regulation of matrix metalloproteinases in epithelial ovarian carcinoma, Future Oncol. 5 (2009) 323–338.
[175] W. Eberhardt, T. Beeg, K.F. Beck, S. Walpen, S. Gauer, H. Bohles, J. Pfeilschifter, Nitric oxide modulates expression of matrix metalloproteinase-9 in rat mesangial cells, Kidney Int. 57 (2000) 59–69.
[176] C.Y. Shin, W.J. Lee, J.W. Choi, M.S. Choi, J.R. Ryu, S.J. Oh, J.H. Cheong, E.Y. Choi, K.H. Ko, Down-regulation of matrix metalloproteinase-9 expression by nitric oxide in lipopolysaccharide-stimulated rat primary astrocytes, Nitric Oxide 16 (2007) 425–432.
[177] C. Jespersen, A. Doller, S. Akool el, M. Bachmann, R. Muller, P. Gutwein, H. Muhl, J. Pfeilschifter, W. Eberhardt, Molecular mechanisms of nitric oxide-dependent inhibition of TPA-induced matrix metalloproteinase-9 (MMP-9) in MCF-7 cells, J. Cell. Physiol. 219 (2009) 276–287.
[178] T. Okamoto, G. Valacchi, K. Gohil, T. Akaike, A. van der Vliet, S-nitrosothiols inhibit cytokine-mediated induction of matrix metalloproteinase-9 in airway epithelial cells, Am. J. Respir. Cell Mol. Biol. 27 (2002) 463–473.
[179] I. Sinha, K.K. Hannawa, G. Ailawadi, D.T. Woodrum, J.W. Ford, P.K. Henke, J.C. Stanley, M.J. Eagleton, G.R. Upchurch Jr., The nitric oxide donor DETA-NONOate decreases matrix metalloproteinase-9 expression and activity in rat aortic smooth muscle and abdominal aortic explants, Ann. Vasc. Surg. 20 (2006) 92–98.
[180] Y. Huang, M.Q. Lu, H. Li, C. Xu, S.H. Yi, G.H. Chen, Occurrence of cGMP/nitric oxide-sensitive store-operated calcium entry in fibroblasts and its effect on matrix metalloproteinase secretion, World J. Gastroenterol. 12 (2006) 5483–5489.
[181] M.V. Gurjar, J. DeLeon, R.V. Sharma, R.C. Bhalla, Mechanism of inhibition of matrix metalloproteinase-9 induction by NO in vascular smooth muscle cells, J. Appl. Physiol. 91 (2001) 1380–1386.
[182] G.R. Upchurch Jr., J.W. Ford, S.J. Weiss, B.S. Knipp, D.A. Peterson, R.W. Thompson, M.J. Eagleton, A.J. Broady, M.C. Proctor, J.C. Stanley, Nitric oxide inhibition increases matrix metalloproteinase-9 expression by rat aortic smooth muscle cells in vitro, J. Vasc. Surg. 34 (2001) 76–83.
[183] B.S. Knipp, G. Ailawadi, J.W. Ford, D.A. Peterson, M.J. Eagleton, K.J. Roelofs, K.K. Hannawa, M.P. Deogracias, B. Ji, C. Logsdon, K.D. Graziano, D.M. Simeone, R.W. Thompson, P.K. Henke, J.C. Stanley, G.R. Upchurch Jr., Increased MMP-9 expression and activity by aortic smooth muscle cells after nitric oxide synthase inhibition is associated with increased nuclear factor-kappaB and activator protein-1 activity, J. Surg. Res. 116 (2004) 70–80.
[184] M.J. Eagleton, D.A. Peterson, V.V. Sullivan, K.J. Roelofs, J.A. Ford, J.C. Stanley, G.R. Upchurch Jr., Nitric oxide inhibition increases aortic wall matrix metalloproteinase-9 expression, J. Surg. Res. 104 (2002) 15–21.
[185] M.W. Radomski, S. Moncada, The biological and pharmacological role of nitric oxide in platelet function, Adv. Exp. Med. Biol. 344 (1993) 251–264.
[186] C. Fernandez-Patron, M.A. Martinez-Cuesta, E. Salas, G. Sawicki, M. Wozniak, M.W. Radomski, S.T. Davidge, Differential regulation of platelet aggregation by matrix metalloproteinases-9 and -2, Thromb. Haemost. 82 (1999) 1730–1735.
[187] F. Lindenmeyer, Y. Legrand, S. Menashi, Upregulation of MMP-9 expression in MDA-MB231 tumor cells by platelet granular membrane, FEBS Lett. 418 (1997) 19–22.
[188] C. Belloc, H. Lu, C. Soria, R. Fridman, Y. Legrand, S. Menashi, The effect of platelets on invasiveness and protease production of human mammary tumor cells, Int. J. Cancer 60 (1995) 413–417.
[189] T. Hamada, S. Duarte, S. Tsuchihashi, R.W. Busuttil, A.J. Coito, Inducible nitric oxide synthase deficiency impairs matrix metalloproteinase-9 activity and disrupts leukocyte migration in hepatic ischemia/reperfusion injury, Am. J. Pathol. 174 (2009) 2265–2277.
[190] M. Marcet-Palacios, K. Graham, C. Cass, A.D. Befus, I. Mayers, M.W. Radomski, Nitric oxide and cyclic GMP increase the expression of matrix metalloproteinase-9 in vascular smooth muscle, J. Pharmacol. Exp. Ther. 307 (2003) 429–436.
[191] S. Babykutty, P. Suboj, P. Srinivas, A.S. Nair, K. Chandramohan, S. Gopala, Insidious role of nitric oxide in migration/invasion of colon cancer cells by upregulating MMP-2/9 via activation of cGMP-PKG-ERK signaling pathways, Clin. Exp. Metastasis 29 (2012) 471–492.
[192] Y. Chen, Y. Aratani, T. Osawa, N. Fukuyama, C. Tsuji, H. Nakazawa, Activation of inducible nitric oxide synthase increases MMP-2 and MMP-9 levels in ApoE-knockout mice, Tokai J. Exp. Clin. Med. 33 (2008) 28–34.
[193] Y. Gursoy-Ozdemir, A. Can, T. Dalkara, Reperfusion-induced oxidative/nitrative injury to neurovascular unit after focal cerebral ischemia, Stroke 35 (2004) 1449–1453.
[194] Y. Gursoy-Ozdemir, H. Bolay, O. Saribas, T. Dalkara, Role of endothelial nitric oxide generation and peroxynitrite formation in reperfusion injury after focal cerebral ischemia, Stroke 31 (2000) 1974–1980[discussion 1981].
[195] L.A. Ridnour, S. Dhanapal, M. Hoos, J. Wilson, J. Lee, R.Y. Cheng, E.E. Brueggemann, H.B. Hines, D.M. Wilcock, M.P. Vitek, D.A. Wink, C.A. Colton, Nitric oxide-mediated regulation of beta-amyloid clearance via alterations of MMP-9/TIMP-1, J. Neurochem. 123 (2012) 736–749.
[196] F. Han, H.G. Zhu, Caveolin-1 regulating the invasion and expression of matrix metalloproteinase (MMPs) in pancreatic carcinoma cells, J. Surg. Res. 159 (2010) 443–450.
[197] Y. Gu, G. Zheng, M. Xu, Y. Li, X. Chen, W. Zhu, Y. Tong, S.K. Chung, K.J. Liu, J. Shen, Caveolin-1 regulates nitric oxide-mediated matrix metalloproteinases activity and blood–brain barrier permeability in focal cerebral ischemia and reperfusion injury, J. Neurochem. 120 (2012) 147–156.
[198] P. Huhtala, A. Tuuttila, L.T. Chow, J. Lohi, J. Keski-Oja, K. Tryggvason, Complete structure of the human gene for 92-kDa type IV collagenase. Divergent regulation of expression for the 92- and 72-kilodalton enzyme genes in HT-1080 cells, J. Biol. Chem. 266 (1991) 16485–16490.
[199] R. Gum, E. Lengyel, J. Juarez, J.H. Chen, H. Sato, M. Seiki, D. Boyd, Stimulation of 92-kDa gelatinase B promoter activity by ras is mitogen-activated protein kinase kinase 1-independent and requires multiple transcription factor binding sites including closely spaced PEA3/ets and AP-1 sequences, J. Biol. Chem. 271 (1996) 10672–10680.
[200] Y. St-Pierre, C. Van Themsche, P.O. Esteve, Emerging features in the regulation of MMP-9 gene expression for the development of novel molecular targets and therapeutic strategies, Curr. Drug Targets Inflamm. Allergy 2 (2003) 206–215.
[201] Y. St-Pierre, J. Couillard, C. Van Themsche, Regulation of MMP-9 gene expression for the development of novel molecular targets against cancer and inflammatory diseases, Expert Opin. Ther. Targets 8 (2004) 473–489.
[202] S. Muhlen, A. Behren, T. Iftner, P.K. Plinkert, C. Simon, AP-1 and ERK1 but not p38 nor JNK is required for CRPV early protein 2-dependent MMP-9 promoter activation in rabbit epithelial cells, Virus Res. 139 (2009) 100–105.
[203] C. Simon, M. Simon, G. Vucelic, M.J. Hicks, P.K. Plinkert, A. Koitschev, H.P. Zenner, The p38 SAPK pathway regulates the expression of the MMP-9 collagenase via AP-1-dependent promoter activation, Exp. Cell Res. 271 (2001) 344–355.
[204] X. Zhao, E.N. Benveniste, Transcriptional activation of human matrix metalloproteinase-9 gene expression by multiple co-activators, J. Mol. Biol. 383 (2008) 945–956.
[205] R. Gum, H. Wang, E. Lengyel, J. Juarez, D. Boyd, Regulation of 92 kDa type IV collagenase expression by the jun aminoterminal kinase- and the extracellular signal-regulated kinase-dependent signaling cascades, Oncogene 14 (1997) 1481–1493.
[206] M. Shin, C. Yan, D. Boyd, An inhibitor of c-jun aminoterminal kinase (SP600125) represses c-Jun activation, DNA-binding and PMA-inducible 92-kDa type IV collagenase expression, Biochim. Biophys. Acta 1589 (2002) 311–316.
[207] C. Simon, H. Goepfert, D. Boyd, Inhibition of the p38 mitogen-activated protein kinase by SB 203580 blocks PMA-induced Mr 92,000 type IV collagenase secretion and in vitro invasion, Cancer Res. 58 (1998) 1135–1139.
[208] A.S. Baldwin Jr., The NF-kappa B and I kappa B proteins: new discoveries and insights, Annu. Rev. Immunol. 14 (1996) 649–683.
[209] E.B. Traenckner, H.L. Pahl, T. Henkel, K.N. Schmidt, S. Wilk, P.A. Baeuerle, Phosphorylation of human I kappa B-alpha on serines 32 and 36 controls I kappa B-alpha proteolysis and NF-kappa B activation in response to diverse stimuli, EMBO J. 14 (1995) 2876–2883.
[210] W. Eberhardt, A. Huwiler, K.F. Beck, S. Walpen, J. Pfeilschifter, Amplification of IL-1 beta-induced matrix metalloproteinase-9 expression by superoxide in rat glomerular mesangial cells is mediated by increased activities of NF-kappa B and activating protein-1 and involves activation of the mitogen-activated protein kinase pathways, J. Immunol. 165 (2000) 5788–5797.
[211] M. Bond, R.P. Fabunmi, A.H. Baker, A.C. Newby, Synergistic upregulation of metalloproteinase-9 by growth factors and inflammatory cytokines: an absolute requirement for transcription factor NF-kappa B, FEBS Lett. 435 (1998) 29–34.
[212] M. Bond, A.J. Chase, A.H. Baker, A.C. Newby, Inhibition of transcription factor NF-kappaB reduces matrix metalloproteinase-1, -3 and -9 production by vascular smooth muscle cells, Cardiovasc. Res. 50 (2001) 556–565.
[213] Y.M. Janssen-Heininger, M.E. Poynter, P.A. Baeuerle, Recent advances towards understanding redox mechanisms in the activation of nuclear factor kappaB, Free Radic. Biol. Med. 28 (2000) 1317–1327.

[214] G. Dijkstra, H. Moshage, P.L. Jansen, Blockade of NF-kappaB activation and donation of nitric oxide: new treatment options in inflammatory bowel disease? Scand. J. Gastroenterol. Suppl. (2002) 37–41.
[215] H.E. Marshall, J.S. Stamler, Inhibition of NF-kappa B by S-nitrosylation, Biochemistry 40 (2001) 1688–1693.
[216] A. delaTorre, R.A. Schroeder, C. Punzalan, P.C. Kuo, Endotoxin-mediated S-nitrosylation of p50 alters NF-kappa B-dependent gene transcription in ANA-1 murine macrophages, J. Immunol. 162 (1999) 4101–4108.
[217] S.K. Park, H.L. Lin, S. Murphy, Nitric oxide regulates nitric oxide synthase-2 gene expression by inhibiting NF-kappaB binding to DNA, Biochem. J. 322 (Pt 2) (1997) 609–613.
[218] K. Katsuyama, M. Shichiri, F. Marumo, Y. Hirata, NO inhibits cytokine-induced iNOS expression and NF-kappaB activation by interfering with phosphorylation and degradation of IkappaB-alpha, Arterioscler. Thromb. Vasc. Biol. 18 (1998) 1796–1802.
[219] V. Umansky, S.P. Hehner, A. Dumont, T.G. Hofmann, V. Schirrmacher, W. Droge, M.L. Schmitz, Co-stimulatory effect of nitric oxide on endothelial NF-kappaB implies a physiological self-amplifying mechanism, Eur. J. Immunol. 28 (1998) 2276–2282.
[220] H.M. Lander, D.P. Hajjar, B.L. Hempstead, U.A. Mirza, B.T. Chait, S. Campbell, L.A. Quilliam, A molecular redox switch on p21(ras). Structural basis for the nitric oxide-p21(ras) interaction, J. Biol. Chem. 272 (1997) 4323–4326.
[221] H. Sugiura, H. Kawabata, T. Ichikawa, A. Koarai, S. Yanagisawa, T. Kikuchi, Y. Minakata, K. Matsunaga, M. Nakanishi, T. Hirano, K. Akamatsu, K. Furukawa, M. Ichinose, Inhibitory effects of theophylline on the peroxynitrite-augmented release of matrix metalloproteinases by lung fibroblasts, Am. J. Physiol. Lung Cell. Mol. Physiol. 302 (2012) L764–L774.
[222] N. Tobar, V. Villar, J.F. Santibanez, ROS-NFkappaB mediates TGF-beta1-induced expression of urokinase-type plasminogen activator, matrix metalloproteinase-9 and cell invasion, Mol. Cell. Biochem. 340 (2010) 195–202.
[223] C.A. Meschiari, T. Izidoro-Toledo, R.F. Gerlach, J.E. Tanus-Santos, Nitric oxide attenuates matrix metalloproteinase-9 production by endothelial cells independent of cGMP- or NFkappaB-mediated mechanisms, Mol. Cell. Biochem. 378 (2013) 127–135.
[224] E. Shaulian, M. Karin, AP-1 as a regulator of cell life and death, Nat. Cell Biol. 4 (2002) E131–E136.
[225] H. Sato, M. Seiki, Regulatory mechanism of 92 kDa type IV collagenase gene expression which is associated with invasiveness of tumor cells, Oncogene 8 (1993) 395–405.
[226] C. Abate, L. Patel, F.J. Rauscher III, T. Curran, Redox regulation of fos and jun DNA-binding activity in vitro, Science 249 (1990) 1157–1161.
[227] D. Nikitovic, A. Holmgren, G. Spyrou, Inhibition of AP-1 DNA binding by nitric oxide involving conserved cysteine residues in Jun and Fos, Biochem. Biophys. Res. Commun. 242 (1998) 109–112.
[228] G.P. Ahern, V.A. Klyachko, M.B. Jackson, cGMP and S-nitrosylation: two routes for modulation of neuronal excitability by NO, Trends Neurosci. 25 (2002) 510–517.
[229] H.E. Marshall, K. Merchant, J.S. Stamler, Nitrosation and oxidation in the regulation of gene expression, FASEB J. 14 (2000) 1889–1900.
[230] M.V. Gurjar, R.V. Sharma, R.C. Bhalla, eNOS gene transfer inhibits smooth muscle cell migration and MMP-2 and MMP-9 activity, Arterioscler. Thromb. Vasc. Biol. 19 (1999) 2871–2877.
[231] M. Marcet-Palacios, M. Ulanova, F. Duta, L. Puttagunta, S. Munoz, D. Gibbings, M. Radomski, L. Cameron, I. Mayers, A.D. Befus, The transcription factor Wilms tumor 1 regulates matrix metalloproteinase-9 through a nitric oxide-mediated pathway, J. Immunol. 179 (2007) 256–265.
[232] T.P. Garrington, G.L. Johnson, Organization and regulation of mitogen-activated protein kinase signaling pathways, Curr. Opin. Cell Biol. 11 (1999) 211–218.
[233] H.S. Park, S.H. Huh, M.S. Kim, S.H. Lee, E.J. Choi, Nitric oxide negatively regulates c-Jun N-terminal kinase/stress-activated protein kinase by means of S-nitrosylation, Proc. Natl. Acad. Sci. U. S. A. 97 (2000) 14382–14387.
[234] D.S. Pei, Y.J. Song, H.M. Yu, W.W. Hu, Y. Du, G.Y. Zhang, Exogenous nitric oxide negatively regulates c-Jun N-terminal kinase activation via inhibiting endogenous NO-induced S-nitrosylation during cerebral ischemia and reperfusion in rat hippocampus, J. Neurochem. 106 (2008) 1952–1963.
[235] H.S. Park, S.H. Huh, M.S. Kim, D.Y. Kim, B.J. Gwag, S.G. Cho, E.J. Choi, Neuronal nitric oxide synthase (nNOS) modulates the JNK1 activity through redox mechanism: a cGMP independent pathway, Biochem. Biophys. Res. Commun. 346 (2006) 408–414.
[236] H.S. Park, J.S. Mo, E.J. Choi, Nitric oxide inhibits an interaction between JNK1 and c-Jun through nitrosylation, Biochem. Biophys. Res. Commun. 351 (2006) 281–286.
[237] J. Fan, X. Yang, W. Wang, W.H. Wood III, K.G. Becker, M. Gorospe, Global analysis of stress-regulated mRNA turnover by using cDNA arrays, Proc. Natl. Acad. Sci. U. S. A. 99 (2002) 10611–10616.
[238] T. Kawai, J. Fan, K. Mazan-Mamczarz, M. Gorospe, Global mRNA stabilization preferentially linked to translational repression during the endoplasmic reticulum stress response, Mol. Cell. Biol. 24 (2004) 6773–6787.
[239] C.J. Wilusz, M. Wormington, S.W. Peltz, The cap-to-tail guide to mRNA turnover, Nat. Rev. Mol. Cell Biol. 2 (2001) 237–246.
[240] C.Y. Chen, A.B. Shyu, AU-rich elements: characterization and importance in mRNA degradation, Trends Biochem. Sci. 20 (1995) 465–470.
[241] X.C. Fan, J.A. Steitz, Overexpression of HuR, a nuclear-cytoplasmic shuttling protein, increases the in vivo stability of ARE-containing mRNAs, EMBO J. 17 (1998) 3448–3460.
[242] S.S. Peng, C.Y. Chen, N. Xu, A.B. Shyu, RNA stabilization by the AU-rich element binding protein, HuR, an ELAV protein, EMBO J. 17 (1998) 3461–3470.
[243] Y. Kuwano, A. Rabinovic, S. Srikantan, M. Gorospe, B. Demple, Analysis of nitric oxide-stabilized mRNAs in human fibroblasts reveals HuR-dependent heme oxygenase 1 upregulation, Mol. Cell. Biol. 29 (2009) 2622–2635.
[244] N. Abdelaziz, F. Colombo, I. Mercier, A. Calderone, Nitric oxide attenuates the expression of transforming growth factor-beta(3) mRNA in rat cardiac fibroblasts via destabilization, Hypertension 38 (2001) 261–266.
[245] V. Raoch, F. Rodriguez-Pascual, V. Lopez-Martinez, D. Medrano-Andres, M. Rodriguez-Puyol, S. Lamas, D. Rodriguez-Puyol, S. Lopez-Ongil, Nitric oxide decreases the expression of endothelin-converting enzyme-1 through mRNA destabilization, Arterioscler. Thromb. Vasc. Biol. 31 (2011) 2577–2585.
[246] S. Wang, J. Zhang, Y. Zhang, S. Kern, R.L. Danner, Nitric oxide-p38 MAPK signaling stabilizes mRNA through AU-rich element-dependent and -independent mechanisms, J. Leukoc. Biol. 83 (2008) 982–990.
[247] F. Rodriguez-Pascual, M. Hausding, I. Ihrig-Biedert, H. Furneaux, A.P. Levy, U. Forstermann, H. Kleinert, Complex contribution of the 3′-untranslated region to the expressional regulation of the human inducible nitric-oxide synthase gene. Involvement of the RNA-binding protein HuR, J. Biol. Chem. 275 (2000) 26040–26049.
[248] S. Kloss, R. Srivastava, A. Mulsch, Down-regulation of soluble guanylyl cyclase expression by cyclic AMP is mediated by mRNA-stabilizing protein HuR, Mol. Pharmacol. 65 (2004) 1440–1451.
[249] S. Kloss, H. Furneaux, A. Mulsch, Post-transcriptional regulation of soluble guanylyl cyclase expression in rat aorta, J. Biol. Chem. 278 (2003) 2377–2383.
[250] Y.S. Hwang, K.K. Park, W.Y. Chung, Kalopanaxsaponin A inhibits the invasion of human oral squamous cell carcinoma by reducing metalloproteinase-9 mRNA stability and protein trafficking, Biol. Pharm. Bull. 35 (2012) 289–300.
[251] A. Huwiler, S. Akool el, A. Aschrafi, F.M. Hamada, J. Pfeilschifter, W. Eberhardt, ATP potentiates interleukin-1 beta-induced MMP-9 expression in mesangial cells via recruitment of the ELAV protein HuR, J. Biol. Chem. 278 (2003) 51758–51769.
[252] S. Akool el, H. Kleinert, F.M. Hamada, M.H. Abdelwahab, U. Forstermann, J. Pfeilschifter, W. Eberhardt, Nitric oxide increases the decay of matrix metalloproteinase 9 mRNA by inhibiting the expression of mRNA-stabilizing factor HuR, Mol. Cell. Biol. 23 (2003) 4901–4916.
[253] W. Eberhardt, S. Akool el, J. Rebhan, S. Frank, K.F. Beck, R. Franzen, F.M. Hamada, J. Pfeilschifter, Inhibition of cytokine-induced matrix metalloproteinase 9 expression by peroxisome proliferator-activated receptor alpha agonists is indirect and due to a NO-mediated reduction of mRNA stability, J. Biol. Chem. 277 (2002) 33518–33528.
[254] W. Liu, G.A. Rosenberg, K.J. Liu, AUF-1 mediates inhibition by nitric oxide of lipopolysaccharide-induced matrix metalloproteinase-9 expression in cultured astrocytes, J. Neurosci. Res. 84 (2006) 360–369.
[255] M.D. Sternlicht, G. Bergers, Matrix metalloproteinases as emerging targets in anticancer therapy: status and prospects, Expert Opin. Ther. Targets 4 (2000) 609–633.
[256] I. Stamenkovic, Extracellular matrix remodelling: the role of matrix metalloproteinases, J. Pathol. 200 (2003) 448–464.
[257] L.M. Coussens, Z. Werb, Matrix metalloproteinases and the development of cancer, Chem. Biol. 3 (1996) 895–904.
[258] S. Vosseler, W. Lederle, K. Airola, E. Obermueller, N.E. Fusenig, M.M. Mueller, Distinct progression-associated expression of tumor and stromal MMPs in HaCaT skin SCCs correlates with onset of invasion, Int. J. Cancer 125 (2009) 2296–2306.
[259] E.L. Williams, M.B. Djamgoz, Nitric oxide and metastatic cell behaviour, Bioessays 27 (2005) 1228–1238.
[260] J.M. Weiss, L.A. Ridnour, T. Back, S.P. Hussain, P. He, A.E. Maciag, L.K. Keefer, W.J. Murphy, C.C. Harris, D.A. Wink, R.H. Wiltrout, Macrophage-dependent nitric oxide expression regulates tumor cell detachment and metastasis after IL-2/anti-CD40 immunotherapy, J. Exp. Med. 207 (2010) 2455–2467.
[261] B. Rigas, K. Kashfi, Nitric-oxide-donating NSAIDs as agents for cancer prevention, Trends Mol. Med. 10 (2004) 324–330.
[262] R.K. Yeh, J. Chen, J.L. Williams, M. Baluch, T.R. Hundley, R.E. Rosenbaum, S. Kalala, F. Traganos, F. Benardini, P. del Soldato, K. Kashfi, B. Rigas, NO-donating nonsteroidal antiinflammatory drugs (NSAIDs) inhibit colon cancer cell growth more potently than traditional NSAIDs: a general pharmacological property? Biochem. Pharmacol. 67 (2004) 2197–2205.
[263] J.L. Williams, K. Kashfi, N. Ouyang, P. del Soldato, L. Kopelovich, B. Rigas, NO-donating aspirin inhibits intestinal carcinogenesis in Min (APC(Min/+)) mice, Biochem. Biophys. Res. Commun. 313 (2004) 784–788.
[264] G.R. Thatcher, A.C. Nicolescu, B.M. Bennett, V. Toader, Nitrates and NO release: contemporary aspects in biological and medicinal chemistry, Free Radic. Biol. Med. 37 (2004) 1122–1143.
[265] S. Fiorucci, E. Antonelli, E. Distrutti, P. Del Soldato, R.J. Flower, M.J. Clark, A. Morelli, M. Perretti, L.J. Ignarro, NCX-1015, a nitric-oxide derivative of prednisolone, enhances regulatory T cells in the lamina propria and protects against 2,4,6-trinitrobenzene sulfonic acid-induced colitis in mice, Proc. Natl. Acad. Sci. U. S. A. 99 (2002) 15770–15775.
[266] M.J. Paul-Clark, L. Mancini, P. Del Soldato, R.J. Flower, M. Perretti, Potent antiarthritic properties of a glucocorticoid derivative, NCX-1015, in an experimental model of arthritis, Proc. Natl. Acad. Sci. U. S. A. 99 (2002) 1677–1682.
[267] F. Turesin, P. del Soldato, J.L. Wallace, Enhanced anti-inflammatory potency of a nitric oxide-releasing prednisolone derivative in the rat, Br. J. Pharmacol. 139 (2003) 966–972.
[268] V. Lagente, C. Advenier, New nitric oxide-donating drugs for the treatment of airway diseases, Curr. Opin. Investig. Drugs 5 (2004) 537–541.
[269] V. Lagente, E. Naline, I. Guenon, M. Corbel, E. Boichot, J.L. Burgaud, P. Del Soldato, C. Advenier, A nitric oxide-releasing salbutamol elicits potent relaxant and anti-inflammatory activities, J. Pharmacol. Exp. Ther. 310 (2004) 367–375.

[270] D.L. Turner, N. Ferrari, W.R. Ford, E.J. Kidd, L. Paquet, P. Renzi, K.J. Broadley, TPI 1020, a novel anti-inflammatory, nitric oxide donating compound, potentiates the bronchodilator effects of salbutamol in conscious guinea-pigs, Eur. J. Pharmacol. 641 (2010) 213–219.
[271] N. Marsh, A. Marsh, A short history of nitroglycerine and nitric oxide in pharmacology and physiology, Clin. Exp. Pharmacol. Physiol. 27 (2000) 313–319.
[272] A.S. Krishnatry, T. Kamei, H. Wang, J. Qu, H.L. Fung, Identification of nitroglycerin-induced cysteine modifications of pro-matrix metalloproteinase-9, Rapid Commun. Mass Spectrom. 25 (2011) 2291–2298.
[273] A.S. Krishnatry, S.M. Fung, D.A. Brazeau, D. Soda, H.L. Fung, Nitroglycerin alters matrix remodeling proteins in THP-1 human macrophages and plasma metalloproteinase activity in rats, Nitric Oxide 24 (2011) 66–76.
[274] A.K. Death, S. Nakhla, K.C. McGrath, S. Martell, D.K. Yue, W. Jessup, D.S. Celermajer, Nitroglycerin upregulates matrix metalloproteinase expression by human macrophages, J. Am. Coll. Cardiol. 39 (2002) 1943–1950.
[275] J. Wang, S. O'Sullivan, S. Harmon, R. Keaveny, M.W. Radomski, C. Medina, J.F. Gilmer, Design of barbiturate–nitrate hybrids that inhibit MMP-9 activity and secretion, J. Med. Chem. 55 (2012) 2154–2162.
[276] S. Huerta, S. Chilka, B. Bonavida, Nitric oxide donors: novel cancer therapeutics (review), Int. J. Oncol. 33 (2008) 909–927.
[277] H.T. Chung, H.O. Pae, B.M. Choi, T.R. Billiar, Y.M. Kim, Nitric oxide as a bioregulator of apoptosis, Biochem. Biophys. Res. Commun. 282 (2001) 1075–1079.
[278] J.S. Beckman, T.W. Beckman, J. Chen, P.A. Marshall, B.A. Freeman, Apparent hydroxyl radical production by peroxynitrite: implications for endothelial injury from nitric oxide and superoxide, Proc. Natl. Acad. Sci. U. S. A. 87 (1990) 1620–1624.
[279] J.B. Mannick, C.M. Schonhoff, Nitrosylation: the next phosphorylation? Arch. Biochem. Biophys. 408 (2002) 1–6.
[280] B.J. Whittle, Nitric oxide and the gut injury induced by non-steroidal anti-inflammatory drugs, Inflammopharmacology 11 (2003) 415–422.
[281] T.L. Wellman, J. Jenkins, P.L. Penar, B. Tranmer, R. Zahr, K.M. Lounsbury, Nitric oxide and reactive oxygen species exert opposing effects on the stability of hypoxia-inducible factor-1alpha (HIF-1alpha) in explants of human pial arteries, FASEB J. 18 (2004) 379–381.
[282] S.B. Abramson, Nitric oxide in inflammation and pain associated with osteoarthritis, Arthritis Res. Ther. 10 (Suppl. 2) (2008) S2.
[283] M.A. Moro, V.M. Darley-Usmar, I. Lizasoain, Y. Su, R.G. Knowles, M.W. Radomski, S. Moncada, The formation of nitric oxide donors from peroxynitrite, Br. J. Pharmacol. 116 (1995) 1999–2004.
[284] E. Darra, A. Rungatscher, A. Carcereri de Prati, B.K. Podesser, G. Faggian, T. Scarabelli, A. Mazzucco, S. Hallstrom, H. Suzuki, Dual modulation of nitric oxide production in the heart during ischaemia/reperfusion injury and inflammation, Thromb. Haemost. 104 (2010) 200–206.
[285] G.A. Blaise, D. Gauvin, M. Gangal, S. Authier, Nitric oxide, cell signaling and cell death, Toxicology 208 (2005) 177–192.