Occasional review

Matrix metalloproteases and lung disease

C M O'Connor, M X FitzGerald

Development, tissue remodelling, cell migration, inflammation, angiogenesis, and wound healing are just some of the physiological processes in which the matrix metalloproteases (MMPs), a family of highly homologous endopeptidases, play a crucial part. Collectively the MMPs can cleave most, if not all, the protein constituents of the extracellular matrix including collagen, proteoglycan, laminin, fibronectin, and elastin. In so doing they facilitate cell movement, reorientation, and dispersal. The production and action of the MMPs are subject to strict control, ensuring limited proteolysis of the extracellular matrix during cell migration, tissue remodelling and repair. Inadequate regulation of MMP production or action has, however, been implicated in a wide range of pathological processes including several lung diseases, rheumatoid arthritis, periodontal and renal diseases, osteoarthritis, fibrotic disorders, and tumour invasion.

Recent studies elucidating (1) the sequence homologies between members of the MMP family, (2) factors involved in the regulation of MMP expression, and (3) mechanisms of MMP activation and inhibition have added considerably to our knowledge of the crucial control mechanisms which can tip the balance of MMP action from normal homoeostasis to pathological process. In this review the salient features of the action and regulation of MMPs which contribute to their role in normal and diseased states will be outlined and evidence for their participation in lung disease discussed.

The matrix metalloproteases (MMPs)
Nine members of the MMP family have been identified. All are produced and secreted in a latent, proenzyme form. They require Zn\(^{2+}\) and Ca\(^{2+}\) ions for activity and are inhibited by a group of specific inhibitors—the tissue inhibitors of metalloproteases (TIMPs). Initially characterised and classified on the basis of their different substrate specificities and molecular weights (table 1), individual MMPs have been given various names by different groups. The International Union of Biochemistry and Molecular Biology has recently recommended a standardised system of nomenclature which will be used in this review. Alternative names are cited in table 1. The cDNA predicted amino acid sequence of the MMPs reflects a high degree of homology between family members. Three functional domains are evident: a peptidase domain which codes for the peptide released upon activation of the proenzyme; a catalytic domain containing the Zn\(^{2+}\) binding site; and a C-terminal domain which exhibits some homology with hemopexin and vironectin (fig

Table 1

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Molecular weight (kDa)</th>
<th>ECM substrates</th>
<th>Other names†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interstitial collagenase (EC 3.4.24.7)</td>
<td>55</td>
<td>Collagens I, II, III (III &gt; I) VII, X, gelatin, proteoglycan (PG-core protein)</td>
<td>MMP-1</td>
</tr>
<tr>
<td>Neutrophil collagenase (EC 3.4.24.34)</td>
<td>75</td>
<td>Same as interstitial collagenase but VII &gt; III</td>
<td>MMP-8</td>
</tr>
<tr>
<td>Gelatinase B (EC 3.4.24.35)</td>
<td>92</td>
<td>Gelatins, collagen IV and V, elastin, PG-core protein</td>
<td>MMP-9</td>
</tr>
<tr>
<td>Stromelysin-1 (EC 3.4.24.17)</td>
<td>57</td>
<td>PG-core protein, laminin, fibronectin, elastin, collagen III, IV, IX, X, interstitial collagenase proenzyme</td>
<td>MMP-3</td>
</tr>
<tr>
<td>Stromelysin-2 (EC 3.4.24.22)</td>
<td>57</td>
<td>Same as stromelysin-1</td>
<td>MMP-10</td>
</tr>
<tr>
<td>Stromelysin-3</td>
<td>ND</td>
<td>PG-core protein, laminin, fibronectin, collagen IV, gelatin, interstitial collagenase proenzyme</td>
<td>MMP-11</td>
</tr>
<tr>
<td>Matrixilysin (EC 3.4.24.23)</td>
<td>28</td>
<td></td>
<td>MMP-7</td>
</tr>
<tr>
<td>Macrophage metalloelastase</td>
<td>55</td>
<td>Elastin, fibronectin</td>
<td>MMP-12</td>
</tr>
</tbody>
</table>

ECM = extracellular matrix. 
* Molecular weight of proenzyme form. 
† MMP numbering according to Nagase et al.19
preferentially degrades type I collagen whereas interstitial collagenase prefers a type III substrate.

The major in vivo role of the gelatinases was initially thought to be the digestion of gelatin peptides released from fibrillar collagen by the collagenases.22 It has since been shown that gelatinases degrade other collagen types, including native type IV collagen, the major constituent of cellular basement membranes.26 This has led to the suggestion that their major in vivo role may be the digestion of basement membranes during inflammatory cell migration and tumour invasion.27

While the gelatinases can also degrade elastin and fibronectin, the MMPs with the broadest substrate range are the stromelysins. They digest fibronectin, laminin, elastin, proteoglycan core protein, and several collagen types.16 An additional feature of stromelysin-1 is its ability to potentiate the activation of latent interstitial collagenase, suggesting a synergistic interaction between these MMPs.28

SOURCE OF MMPS

Interstitial collagenase is produced by a range of stromal cells including fibroblasts, endothelial cells, osteoblasts, keratinocytes, chondrocytes, and hepatocytes.1 Cells of the monocyte/macrophage lineage also produce this enzyme. In contrast, neutrophil collagenase is found only in polymorphonuclear leucocytes where it is produced during maturation and stored in intracellular granules prior to release.29

Gelatinase A and B also differ in their cellular distribution. Gelatinase B is the only form found in polymorphonuclear leucocytes and is also the major gelatinase produced by macrophages.30-31 By comparison, connective tissue cells preferentially produce gelatinase A, although transformed fibroblasts, cells of neoplastic origin and stromal cells surrounding tumours can produce both enzymes.12,32-35 It is suggested that fibroblasts may be induced to express gelatinase B by tumour derived factors.34

Stromelysins-1 and 2 are produced by various connective tissue cells and by macrophages. Distribution of stromelysin-3 is less well characterised. Similarly, while expression of matrixin has been observed in monocytes and cells of the involuting uterus,36 its distribution is, as yet, poorly defined.

REGULATION OF MMP PRODUCTION BY CYTOKINES

In stromal cells MMP production is regulated at transcriptional level by a range of cytokines which influence the production and stability of MMP mRNAs (table 2). Expression of interstitial collagenase and stromelysin-1 is coordinately upregulated by interleukin 1 (IL-1), tumour necrosis factor α (TNFα), platelet derived growth factor (PDGF), endothelial growth factor (EGF), basic fibroblast growth factor (bFGF), neural growth factor (NGF), and the phorbol ester tumour promoters.18
Table 3  Differential degradation of neutrophils in response to various stimuli\(^{45-50}\)

<table>
<thead>
<tr>
<th>Stimulus for degradation</th>
<th>Granule type</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primary (elastase)</td>
</tr>
<tr>
<td>FMLP:</td>
<td>-</td>
</tr>
<tr>
<td>&lt;10(^{-6}) mol/l</td>
<td>-</td>
</tr>
<tr>
<td>&gt;10(^{-6}) mol/l</td>
<td>-</td>
</tr>
<tr>
<td>Ca(^{2+}) ionophore:</td>
<td>-</td>
</tr>
<tr>
<td>&lt;0.1 mol/l</td>
<td>-</td>
</tr>
<tr>
<td>&gt;0.5 mol/l</td>
<td>+</td>
</tr>
<tr>
<td>Fluoride (20 \mu mol/l)</td>
<td>-</td>
</tr>
<tr>
<td>Interleukin-8 (0.3 units/ml)</td>
<td>-</td>
</tr>
<tr>
<td>TNFα (1.0 \mu mol/l)</td>
<td>-</td>
</tr>
</tbody>
</table>

FMLP = f-Met-Leu-Phe; TNFα = tumour necrosis factor.

Many of these cytokines also enhance production of TIMP-1 (table 2). This co-expression of enzyme and inhibitor may be important in confining degradation of extracellular matrix to areas close to the protease producing cell. In polarised cells MMPs exhibit a directional preference for secretion - for example, endothelial cells secrete MMPs from their basal compartment and not into the apical lumen.\(^{37}\) In cell migration it is suggested that enzyme and inhibitor may be generated at different sites to enhance directional movement of the cell.\(^{9}\) Most authors report the downregulation of interstitial collagenase and stromelysin-1 gene expression by transforming growth factor β (TGFβ), interferon γ (IFNγ) and IL-4. TGFβ also abrogates the effects of IL-1, TNFα, EGF, and BFGF on the expression of both these genes.\(^{38}\) TIMP-1 expression is enhanced by TGFβ, as is the production of collagen, fibronectin, proteoglycans, and glycosaminoglycans.\(^{39}\) Thus, the overall effects of TGFβ is to enhance interstitial matrix formation by increasing production of matrix components, decreasing production of interstitial collagenase and stromelysin-1, and increasing production of TIMP-1. The effect of TGFβ on basement membrane components may be somewhat different. Recent studies indicate that expression of the gelatinases by fibroblasts and keratinocytes is significantly increased by TGFβ.\(^{39-41}\) Expression of TIMP-2, which is a more effective inhibitor of the gelatinases than TIMP-1, is also upregulated by TGFβ.\(^{42-43}\) These effects may be of significance in regulating cell detachment from basement membranes during wound healing and tumour invasion.

Pharmacological modulation of stromal cell MMP production is observed with retinoids and corticosteroids.\(^{44}\) Both decrease transcription of interstitial collagenase and stromelysin-1. The retinoids also enhance TIMP-1 production.\(^{44}\) The effects of these agents on gelatinase expression is not, as yet, defined.

MMP RELEASE FROM NEUTROPHILS

Neutrophil MMPs are stored in intracellular granules and released upon stimulation. Control of neutrophil MMP production is therefore governed by factors which affect neutrophil activation rather than gene transcription. Available evidence indicates that neutrophil collagenase and gelatinase B are stored in separate granules - collagenase in the secondary (or specific) granules and the gelatinase B in the tertiary granules.\(^{45-47}\) Although the contents of both granules are released upon neutrophil stimulation by a range of chemotactic and activation factors (table 3), gelatinase B release is observed at stimulus concentrations lower than those required to promote release of secondary granule contents. Sequential MMP release along a chemotactic gradient is therefore proposed.\(^{45-49}\) Exocytosis of MMP-containing granules is observed during neutrophil adherence and exudation suggesting that these enzymes play a part in neutrophil migration and connective tissue remodelling in early inflammation and wound healing.\(^{50}\)

MMP ACTIVATION

Activation of latent MMPs is a stepwise process involving destabilisation of the coordinate bond between the active size Zn\(^{2+}\) and a free cysteine in the conserved PRCG(V/N)PD propeptide sequence. This destabilisation induces a conformational change which unmasks the active site, leading to autolytic cleavage of the N-terminal propeptide (fig 2).\(^{51}\) In vitro a range of disparate reagents, including organomercurials and detergents, activate MMPs by disrupting the cystine–Zn\(^{2+}\) bond. Serine proteases activate MMPs by digesting part of the propeptide sequence which stabilises the cystine–Zn\(^{2+}\) bond. In the case of interstitial collagenase, the enzyme produced following activation by these agents can be further activated by stromelysin-1.\(^{13}\) The identity of the in vivo activators of the MMPs is still uncertain. The serine protease, plasmin, has been implicated in the activation of stromelysin-1 and interstitial collagenase, suggesting a cascade mechanism involving plasminogen, plasminogen activator, and stromelysin-1 in the activation of interstitial collagenase.\(^{52}\) Unlike the other MMPs, gelatinase A is not activated by serine proteases.\(^{16}\) This enzyme is activated by binding to a membrane associated protein which is sensitive to metalloprotease inhibitors and is induced by phorbol esters and TGFβ.\(^{53}\) Whether the membrane associated protein is itself a protease or acts by enhancing the autolytic activation of the gelatinase is not clear. Neutrophil collagenase and gelatinase can be activated by hypochlorous acid (HOCI), a pro-

Figure 2  Schematic representation of the proposed mechanism for activation of matrix metalloproteases

Conformational change

Latent proenzyme

Prevention of disulphide bond

Active enzyme

Activation by plasmin

Active enzyme

Autoinhibitory peptide

Active enzyme

OH₂

OH₂
duct of the respiratory burst which oxidises the Zn\textsuperscript{2+} chelating cystine. However, as activation of neutrophil MMPs can occur prior to, and independently of, the respiratory burst, the in vivo relevance of this activation mechanism remains speculative.

**MMP Inhibition**

The coordinated production of MMPs and their specific tissue inhibitors in a range of developing and remodelling situations suggest that TIMPs play a significant role in the regulation of MMP activation in vivo. Four TIMPs have been reported and two – TIMP-1 and TIMP-2 – have been characterised. Both characterised TIMPs inhibit the active forms of all MMPs, binding in a non-covalent manner to form a 1:1 complex. Interestingly, the inhibitors can also bind to the latent form of both gelatinases – TIMP-1 binding to the gelatinase B proenzyme and TIMP-2 to latent gelatinase A. In this manner TIMPs may exert additional control on MMP action by inhibiting the auto-activation of the gelatinases.

The plasma protein \( \alpha_1 \)-macroglobulin is an effective inhibitor of MMP action in vitro. Given the large size of this protein, however, its role in inhibiting MMPs released by stromal cells is probably minor except at inflammatory sites where increased capillary permeability causes leakage of plasma proteins. In these instances inhibition of \( \alpha_1 \)-macroglobulin may be important as TIMP activity is destroyed by the action of serine proteases released by infiltrating neutrophils.

**Matrix metalloproteases and the lung**

Maintenance of the extracellular matrix scaffold which supports the alveolar structure is essential for normal lung function and is achieved by a dynamic balance between synthesis and degradation of extracellular matrix components. In the healthy lung MMPs – which are produced by virtually all resident lung cells including fibroblasts, alveolar macrophages, epithelial and endothelial cells – are involved in normal extracellular matrix turnover and also participate in the wound healing response following injury. Given their role in normal lung homeostasis, it is not surprising that the MMPs are implicated in a range of pulmonary diseases characterised by alterations in alveolar structure, or abnormal wound healing responses, including emphysema, adult respiratory distress syndrome (ARDS), interstitial fibrosis, granulomatous disease, lung cancer, and pleural disease. In subsequent sections of this review evidence for the participation of MMPs in the pathogenesis of these diseases is outlined (with the exception of emphysema, which has been the subject of a recent review in *Thorax*).

**MMPs and ARDS**

Neutrophil collagenase has been detected in bronchoalveolar lavage (BAL) fluid from patients with ARDS. The enzyme is present in active form, indicating that it has been activated subsequent to release and has evaded in vivo inhibition by TIMPs and \( \alpha_2 \)-macroglobulin. The destructive potential of this unopposed activity in the lung is considerable and may contribute to the tissue damage observed during the acute inflammatory stage of disease. To our knowledge, lung tissue or BAL fluid from patients with ARDS have not been assessed for the presence of gelatinase B, the second MMP stored in polymorphonuclear leucocytes. Indirect evidence would, however, suggest that this enzyme is likely to be released during the process of neutrophil adhesion and migration into the lung in ARDS. The tertiary granules which contain both gelatinase B and the adhesion molecule Mac-1 (CD11b/CD18) are rapidly transported to the cell surface following stimulation of neutrophils by chemotactic and activation factors. In addition, IL-8, which appears to have a significant role in promoting neutrophil-mediated inflammation and injury in ARDS, stimulates release of gelatinase B from neutrophils. Release of this MMP could contribute to the breakdown of alveolar basement membrane observed in ARDS. Morphological studies indicate that preservation of basement membrane is vital for effective repair, as this provides tissue cells with migratory pathways that ensure the maintenance of the original alveolar architecture. Thus, the extent of basement membrane digestion by gelatinase B may be a significant factor in determining disease outcome in ARDS.

Evidence from wound healing systems indicates that regulated MMP expression and production by stromal cells is required for tissue remodelling – a process which presumably takes place in the lungs of ARDS survivors. It is suggested that the excessive fibrosis observed in the lungs of non-survivors is a result of an unregulated repair process. Whether the outcome is repair or fibrosis, MMPs produced by alveolar fibroblasts, macrophages, epithelial and endothelial cells are likely to have a significant role. To date, however, the participation of these MMPs in ARDS has received little attention. A recent study which demonstrates increased interstitial collagenase expression in the lungs of rats following hyperoxic injury (a model with similarities to ARDS) suggests that this may prove a fruitful area for future investigation.

**MMPs and Interstitial Fibrosis**

As indicated above, fibrosis – the common end stage of several interstitial lung diseases – is thought to reflect an aberrant wound healing response. The injury which triggers the response varies from neutrophil mediated tissue damage (cryptogenic fibrosing alveolitis) to granuloma formation in response to known (extrinsic allergic alveolitis) and unknown (sarcoidosis) antigens, direct tissue damage (asbestos, silica), and injury resulting from abnormal immune responses (collagen vascular diseases). Whatever the initial cause, a
A unifying hypothesis on the involvement of MMPs in fibrosis encompassing all the above observations would involve (1) collagenase (and probably gelatinase B) released from inflammatory polymorphonuclear leucocytes contributing to initial tissue injury, and (2) a decrease in interstitial collagenase expression by fibroblasts and/or other stromal cells contributing to subsequent aberrant repair and accumulation of collagen. In this regard, Selman and colleagues have noted that lung fibroblast lines from patients with cryptogenic fibrosing alveolitis constitutively produce less interstitial collagenase than lines from normal lung. We have also observed decreased collagenase production in a fibroblast line derived from BAL cells recovered from a patient with systemic lupus erythematosus (unpublished observations). In vitro studies indicate that several cytokines known to be present in inflammatory situations, including TGFβ, IL-4 and IFNγ, are capable of reducing expression of interstitial collagenase by fibroblasts and monocytes/macrophages (table 2). As previously indicated, TGFβ also increases collagen production and production of TIMP-1. Studies which indicate that TGFβ promotes gelatinase expression in fibroblasts86-88 raise the intriguing possibility that, while "driving" fibroblasts to produce and deposit components of the interstitial matrix, this cytokine also enhances their capability to degrade basement membrane. Thus, under the influence of this cytokine the action of fibroblasts would ideally "fit" that required for producing fibrosis in situations where the extent of injury and/or continued inflammation prevented healing.

While most studies have concentrated on the role of interstitial and neutrophil collagenases in interstitial fibrosis, the potential involvement of other MMPs cannot be ignored. We have detected gelatinase B in BAL fluids from patients with cryptogenic fibrosing alveolitis, extrinsic allergic alveolitis and sarcoidosis (unpublished results), and the transient expression and activity of gelatinase A by alveolar macrophages from patients with sarcoidosis has been shown to be associated with the metastatic potential of both cultured tumour cells and malignant tissue.12 In the lung, expression of both gelatinases, stromelysin-3 and interstitial collagenase has been observed in various primary and metastatic tumours including adenocarcinomas, squamous cell, and small cell carcinomas.49 Because of their role in basement membrane digestion, the expression and production of the two forms of gelatinase has
Matrix metalloproteases and lung disease

received particular attention. While initial immunohistochemical localisation of gelatina-

se A suggested its production by malignant
cells, subsequent in situ hybridisation studies have revealed that stromal cells are the major
source of this enzyme in many tumors,

including lung carcinomas.83,84 Emonard et al
have recently reported the presence of a bind-
ingsite for gelatinase A on the surface of breast
adeno-carcinoma cells.85 These observations
suggest a parasitic type interaction between
malignant and stromal cells with the malignant
cell binding gelatinae produced by stromal
cells, hence gaining the capacity to migrate
through tissue basement membrane. In situ
hybridisation experiments indicate that gelati-

nase B is produced by both tumour and stro-
mal cells, particularly tumor associated mac-
rophages.12 Decreased production of MMP
inhibitors may also contribute to tumour metastatic potential.86 Khokha et al have demon-
strated that antisense DNA RNA down
modulation of TIMP transforms normal Swiss
3T3 fibroblasts into malignant cells capable of
forming metastatic tumours.87 This transfor-
mation is accompanied by an increase in MMP
expression. The opposite effect was observed by DeClerck et al.88 These investigators trans-
fected malignant cells with TIMP-2 cDNA and
noted a decreased capacity for invasion in the
transfected cells. Direct inhibition of MMP
activity by a synthetic peptide contain-
ing a modified "copy" of the MMP Zn-binding
sequence has also been shown to inhibit tumour cell invasion.89 While still at an early
stage, these studies suggest that therapies
aimed at decreasing MMP expression by
tumour and stromal cells and/or inhibiting MMP activity may be of value in limiting the
metastatic spread of a range of tumours.

MMPs IN PLEURAL FLUID
A role for MMPs in maintaining the integrity of
the pleural space has recently been sug-
gested by Hurewitz and colleagues. These in-
vestigators noted high levels of both gelatin-
as in pleural effusions from patients with
malignant and nonmalignant inflammatory
diseases.90 The enzyme activity observed was
inhibited by tetracyclines.91 The authors
suggest that gelatinaes in pleural fluid may
serve to dissolve adhesions and accumulated
connective tissue following pleural injury, and
that the action of tetracyclines in pleurorhesis
may be attributable to their ability to inhibit
these enzymes.

Future directions
Research in recent years has highlighted the
involvement of common cytokines and growth
factors in a range of seemingly diverse pro-
cesses including cell migration, proliferation
and transformation; destructive inflammatory
disorders; resorptive processes; fibrosis and
tumorigenesis. The involvement of common
mediators suggests similarities in underlying
cellular mechanisms. In vivo, all of these pro-
cesses require or are accompanied by change
and reorganisation of the surrounding extra-
cellular matrix. The most likely mechanism by
which cytokines and growth factors exert their
modulating effects on the extracellular matrix
is via the induction or repression of MMPs and
their inhibitors.5 Thus, the potential applica-
tion of therapies targeted at MMP regulation
is considerable. As outlined in this review,
recent advances in our understanding of these
regulatory mechanisms now make it possible
to design and examine such therapies.

1 Birkedal-Hansen H, Moore WG, Bodden MK, Windsor
LJ, Birkedal-Hansen B, DeCarlo A, et al. Matrix metallo-
250.
2 Matrisian LM. The matrix-degrading metalloproteinases.
3 Murphy G, Docherty AJP. The matrix metalloproteinases
and their inhibitors. Am J Respir Cell Mol Biol 1992;
7:120–5.
4 Emonard H, Grimaud J-A. Matrix metalloproteinases. A
5 Matrisian LM, Hogan BL. Growth factor-regulated pro-
tases and extracellular matrix remodelling during mam-
6 Alexander DM, Whittaker E. Extracellular matrix degra-
7 Davidson, JM. Biochemistry and turnover of lung inter-
8 Brickerhoff CE, Delany AM. Cytokines and growth fac-
tors in arthritic diseases: mechanisms of cell proliferation
and matrix degradation in rheumatoid arthritis: In: Kim-
ball ES, ed. Cytokines and inflammation. Boca Raton:
9 Birkedal-Hansen H. Role of matrix metalloproteinases in
84.
10 Davies M, Martin J, Thomas GJ, Lovett DH. Proteinases
8.
11 Brickerhoff CE. Regulation of metalloproteinase gene
expression: implications for osteoarthritis. Crit Rev Eukaryot
12 Tryggvason K, Hoytia M, Pyke C. Type IV collagenases in
18.
13 Docherty AJP, Murphy G. The tissue metalloproteinase
family and the inhibitor TIMP: a study using cDNAs and
14 Jonat C, Stein B, Ponta H, Herrlich P, Rahmsdorf HJ.
Positive and negative regulation of collagenase gene
15 Matrisian LM, Gansler GL, Kerr, LD, Pelton RW, Wood
LD. Negative regulation of gene expression by TGFβ. Mol
16 Nagase H, Ogata Y, Suzuki K, Enghild JJ, Salvesen G.
Substrate specificities and activation mechanisms of
17 Murphy G. The regulation of connective tissue metallo-
proteinases by natural inhibitors. Agents Actions 1991;
35(Suppl):69–76.
18 Enzyme Nomenclature 1991. Recommendations of the
Nomenclature Committee of the International Union of
Biochemistry and Molecular Biology on the nomenclature
and classification of enzymes. New York: Academic Press,
19 Sanchez-Lopez R, Nicholson R, Gesnel MC, Matrisian
LM, Breathnach R. Structure-function relationships in
the collagenase family member transin. J Biol Chem
20 Murphy G, Allan JA, Willenbrock F, Cockett MJ, O’Connell
JP, Docherty AJP. The role of the C-terminal domain in
collagenase and Stromelysin specificity. J Biol Chem
21 Murphy G, Willenbrock F, Ward RV, Cockett MJ, Eaton,
D, Docherty AJP. The C-terminal domain for 72 kDa
gelatinae is not required for catalysis but it is essential for
membrane activation and modulates interactions with
tissue inhibitors of metalloproteinases. Biochem J
22 Collier IE, Krasnov PA, Strongin YA, Birkedal-Hansen H,
Goldberg GJ. Alkaline scanning mutagenesis and func-
tional analysis of the fibronectin-like collagen binding
domain from human 92 kDa type IV collagenase. J Biol
23 Fields GB, van Wart HE, Birkedal-Hansen H. Sequence
specificity of human skin fibroblast collagenase. Evidence
for the role of collagen structure in determining the
24 Malicky SK, Mookhtar KA, Gao Y, Brew K, Diss zaghi M,
Birkedal-Hansen H, et al. Characterization of 58-kilo-
dalton human neutrophil collagenase: comparison with
human fibroblast collagenase. Biochemistry 1990;289:
1028–34.
25 Harris ED, Krane SM. An endopeptidase from rheumatoid
rheumatoid
608

O'Connor, FitzGerald

609


Downloaded from http://thorax.bmj.com/ on April 20, 2017 - Published by group.bmj.com


88 Ponton A, Coulombo B, Skup D. Decreased expression of tissue inhibitor of metalloproteinases in metastatic tumor cells leading to increased levels of collagenase activity. Cancer Res 1991;51:2138-43.


Matrix metalloproteases and lung disease.

C M O'Connor and M X FitzGerald

Thorax 1994 49: 602-609
doi: 10.1136/thx.49.6.602

Updated information and services can be found at:
http://thorax.bmj.com/content/49/6/602.citation

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/