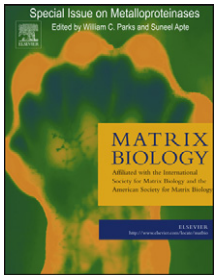
Review



MMP generated matrikines☆,☆☆

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Abstract

Matrikines originate from the fragmentation of extracellular matrix proteins and regulate cellular activities by interacting with specific receptors. Matrikines are implicated in inflammation, immune responses, organ development, wound repair, angiogenesis, atherosclerosis, tumor progression and metastasis due to their ability to alter cellular migration, chemotaxis, and mitogenesis. Matrix metalloproteinases (MMPs) degrade extracellular matrix components under normal circumstances and in disease processes. Of the 20 MMPs identified, MMP-1, MMP-2, MMP-8, MMP-9, and MMP-12 have been implicated in regulating the matrikines Val-Gly-Val-Ala-Pro-Gly (elastin peptide) and proline–glycine–proline (PGP). Elastin peptide fragments are generated by elastolytic enzymes and have implications in atherosclerosis, neovascularization, chronic obstructive pulmonary disease, skin disease, as well as tumor invasion and spread. PGP is produced through a multistep pathway that liberates the tripeptide fragment from extracellular collagen. PGP is best described for its role in neutrophil chemotaxis and is implicated in the pathogenesis of corneal ulcers and in chronic lung conditions. In chronic cigarette smoke related lung disease, the PGP pathway can become a self-propagating cycle of inflammation through cigarette-smoke mediated inhibition of leukotriene A4 hydrolase, the enzyme responsible for degrading PGP and halting acute inflammation. This review highlights the roles of MMPs in generating these important matrikines.

Background

Matrikines are peptides originating from the fragmentation of extracellular matrix proteins and regulate cellular activities by interacting with specific receptors [1]. Matrikines are involved in the process of extracellular matrix renewal and cellular proliferation. Currently, intact proteins including elastin [1], extracellular matrix collagen [2], osteopontin [3], tenascin, laminin, decorin, thrombospondin, integrin, versican [4], type XIX collagen [5], biotinylated peptide [6], mactinin [7], tetrastatin [8], and lumican [9] have been identified as the sources of matrikines.

Matrikines have been implicated in inflammation, immune responses, organ development [9], wound repair [10], angiogenesis, atherosclerosis, tumor progression and metastasis due to their ability to alter cellular migration, chemotaxis, and mitogenesis [8,11,12]. Inhibition of matrikine signaling has been implicated in halting tumor growth [5]. Matrikine activity is dictated via differing regulatory mechanisms.

Matrix-metalloproteinases (MMPs) are a family of zinc-dependent metalloendopeptidases that can degrade or cleave many components of the extracellular matrix, as well as a wide range of other extracellular proteins, during both normal and disease processes. MMPs are produced as proenzymes or zymogens and their action is typically in concert with other proteases [13]. MMP-1, MMP-2, MMP-8, MMP-9, and MMP-12 have been implicated

in regulating the matrikines Val-Gly-Val-Ala-Pro-Gly (VGVAPG; elastin peptide) and PGP and will be discussed. The biology of the parent proteins of these matrixins will be highlighted in a separate dedicated issue of *Matrix Biology*.

Elastin peptides as matrikines

Elastin is present in elastic fibers in the extracellular matrix and contributes to the elastic properties of skin, lungs, and larger blood vessels. Elastin is a polymer of tropoelastin, which is characterized by domains rich in Lys and Ala that function in generating desmosine–isodesmosine cross-linking and hydrophobic domains rich in Gly, Val, and Pro and occur in repeats of three to six-mers [14]. Tropoelastin is coded by the ELN gene [15]. ELN expression, and subsequent elastin production, is down regulated in the first years of life [16], highlighting the need for elastic connective tissues to rely on the persistence of elastin. Elastolytic enzymes, including aspartic proteases, cysteine proteases, serine proteases, and metalloproteinases, degrade elastin and play significant roles in disease processes [17]. Val-Gly-Val-Ala-Pro-Gly (VGVAPG) is an elastin peptide fragment that is a repeating peptide sequence from the c-terminal portion of the tropoelastin molecule. This sequence is chemotactic for both monocytes and fibroblasts [18,19] and can be detected by HPLC [20].

The pathobiologic importance of elastin fragments is especially significant in the organ systems with an abundance of elastin. For instance, overproduction of elastin in vascular walls contributes to the development of atherosclerosis. Exogenous administration of elastin peptides stimulates vascular smooth muscle cell proliferation while simultaneously inhibiting elastin expression [21], cause neovascularization, increased vascular wall thickness, and wall diameter [22], and decrease vascular tone in a dose-dependent manner [23]. Some groups have reported that elastin binding protein (EBP67) binds VGVAPG resulting in smooth muscle migration through elastin fiber membranes, leading to vascular intimal thickening and development of vascular disease [24,25]. These highlight the role of elastin peptides in vascular disease. In the lungs, elastin peptides are generated at diseased sites and specifically attract monocytes, the precursors to macrophages [26] while impairing neutrophil reactivity [27]. The chemotactic sites on elastin fragments contain lysyl-derived cross-links that recruit inflammatory cells to the lungs, resulting in elastase-induced emphysema [28]. In melanocyte precursors, VGVAPG stimulates melanogenesis and dendrite formation [29]. Finally, elastin fragments have pathologic roles in tumor migration, invasion, adhesion, and angiogenesis. VGVAPG has implications for lung cancer tumor progression through several mechanisms including the high affinity binding of the peptide to distinct surface receptors [30], altered receptor affinity and chemotactic responsiveness through a membrane-bound protein kinase C dependent process [31], and post-transcriptional regulation of MMP-2 and uPA [32]. In fibrosarcoma, VGVAPG stimulates heat-shock protein 90, pro-MMP-2, and urokinase plasminogen activator secretion and cell-invasive capacity [33]. In melanoma, VGVAPG increases tumor cell migration and expression of MMP-2 and MMP-3 [34], NF-kappaB activation, and IL-1beta upregulation [35] resulting in increased metastatic and invasive potential.

Elastin peptides are generation by MMPs

The elastin fragments XGXXPG (where X is a generic hydrophobic residue) lead to expression and activation of MMP-1 and MMP-3 in human fibroblasts, suggesting that the consensus sequence found in VGVAPG is important for binding to the elastin binding protein (EBP) receptor [36,37]. This MMP activation in turn worsens local connective tissue damage. In melanoma, VGVAPG increases the expression of MMP-2 and MMP-3, which in turn further degrade elastin [34]. The invasive potential occurs predominantly through the galectin-3 receptor. Similarly, MMP-2, MMP-3, and MMP-9 expressions are increased in smooth muscle cells in the intimal layer of the aorta [38]. This increased expression occurs at sites where spiral collagen and degenerated elastin are abundant [39]. In the vascular tissue, these occur at sites of hemodynamic stress, leading to vascular wall vulnerability which has implications for development of aortic dissection and remodeling. Administration of doxycycline, an MMP inhibitor, results in preservation of aortic elastin accompanied by a reduction in MMP-9 [40].

In mice, MMP-12 action on elastin results in the generation of GXXPG and XGXPG peptide fragments. Cleavage sites include Leu and Ile, amino acids with large aliphatic side chains in the P_1' position. These sites are readily accessible to MMP-12 [41]. Antibodies to the GXXPG and XGXPG sequences abolish chemotactic activity to monocytes and prevent elastase-induced emphysema [28,42]. Macrophages accumulate in the lungs of mice chronically exposed to cigarette smoke, and this accumulation is ameliorated in *Mmp* $12^{-/-}$ mice [43].

Recently, investigators have directly examined patients with emphysema for the presence of bioactive elastin fragments via mass spectrometry, identifying 4 distinct elastin-derived fragments in chronic obstructive pulmonary disease (COPD) subjects compared to the non-lung disease control [44], suggesting that these elastin-derived peptides are operative in COPD. In addition, there is accumulating data that patients with COPD generate autoantibodies directed at portions of

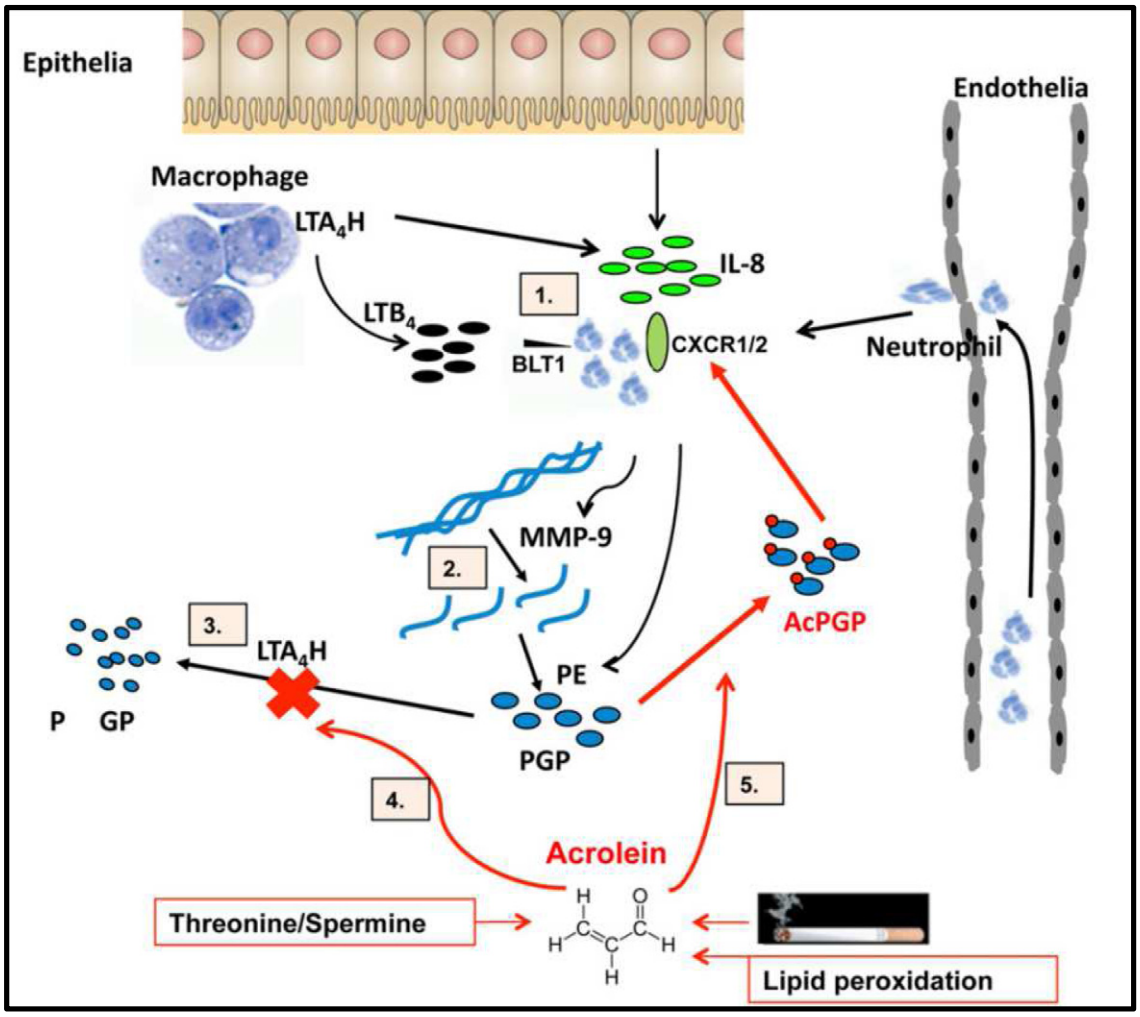

Fig. 1. Central role of MMP-derived PGP in smoking-induced pulmonary inflammation. (1) In response to infection or injury, resident cells within the lung release chemoattractants that promote neutrophil recruitment from the vasculature into the tissue. Epithelial cells and alveolar macrophages, for example, release IL-8 that binds to CXCR1/2 on the neutrophil surface and promote recruitment. The intracellular activity of LTA4H within leukocytes can generate the lipid mediator LTB4 that promotes neutrophil recruitment by binding to LTB4 receptor (BLT1). (2) Neutrophils release an array of proteases within the lung tissue—the coordinated action of matrix metalloproteinases (MMPs; especially MMP-1, -8, and -9) and prolyl endopeptidase (PE) released from the neutrophil target extracellular matrix collagen, releasing the neutrophil chemoattractant, proline–glycine–proline (PGP). PGP binds CXCR1/2 on the neutrophil and sustains neutrophil recruitment. (3) To terminate PGP-directed neutrophilic inflammation, LTA4H is released into an extracellular environment to degrade the peptide. (4) Acrolein, derived from cigarette smoke or physiologically during inflammation (lipid peroxidation, metabolism of threonine or spermine), can inhibit LTA4H-mediated degradation of PGP, allowing the peptide to accumulate and maintain neutrophilic inflammation. (5) Acrolein (and other components of cigarette smoke) can also chemically acetylate PGP on its N terminus, completely protecting the peptide from LTA4H-mediated degradation, and thus facilitating neutrophil recruitment. AcPGP = acetylated PGP; PE = prolyl endopeptidase. Reproduced with permission [73].

elastin suggesting a potential autoimmune component directed at specific epitopes of elastin [45,46].

PGP as a matrikine

The neutrophil chemotactic activity of the collagen-derived tri-peptide PGP and its acetylated form (AcPGP) were originally described in models of direct alkaline hydrolysis of corneal proteins leading to corneal ulcers [47]. The biologic activities of many similar synthetic peptides, including possible antagonist peptides were investigated. PGP alone was found to be sufficient to elicit bioactivity and the synthetic peptide gly-pro-hyp was able to inhibit PGP-mediated chemotaxis. Chemotaxis stimulated

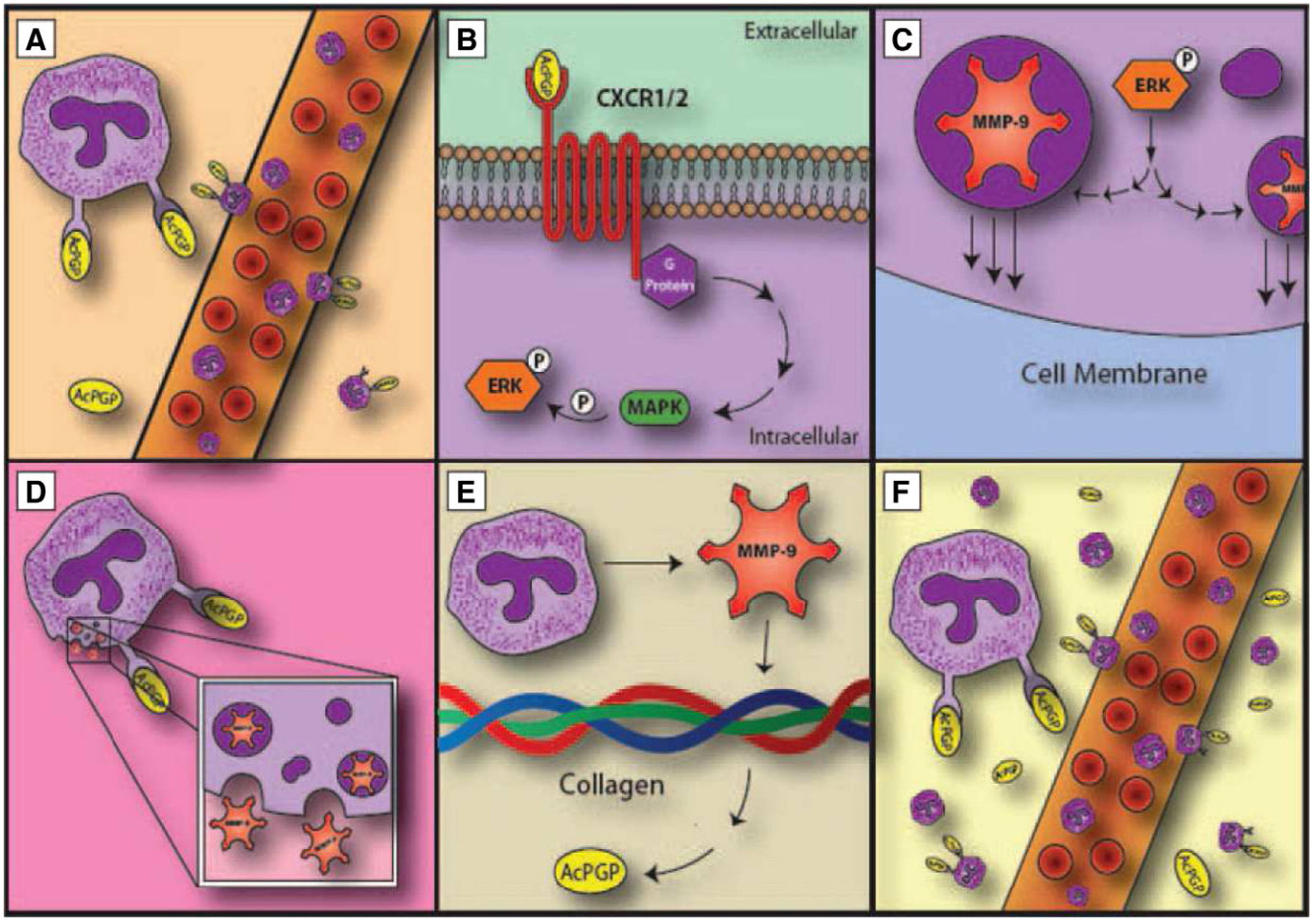

Fig. 2. A model of persistent matrikine production and neutrophilic inflammation. During chronic PMN inflammation, collagen is hydrolyzed and releases AcPGP causing ongoing neutrophilic influx (A). In addition to causing neutrophilic influx, AcPGP ligation of CXCR1 and CXCR2 leads to intracellular ERK phosphorylation and activation (B) and degranulation of MMP-9 from tertiary granules of neutrophils (C and D). This MMP-9 acts on exposed collagen leading to AcPGP generation (E) and a feed-forward inflammatory response on neutrophils (F). Reproduced with permission [66].

by PGP/AcPGP is dose dependent [48] and occurs through CXCR2 interaction [2,49,50]. Neutrophil chemotaxis is more pronounced for AcPGP compared with PGP, and the acetylated form present in the lung compartment of smokers may be due in part to direct chemical acetylation by components found in cigarette smoke [51].

Using NMR conformational analysis, the dominant solution conformation for each cis- and trans-isomer of PGP was described, aiding in peptide and non-peptide inhibitors for the chemoattractant [52,53]. Complementary peptides to PGP including arginine–threonine–arginine (RTR), an RTR–dimer, an RTR–tetramer, RTR–glycine–glycine, and alanine–serine–alanine (ASA) were tested on PGP-mediated neutrophil activation [54]. Of these, the RTR-tetramer was found to be the most powerful antagonist of AcPGP induced neutrophilic chemotaxis. This inhibition was not observed for leukotriene B4 (LTB4) mediated chemotaxis, highlighting the specificity of RTR for PGP. PGP-mediated corneal ulceration was reduced by RTR [55,56]. RTR impedes PGP and IL-8 induced chemotaxis and ameliorates the development of an AcPGP mediated emphysema-like phenotype in mice [48].

The multistep pathway that generates PGP from extracellular collagen was reported in a cystic fibrosis model [57], chronic lung transplant rejection [58], and in models of chronic cigarette smoke exposure [59] and COPD [60]. Through a stepwise process, collagen is degraded by MMP-8, MMP-9, and prolyl endopeptidase (PE) [59,61,62]. Cigarette smoke induced increases in MMP-8, MMP-9, PE, and PGP accompany neutrophil influx and improve following smoking cessation [59]. Sputum from patients with cystic fibrosis is able to generate PGP from collagen ex vivo, and this cascade is disrupted by inhibitors of MMP-8, MMP-9, and PE. Leukotriene A4 hydrolase (LTA4H), the pro-inflammatory enzyme responsible for the generation of LTB4 also possesses aminopeptidase activity that serves to degrade PGP [63]. In the setting of acute inflammation, this serves to stop the PGP-mediated neutrophil chemotaxis. However, cigarette smoke selectively inactivates LTA4H's aminopeptidase function, leading to accumulation of PGP and neutrophils. This ultimately results in the development of COPD [60,63]. Once COPD is established, aminopeptidase activity remains selectively inactive through the effects of acrolein. This pathway is depicted in Fig. 1.

MMPs in PGP generation

MMP-8 and MMP-9 play several roles in inflammation, including extracellular matrix degradation. Neutrophils contribute to the production of both MMPs. In a lipopolysaccharide (LPS) model of corneal inflammation, MMP-8 and MMP-9 expressions are increased [64]. Both MMP-8 and MMP-9 activities are absent in CXCR2$^{-/-}$ mice [64], which have impaired neutrophil recruitment. In response to LPS, MMP-8$^{-/-}$ mice had diminished neutrophil migration and decreased PGP production. In contrast, MMP-9$^{-/-}$ mice had preserved LPS-induced neutrophil accumulation without alterations to PGP production, highlighting the contribution of MMP-8 to PGP generation. These findings were recapitulated in a murine model of chronic cigarette smoke [62]. In an ex vivo PGP generation assay, inhibitors to MMP-1, MMP-9, and PE prevent PGP release from neutrophils [65]. MMP-9 blockade was the strongest inhibitor of PGP generation. Further, AcPGP induces time-dependent MMP-9 release from activated neutrophil tertiary granules. Activation of the ERK1/2 MAPK pathway is necessary for this MMP-9 release in response to AcPGP. This in turn mediates intracellular ERK1/2 phosphorylation, suggesting a feed-forward pathway to augment AcPGP production [66]. This model is represented in Fig. 2. In a murine model of cigarette smoke exposure, chronic smoke exposure increases MMP-8 and MMP-9 expression and activity [59]. These are highly correlated with AcPGP ($r^2 = 0.82$ for MMP-8 and $r^2 = 0.96$ for MMP-9, $p < 0.001$ for both). MMP-8, -9, and AcPGP levels fall following cigarette smoke cessation, demonstrating the importance of these proteinases in the formation of PGP.

Other bioactive ECM fragments generated by MMPs

Although much of the current literature on ECM fragments has focused on collagen and elastin, other components of ECM have been shown to be fragmented by MMPs leading to bioactive peptides. Laminins are glycoprotein found in the basement membrane important in maintaining tissue architecture and may have important roles in regulating cellular differentiation, survival, and adhesion. A number of laminins have been shown to be cleaved by MMPs, leading to bioactive ECM products. A previous manuscript highlighted that liberation of a specific cryptic epitope of laminin α5 (presumably by proteolytic digestion) releases a 16 amino acid peptide capable of recruiting PMNs and macrophages, along with inducing MMP-9 release from immune cells [67]. More recently, MMP-2 has been shown to cleave laminin-111, liberating a 60kD fragment capable of inducing epithelial-mesenchymal transition in embryonic stem cells [68]. These results strongly suggest that proteolytic cleavage of laminins may impart critical paracrine regulation of structural cells and immune cells. Additionally, matrikines generated from type IV collagen, including tumstatin, have effects on angiogenesis. Tumstatin is a cleavage fragment of the α3 chain of type IV collagen which is associated with normal tissue growth and regulation of angiogenesis. In mice deficient of either the α3 chain of type IV

collagen or MMP-9, the enzyme responsible for generating tumstatin, angiogenesis is enhanced and accelerated tumor growth occurs [69]. Other MMP-9 generated ECM fragments have similar angiogenesis inhibiting properties and have implications in cardiac disease [70] and are therapeutic in cancer treatment [71,72].

Summary and conclusion

Recent data provide strong evidence that rather than being mere processors of matrix proteins, MMPs are major regulators of normal and pathologic processes. Two important cleavage products — VGVAPG and PGP can both promote well-defined processes such as angiogenesis and chronic lung disease. Targeting the MMPs central to these pathways may result in more selective and efficient therapeutic targets for disease and represent an exciting area of investigation.

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References

[1] Duca L, Floquet N, Alix AJ, Haye B, Debelle L. Elastin as a matrikine. Crit Rev Oncol Hematol 2004;49:235–44.
[2] Weathington NM, van Houwelingen AH, Noerager BD, Jackson PL, Kraneveld AD, Galin FS, et al. A novel peptide CXCR ligand derived from extracellular matrix degradation during airway inflammation. Nat Med 2006;12:317–23.
[3] Yamanaka O, Sumioka T, Saika S. The role of extracellular matrix in corneal wound healing. Cornea 2013;32(Suppl. 1): S43–5.
[4] Tran KT, Griffith L, Wells A. Extracellular matrix signaling through growth factor receptors during wound healing. Wound Repair Regen 2004;12:262–8.
[5] Ramont L, Brassart-Pasco S, Thevenard J, Deshorgue A, Venteo L, Laronze JY, et al. The NC1 domain of type XIX collagen inhibits in vivo melanoma growth. Mol Cancer Ther 2007;6:506–14.
[6] Arul V, Gopinath D, Gomathi K, Jayakumar R. Biotinylated GHK peptide incorporated collagenous matrix: a novel biomaterial for dermal wound healing in rats. J Biomed Mater Res B Appl Biomater 2005;73:383–91.
[7] Luikart SD, Panoskaltsis-Mortari A, Hinkel T, Perri RT, Gupta K, Oegema TR, et al. Mactinin, a fragment of cytoskeletal alpha-actinin, is a novel inducer of heat shock protein (Hsp)-90 mediated monocyte activation. BMC Cell Biol 2009;10:60.
[8] Brassart-Pasco S, Senechal K, Thevenard J, Ramont L, Devy J, Di Stefano L, et al. Tetrastatin, the NC1 domain of the alpha4(IV) collagen chain: a novel potent anti-tumor matrikine. PLoS One 2012;7:e29587.
[9] Kao WW. Ocular surface tissue morphogenesis in normal and disease states revealed by genetically modified mice. Cornea 2006;25:S7–S19.
[10] Yamanaka O, Yuan Y, Coulson-Thomas VJ, Gesteira TF, Call MK, Zhang Y, et al. Lumican binds ALK5 to promote epithelium wound healing. PLoS One 2013;8:e82730.
[11] Tran KT, Lamb P, Deng JS. Matrikines and matricryptins: implications for cutaneous cancers and skin repair. J Dermatol Sci 2005;40:11–20.
[12] Vassiliadis E, Barascuk N, Didangelos A, Karsdal MA. Novel cardiac-specific biomarkers and the cardiovascular continuum. Biomark Insights 2012;7:45–57.
[13] Ra HJ, Parks WC. Control of matrix metalloproteinase catalytic activity. Matrix Biol 2007;26:587–96.
[14] Vrhovski B, Weiss AS. Biochemistry of tropoelastin. Eur J Biochem 1998;258:1–18.
[15] Bashir MM, Indik Z, Yeh H, Ornstein-Goldstein N, Rosenbloom JC, Abrams W, et al. Characterization of the complete human elastin gene. Delineation of unusual features in the 5'-flanking region. J Biol Chem 1989;264:8887–91.
[16] Wirtschafter ZT, Cleary EG, Jackson DS, Sandberg LB. Histological changes during the development of the bovine nuchal ligament. J Cell Biol 1967;33:481–8.
[17] Werb Z, Banda MJ, McKerrow JH, Sandhaus RA. Elastases and elastin degradation. J Invest Dermatol 1982;79(Suppl. 1):154s–9s.
[18] Senior RM, Griffin GL, Mecham RP, Wrenn DS, Prasad KU, Urry DW. Val-Gly-Val-Ala-Pro-Gly, a repeating peptide in elastin, is chemotactic for fibroblasts and monocytes. J Cell Biol 1984;99:870–4.
[19] Bisaccia F, Morelli MA, De Biasi M, Traniello S, Spisani S, Tamburro AM. Migration of monocytes in the presence of elastolytic fragments of elastin and in synthetic derivates. Structure-activity relationships. Int J Pept Protein Res 1994; 44:332–41.
[20] Price LS, Roos PJ, Shively VP, Sandberg LB. Valyl-alanyl-prolyl-glycine (VAPG) serves as a quantitative marker for human elastins. Matrix 1993;13:307–11.
[21] Wachi H, Seyama Y, Yamashita S, Suganami H, Uemura Y, Okamoto K, et al. Stimulation of cell proliferation and autoregulation of elastin expression by elastin peptide VPGVG in cultured chick vascular smooth muscle cells. FEBS Lett 1995;368:215–9.

[22] Nackman GB, Karkowski FJ, Halpern VJ, Gaetz HP, Tilson MD. Elastin degradation products induce adventitial angiogenesis in the Anidjar/Dobrin rat aneurysm model. Surgery 1997;122:39–44.
[23] Faury G, Garnier S, Weiss AS, Wallach J, Fulop Jr T, Jacob MP, et al. Action of tropoelastin and synthetic elastin sequences on vascular tone and on free Ca2+ level in human vascular endothelial cells. Circ Res 1998;82: 328–36.
[24] Wasano K, Hirakawa Y, Nakamura K. Immunolocalization of 67 kDa elastin-binding protein in perinatal rat lungs. Cell Tissue Res 1992;268:277–81.
[25] Hinek A, Boyle J, Rabinovitch M. Vascular smooth muscle cell detachment from elastin and migration through elastic laminae is promoted by chondroitin sulfate-induced "shedding" of the 67-kDa cell surface elastin binding protein. Exp Cell Res 1992;203:344–53.
[26] Senior RM, Griffin GL, Mecham RP. Chemotactic activity of elastin-derived peptides. J Clin Invest 1980;66:859–62.
[27] Dupont A, Dury S, Gafa V, Lebargy F, Deslee G, Guenounou M, et al. Impairment of neutrophil reactivity to elastin peptides in COPD. Thorax 2013;68:421–8.
[28] Hunninghake GW, Davidson JM, Rennard S, Szapiel S, Gadek JE, Crystal RG. Elastin fragments attract macrophage precursors to diseased sites in pulmonary emphysema. Science 1981;212:925–7.
[29] Chang CH, Kawa Y, Tsai RK, Shieh JH, Lee JW, Watabe H, et al. Melanocyte precursors express elastin binding protein and elastin-derived peptide (VGVAPG) stimulates their melanogenesis and dendrite formation. J Dermatol Sci 2008;51:158–70.
[30] Blood CH, Sasse J, Brodt P, Zetter BR. Identification of a tumor cell receptor for VGVAPG, an elastin-derived chemotactic peptide. J Cell Biol 1988;107:1987–93.
[31] Blood CH, Zetter BR. Membrane-bound protein kinase C modulates receptor affinity and chemotactic responsiveness of Lewis lung carcinoma sublines to an elastin-derived peptide. J Biol Chem 1989;264:10614–20.
[32] Toupance S, Brassart B, Rabenoelina F, Ghoneim C, Vallar L, Polette M, et al. Elastin-derived peptides increase invasive capacities of lung cancer cells by post-transcriptional regulation of MMP-2 and uPA. Clin Exp Metastasis 2012;29:511–22.
[33] Donet M, Brassart-Pasco S, Salesse S, Maquart FX, Brassart B. Elastin peptides regulate HT-1080 fibrosarcoma cell migration and invasion through an Hsp90-dependent mechanism. Br J Cancer 2014;111:139–48.
[34] Pocza P, Suli-Vargha H, Darvas Z, Falus A. Locally generated VGVAPG and VAPG elastin-derived peptides amplify melanoma invasion via the galectin-3 receptor. Int J Cancer 2008;122:1972–80.
[35] Debret R, Le Naour RR, Sallenave JM, Deshorgue A, Hornebeck WG, Guenounou M, et al. Elastin fragments induce IL-1beta upregulation via NF-kappaB pathway in melanoma cells. J Invest Dermatol 2006;126:1860–8.
[36] Brassart B, Fuchs P, Huet E, Alix AJ, Wallach J, Tamburro AM, et al. Conformational dependence of collagenase (matrix metalloproteinase-1) up-regulation by elastin peptides in cultured fibroblasts. J Biol Chem 2001;276: 5222–7.
[37] Blanchevoye C, Floquet N, Scandolera A, Baud S, Maurice P, Bocquet O, et al. Interaction between the elastin peptide VGVAPG and human elastin binding protein. J Biol Chem 2013;288:1317–28.
[38] Ishii T, Asuwa N. Collagen and elastin degradation by matrix metalloproteinases and tissue inhibitors of matrix metalloproteinase in aortic dissection. Hum Pathol 2000; 31:640–6.
[39] Ishii T, Asuwa N. Spiraled collagen in the major blood vessels. Mod Pathol 1996;9:843–8.
[40] Boyle JR, McDermott E, Crowther M, Wills AD, Bell PR, Thompson MM. Doxycycline inhibits elastin degradation and reduces metalloproteinase activity in a model of aneurysmal disease. J Vasc Surg 1998;27:354–61.
[41] Mecham RP, Broekelmann TJ, Fliszar CJ, Shapiro SD, Welgus HG, Senior RM. Elastin degradation by matrix metalloproteinases. Cleavage site specificity and mechanisms of elastolysis. J Biol Chem 1997;272:18071–6.
[42] Houghton AM, Quintero PA, Perkins DL, Kobayashi DK, Kelley DG, Marconcini LA, et al. Elastin fragments drive disease progression in a murine model of emphysema. J Clin Invest 2006;116:753–9.
[43] Hautamaki RD, Kobayashi DK, Senior RM, Shapiro SD. Requirement for macrophage elastase for cigarette smoke-induced emphysema in mice. Science 1997;277: 2002–4.
[44] He J, Turino GM, Lin YY. Characterization of peptide fragments from lung elastin degradation in chronic obstructive pulmonary disease. Exp Lung Res 2010;36: 548–57.
[45] Lee SH, Goswami S, Grudo A, Song LZ, Bandi V, Goodnight-White S, et al. Antielastin autoimmunity in tobacco smoking-induced emphysema. Nat Med 2007;13:567–9.
[46] Xu C, Hesselbacher S, Tsai CL, Shan M, Spitz M, Scheurer M, et al. Autoreactive T Cells in human smokers is predictive of clinical outcome. Front Immunol 2012;3:267.
[47] Haddox JL, Pfister RR, Muccio DD, Villain M, Sommers CI, Chaddha M, et al. Bioactivity of peptide analogs of the neutrophil chemoattractant, N-acetyl-proline-glycine-proline. Invest Ophthalmol Vis Sci 1999;40:2427–9.
[48] van Houwelingen AH, Weathington NM, Verweij V, Blalock JE, Nijkamp FP, Folkerts G. Induction of lung emphysema is prevented by L-arginine-threonine-arginine. FASEB J 2008;22: 3403–8.
[49] Braber S, Overbeek SA, Koelink PJ, Henricks PA, Zaman GJ, Garssen J, et al. CXCR2 antagonists block the N-Ac-PGP-induced neutrophil influx in the airways of mice, but not the production of the chemokine CXCL1. Eur J Pharmacol 2011; 668:443–9.
[50] Kim SD, Lee HY, Shim JW, Kim HJ, Yoo YH, Park JS, et al. Activation of CXCR2 by extracellular matrix degradation product acetylated Pro-Gly-Pro has therapeutic effects against sepsis. Am J Respir Crit Care Med 2011;184:243–51.
[51] Hardison MT, Brown MD, Snelgrove RJ, Blalock JE, Jackson P. Cigarette smoke enhances chemotaxis via acetylation of proline-glycine-proline. Front Biosci (Elite Ed) 2012;4:2402–9.
[52] Lee YC, Jackson PL, Jablonsky MJ, Muccio DD, Pfister RR, Haddox JL, et al. NMR conformational analysis of cis and trans proline isomers in the neutrophil chemoattractant, N-acetyl-proline-glycine-proline. Biopolymers 2001;58:548–61.
[53] Jackson PL, Noerager BD, Jablonsky MJ, Hardison MT, Cox BD, Patterson JC, et al. A CXCL8 receptor antagonist based on the structure of N-acetyl-proline-glycine-proline. Eur J Pharmacol 2011;668:435–42.
[54] Pfister RR, Haddox JL, Blalock JE, Sommers CI, Coplan L, Villain M. Synthetic complementary peptides inhibit a neutrophil chemoattractant found in the alkali-injured cornea. Cornea 2000; 19:384–9.

[55] Haddox JL, Pfister RR, Sommers CI, Blalock JE, Villain M. Inhibitory effect of a complementary peptide on ulceration in the alkali-injured rabbit cornea. Invest Ophthalmol Vis Sci 2001;42: 2769–75.
[56] Pfister RR, Sommers CI. L-arginine-threonine-arginine (RTR) tetramer peptide inhibits ulceration in the alkali-injured rabbit cornea. Cornea 2006;25:1187–92.
[57] Gaggar A, Jackson PL, Noerager BD, O'Reilly PJ, McQuaid DB, Rowe SM, et al. A novel proteolytic cascade generates an extracellular matrix-derived chemoattractant in chronic neutrophilic inflammation. J Immunol 2008;180:5662–9.
[58] Hardison MT, Galin FS, Calderon CE, Djekic UV, Parker SB, Wille KM, et al. The presence of a matrix-derived neutrophil chemoattractant in bronchiolitis obliterans syndrome after lung transplantation. J Immunol 2009;182:4423–31.
[59] Braber S, Koelink PJ, Henricks PA, Jackson PL, Nijkamp FP, Garssen J, et al. Cigarette smoke-induced lung emphysema in mice is associated with prolyl endopeptidase, an enzyme involved in collagen breakdown. Am J Physiol Lung Cell Mol Physiol 2011;300:L255–65.
[60] Wells JM, O'Reilly PJ, Szul T, Sullivan DI, Handley G, Garrett C, et al. An aberrant leukotriene A4 hydrolase-proline-glycine-proline pathway in the pathogenesis of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2014;190: 51–61.
[61] O'Reilly PJ, Hardison MT, Jackson PL, Xu X, Snelgrove RJ, Gaggar A, et al. Neutrophils contain prolyl endopeptidase and generate the chemotactic peptide, PGP, from collagen. J Neuroimmunol 2009;217:51–4.
[62] Overbeek SA, Braber S, Koelink PJ, Henricks PA, Mortaz E, LoTam Loi AT, et al. Cigarette smoke-induced collagen destruction; key to chronic neutrophilic airway inflammation? PLoS One 2013;8:e55612.
[63] Snelgrove RJ, Jackson PL, Hardison MT, Noerager BD, Kinloch A, Gaggar A, et al. A critical role for LTA4H in limiting chronic pulmonary neutrophilic inflammation. Science 2010;330:90–4.
[64] Lin M, Jackson P, Tester AM, Diaconu E, Overall CM, Blalock JE, et al. Matrix metalloproteinase-8 facilitates neutrophil migration through the corneal stromal matrix by collagen degradation and production of the chemotactic peptide Pro-Gly-Pro. Am J Pathol 2008;173:144–53.
[65] O'Reilly P, Jackson PL, Noerager B, Parker S, Dransfield M, Gaggar A, et al. N-alpha-PGP and PGP, potential biomarkers and therapeutic targets for COPD. Respir Res 2009;10:38.
[66] Xu X, Jackson PL, Tanner S, Hardison MT, Abdul Roda M, Blalock JE, et al. A self-propagating matrix metalloprotease-9 (MMP-9) dependent cycle of chronic neutrophilic inflammation. PLoS One 2011;6:e15781.
[67] Adair-Kirk TL, Atkinson JJ, Kelley DG, Arch RH, Miner JH, Senior RM. A chemotactic peptide from laminin alpha 5 functions as a regulator of inflammatory immune responses via TNF alpha-mediated signaling. J Immunol 2005;174:1621–9.
[68] Horejs CM, Serio A, Purvis A, Gormley AJ, Bertazzo S, Poliniewicz A, et al. Biologically-active laminin-111 fragment that modulates the epithelial-to-mesenchymal transition in embryonic stem cells. Proc Natl Acad Sci U S A 2014;111: 5908–13.
[69] Hamano Y, Zeisberg M, Sugimoto H, Lively JC, Maeshima Y, Yang C, et al. Physiological levels of tumstatin, a fragment of collagen IV alpha3 chain, are generated by MMP-9 proteolysis and suppress angiogenesis via alphaV beta3 integrin. Cancer Cell 2003;3:589–601.
[70] Nikolova A, Ablasser K, Wyler von Ballmoos MC, Poutias D, Kaza E, McGowan FX, et al. Endogenous angiogenesis inhibitors prevent adaptive capillary growth in left ventricular pressure overload hypertrophy. Ann Thorac Surg 2012;94: 1509–17.
[71] O'Reilly MS, Holmgren L, Chen C, Folkman J. Angiostatin induces and sustains dormancy of human primary tumors in mice. Nat Med 1996;2:689–92.
[72] Bergers G, Javaherian K, Lo KM, Folkman J, Hanahan D. Effects of angiogenesis inhibitors on multistage carcinogenesis in mice. Science 1999;284:808–12.
[73] Snelgrove R, Kheradmand F. Leukotriene A4 hydrolase: the Janus enzyme shows its ugly side in smokers. Am J Respir Crit Care Med 2014;190:5–7.