Extracellular proteolysis plays a key role in many pathophysiologic processes including cancer, inflammatory diseases, and cardiovascular conditions such as atherosclerosis and restenosis. Whereas matrix metalloproteinases are their best known member, many others are becoming better known. The extracellular proteases are a complex and heterogeneous superfamily of enzymes. They include metalloproteinases (matrix metalloproteinases, adalysins, or pappalysins), serine proteases (elastase, coagulation factors, plasmin, tissue plasminogen activator, urokinase plasminogen activator), and the cysteine proteases (such cathepsins). In addition to their matrix degradation capabilities, they have other less well known biologic functions that include angiogenesis, growth factor bioavailability, cytokine modulation, receptor shedding, enhancing cell migration, proliferation, invasion, and apoptosis. This review discusses extracellular proteases relevant to the vasculature, their classification and function, and how protease disorders contribute to arterial plaque growth, including chronic atherosclerosis, acute coronary syndromes, restenosis, and vascular remodeling. These broad extracellular protease functions make them potentially interesting therapeutic targets.

**Key Words:** acute coronary syndromes ■ aneurysms ■ atherosclerosis ■ proteases ■ restenosis

Extracellular proteolysis is important to many biological processes including tissue remodeling, wound healing, and embryogenesis. It also has a key role in pathophysiologic processes including cancer, chronic inflammatory diseases, and cardiovascular conditions such as atherosclerosis and restenosis. Extracellular proteases (ECP) form a heterogeneous family that is becoming increasingly well understood. Whereas matrix metalloproteinases are the best described, many others are also becoming known. For example, a new protease family, the pappalysins, is now included. Other enzymes such as cysteine proteases were previously considered intracellular enzymes but have recently been shown to function in the extracellular space. In parallel with these discoveries, ECP have generated special interest because they degrade extracellular matrix (ECM). Although recent attention has focused on their impact in vulnerable plaques, promoting weakness and rupture, they are also involved in many other important biological functions.

This review discusses extracellular proteases relevant to the vasculature, their function, and how protease disorders contribute to multiple stages of arterial plaque growth, including chronic atherosclerosis, acute coronary syndromes (ACS), restenosis, and vascular remodeling.

**Extracellular Protease Classification**
Proteases or peptidases are enzymes that hydrolyze peptide bonds. They are classified as endopeptidases (cleaving the inner regions of peptide chains) and exopeptidases, which act at or near the peptide ends, liberating a single, dipeptide, or a tripeptide amino acid residue. Endopeptidases are the principal enzymes degrading extracellular proteins. Endopeptidases are divided further by their mechanisms of hydrolytic cleavage and their active site. These include threonine endopeptidase, aspartate endopeptidase, metalloproteinase, serine peptidase, and cysteine endopeptidases. Additional endopeptidases exist that cannot be assigned to any of these subclasses and include the ATP-dependent peptidases, which require ATP for activity.

**Metalloproteinases**
Metalloproteinases are characterized by an active site containing a metal atom, typically zinc. Zinc-dependent endopeptidases or zincins are characterized by a zinc-binding...
motif consisting of histidine-glutamic-X-X-histidine (HEXXH), in which X may be any residue. An important subgroup contains an extended zinc-binding sequence, HEXXHXXGXXH. This subgroup is called the metzincins because they also share a conserved methionine residue, spatially located close to the zinc ion and its 3 histidine residues. The metzincin superfamily is further divided into matrixins or matrix metalloproteinases, adamalysins or reprolysins, pappalysins, serralysins, and astacins.3 The first 3 have been found in atheromatous plaque (Figure 1).

Matrix metalloproteinases (MMPs) are a family with at least 24 zinc endopeptidases. Several names are still in use and were historically assigned to the MMPs. These names are based on substrate-focused nomenclature, MMP number or their preferential substrates and similar structural domains (Table).

Adamalysins comprise the ADAM proteases, the ADAMTS, and the class III snake venom metalloproteinases.4 The ADAMS proteases are found in atheromatous plaque.5 It is their 2 principal domains that give ADAMS its name (a disintegrin and metalloproteinase). ADAM combines features of cell surface adhesion molecules (disintegrin domain) and proteolysis (metalloproteinase domain). At present there are 30 members identified.

Pappalysins include PAPP-A and PAPP-A2. The pappalysins are classified as a fifth metzincin family, after the recent discovery that PAPP-A is highly expressed in coronary plaques associated with ACS.6

Serine Proteases
The serine proteases are a heterogeneous enzyme group. In this family, many enzymes are important for human vascular biology and include coagulation factors (thrombin, protein C, factor VII, IX, X, and XII), and the well-known fibrinolytic system.1 Inflammatory cells in human atheroma contain serine proteolytic enzymes. Neutrophils, for example, contain human neutrophil elastase and cathepsin G. Mast cells contain chymase and tryptase, and the last may play a role as a fibrogenic factor. Cytotoxic T cells contain cytolytic granules filled with multiple serine proteases termed granzymes. The fibrinolytic system deserves special attention because plasminogen conversion to the active serine protease plasmin occurs through 2 serine proteases: urokinase-type plasminogen activator (uPA) and tissue-type plasminogen activator (tPA). These attracted special attention since discovery. Despite their common enzymatic activities, the 2 plasminogen activators play distinct roles through 2 different biological behaviors. tPA has a high affinity for fibrin, resulting in a potent fibrinolytic process and clot dissolution. uPA, however, is recruited to the cell surface immediately after its secretion via a specific uPA receptor (uPAR). This plays a central role localizing uPA to cell-associated proteolysis. Thus, in addition to a major role in clot dissolution, the fibrinolytic system plays a defining role in many important vascular biological processes through pericellular proteolysis.

Cysteine Proteases
Cysteine proteases can be grouped into 2 superfamilies: the family of enzymes related to interleukin (IL)-1β–converting enzyme and the papain superfamily of cysteine proteases.7 Many cathepsins (lysosomal proteases) belong to the papain superfamily, including cathepsins B, H, L, S, C, K, O, F, V, X, and W. These enzymes function to degrade intracellular proteins, optimally within acidic lysosomes. However, cells
such as macrophages, smooth muscle cells, and endothelial cells can also mobilize them extracellularly, for example, the cathepsins B, L, S, and K,2,8 where they may participate in plaque extracellular proteolysis.

**Synthesis and Control**

Proteolysis is a ubiquitous mechanism used by the cell to regulate protein function and fate. Although proteins undergo reversible post-translational modification during their lifespan (phosphorylation for example), proteolysis is irreversible. Once proteins are hydrolyzed, the only means for rebuilding the intact molecule is via new protein synthesis. Because of their potent influence on cell function and because of irreversibility of action, ECP are finely controlled at various levels (Figure 2).

A variety of extracellular stimuli such as cytokines or growth factors induce MMP,9 uPA, and uPAR10–12 gene transcription. Many stimuli such tumor necrosis factor (TNF)-α, IL-1, basic fibroblast growth factor (bFGF), and platelet derived growth factor (PDGF) mediate atherosclerosis and restenosis. The cathepsins are special because some are weakly regulated at the transcriptional level.

Protease transcription is not indiscriminate because cells do not simultaneously transcribe all types of proteases. It is probable that stimuli such as cell–matrix and cell–cell interactions upregulate or downregulate specific proteases. Human cutaneous wounds are examples of such regulation. Only the basal keratinocytes in contact with dermal type I collagen in the underlying dermis express collagenase-1.13

With rare exception, the metalloproteases, uPA, and extracellular cathepsins are synthesized and secreted as inactive proenzymes,14–17 remaining anchored to the cell surface or in the extracellular matrix near the cell surface. These
unions imply that once activated, they target catalytic activity to the specific substrates only at the leading edge of the cell and within the pericellular space so that proteolysis does not lead to widespread protein destruction. In addition, surface anchoring brings proenzymes and activators into proximity, leading to efficient activation and affording additional but incomplete protease protection from their inhibitors. Special examples are uPA/uPAr and MMP-2/MT1-MMP/tissue inhibitor of metalloproteinase 2 (TIMP-2) interactions: pro-uPA is secreted as a soluble protein-binding entity with high affinity for the uPAr. Cellular plasminogen receptors bring into proximity the uPA–uPAr complex, increasing efficiency of plasminogen activation and subsequent plasmin-dependent proteolysis. Similarly, pro-MMP-2 interaction with TIMP-2 and MT1-MMP on the cell surface is necessary for activation of this gelatinase.

In general, ECP in the extracellular space can be activated by other ECPs, highlighting the link between these enzymes. MMPs are activated by many serine proteases (plasmin is a potent activator of most MMPs), cysteine proteases, by other MMPs such MT-MMP, or even by autocatalysis. In the plasminogen/plasmin system, secreted pro-uPA is converted to active uPA by plasmin. Other enzymes such as the MMPs, other serine proteases like kallikrein, factor XIla, and the cysteine cathepsins can also activate it. In the same manner, proteolytic cathepsin propeptide removal is accomplished by the action of different proteases such as pepsin, neutrophil elastase, various cysteine proteases, or even by autocatalytic activation at acidic pH. However, it remains uncertain how extracellular cysteine proteases are secreted from the cell and activated.

Despite these controls, unrestrained proteolytic activity by even low protease levels is potentially hazardous for cells. Additional protection is needed, and protease inhibitors help guarantee restraint of pericellular proteolysis.

TIMPs are important regulators of matrix metalloproteinase and adamalysin activity. Four members of the TIMP family are known (TIMP-1, -2, -3, and -4). They form noncovalent complexes with the active MMPs, and with some pro-MMPs, thereby inhibiting active MMPs and impairing pro-MMP activation. Less specifically, MMPs are inhibited by nonspecific circulating protease inhibitor proteins such as α-2 macroglobulin. Exogenous substances such as heparin can also inhibit MMPs.

Fibrinolytic inhibition may occur either at the level of the plasminogen activators, by inhibitors (plasminogen activator inhibitor [PAI]-1 and PAI-2), or at the level of plasmin, mainly by α2-antiplasmin. Plasminogen activator inhibitors belong to the serpins. Serpins are serine proteases inhibitors and hence derive their name (SErine PRotease INhibitors). PAI-1 inhibits both tPA and uPA, whereas PAI-2 inhibits only uPA. Interestingly, α2-antiplasmin and PAI-1 can be cleaved by MMP-3, resulting in neutralization of the inhibitor, and thus MMPs may also regulate the activity of other proteases by degradation of their inhibitors.

Lysosomal cysteine proteases are inhibited by the cystatins. Type 1 cystatins (A and B) are mainly intracellular, the type 2 cystatins (C, D, E/M, F, G, S, SN, and SA) are extracellular, and the type 3 cystatins (L-kininogen and H-kininogen) are intravascular proteins.

**Extracellular Proteases in the Vasculature**

Human arteries express small amounts of ECP such as MMP-2, tPA, and cathepsins that participate in tissue homeostasis. Atheromatous plaque, however, shows enhanced expression and activity of many MMPs (1, 2, 3, 7, 8, 9, 11, 12, 13, and 14), ADAMS (9 and 15), papalysins, neutrophil elastase, the fibrinolytic system (tPA and uPA), and cysteine proteases such cathepsin K, S, and V. Infiltrating macrophages are the principal and best known protease source, but common components of the vascular wall such as smooth muscle cells, endothelial cells, or fibroblasts also produce ECP such as MMPs, ADAMS, PAPP-A, tPA, uPA, and cathepsins.

The primary cause of this dysregulation remains unknown, but both increased transcription and protease activation and decreased protease inhibition may play important roles. It is interesting that ECP levels increase with the major coronary risk factors. Smoking increases plasma elastase levels. Hypertension and hypercholesterolemia induce elastase in rats and rabbits, respectively. Type 1 diabetic patients also have increased plasma and total neutrophil elastase. The significance of early protease presence in animal models exposed to cardiovascular risk factors is unknown but highlights how proteases contribute to disease even before vascular injury is established. ECP may contribute from early stages of vascular disease through multiple and complex mechanisms (Figure 3).

**ECM Degradation and Turnover**

Along with thrombus formation and clot fibrinolysis, ECM degradation is one of the best-studied extracellular protease functions and one of the earliest described. Collagenolytic activity was observed >40 years ago during amphibian metamorphosis in tadpole tails. MMPs degrade fibrillar elements such as fibrillar collagens and elastin, and nonfibrillar elements (nonfibrillar collagens, glycoproteins, and proteoglycans) such as type IV collagen, the proteoglycan perlecain or glycoproteins laminin and entactin, all constitut-
ents of most mature basal laminae. MMP subgroups are especially active against specific ECM components. Collagenases are active mainly against fibrillar collagens, gelatinases against elastin and nonfibrillar collagens, and stromelysins against noncollagen ECM components. Whereas MMPs are the best known ECM degradative enzymes, other ECPs can also degrade ECM components. The cysteine proteases cathepsin K, S, and L (for example) have potent elastolytic and collagenolytic activity. Recently, cathepsin V has been identified in atherosclerotic plaque specimens and exhibits the most potent elastase activity yet described among human proteases. The plasminogen system degrades laminin, fibronectin, vitronectin, and proteoglycans. Neutrophil elastase degrades collagen, elastin, laminin, fibronectin, and proteoglycan. In addition, ADAM 10 is widely expressed and cleaves collagen type IV in vitro.

ECM degradation by ECP plays a key role in plaque remodeling from early to advanced plaques. Excessive elastin and collagen degradation promoted by ECP may also lead to vascular wall weakening and progressive expansion of the coronary wall, as occurs in two-thirds of coronary atherosclerotic lesions. Positively remodeled coronary plaques contain MMP-2 and MMP-9, and show more MMP-2 activity than negatively remodeled segments. Many experimental data support a protease role in vascular enlargement. When proteases are increased, as occurs with MMP-9 overexpression in rat carotid arteries, or in circumstances in which there is protease inhibitor deficiency (as in TIMP-1–deficient mice), vessel circumference increases. Conversely, vessel enlargement is restricted when proteases are decreased, as in uPA-deficient mice or with increased protease inhibitor activity as in mice and rats with increased PAI or MMP inhibitors.

MMP inhibitors reduce constrictive remodeling after balloon angioplasty, as well, and excessive ECM degradation may be key for ACS development. MMP in situ matrix-degrading activity, tPA, neutrophil elastase, and cathepsin S and K overexpression are found in plaque shoulders where these ECPs act by reducing fibrous cap thickness and favoring rupture. In the advanced carotid atheromatous lesions of apolipoprotein E−/− mice, Serp-1 (a serine protease inhibitor) may improve plaque stability because it induces smooth muscle cell hypercellularity and increases the collagen content of the lesion core.

Cell Invasion Migration and Proliferation in Atherosclerosis and Restenosis

Vascular leukocyte and medial smooth muscle cell invasion, migration, and proliferation into the subendothelial space are major pathobiologic vascular hallmarks leading to initiation of atheromatous plaque. Similarly, intimal smooth muscle cell accumulation caused by invasion, proliferation, and migration from the media is key to neointimal formation after balloon or stent angioplasty. ECPs are fundamental in these cellular actions as demonstrated by plasminogen activator and MMPs such as gelatinases, which increase markedly after artery injury during vascular smooth muscle cell proliferation and migration from the media to the intima. Vascular lumen cells such as monocytes and lymphocytes use ECP to erode the basement membrane. Similarly, medial smooth muscle cells use these molecules to break the internal elastic lamina. Proteases are especially important in the latter because the internal elastic lamina is rich in elastin, one of the most resistant molecules to proteolysis. ECPs also induce intracellular signals for vascular cell migration and proliferation both by direct cell stimulation (such as uPA and uPAR or indirectly by modifying cell–cell or cell–matrix interactions such as laminin-5 cleavage by MMP-2 or liberation of E-cadherin by MMP-3 and MMP-7.

Protease contribution to invasion, migration, and proliferation is supported by many experimental studies. Protease overexpression as with uPA and MMP-9 after balloon angioplasty increase cell migration, proliferation, and neointimal formation. Conversely, protease deficiency such uPA and MMP-9−/− knockout mice show less neointimal formation after vascular injury. Protease contribution is also supported by studies in which MMP inhibitors slow smooth muscle cell chemotaxis and invasion through reconstituted basement membranes. Serine protease inhibitors such Serp-1 inhibit de novo carotid artery plaque growth in apolipoprotein E−/− mice and after balloon injury, mainly by a striking reduction in macrophage infiltration. Similarly, PAI-1 inhibits the invasion of human monocytes into interstitial tissue.

ECP as Autocrine Cell Modulators: Autocrine, Paracrine, and Endocrine Mode of Actions

ECPs released into the extracellular space can modulate cell behavior by cleaving other molecules through autocrine, paracrine, and endocrine modes of actions.

Growth Factor Modulation

ECPs activate many growth factors important to the vasculature through diverse mechanisms. They can directly cleave latent growth factors as in the activation of latent transforming growth factor (TGF)–β by plasmin, MMP-2, and MMP-9. They can cleave the growth factor-binding proteins, as with insulin-like growth factor-binding protein-4 and insulin-like growth factor-binding protein-5 being cleaved by PAPP-
A.75 or cleavage of insulin-like growth factor-binding protein-5 by MMP-1 or MMP-2.68 Many growth factors such as fibroblast growth factor (FGF), TGF-β, or vascular endothelial growth factor have strong affinity for specific matrix components. This allows the factor to be stored in a biologically inactive form. Proteolysis of these matrix molecules is the third mechanism by which ECPs modulate growth factors availability. Thus, cleavage of the proteoglycan perlecan by MMP-1, MMP-3, or plasmin,69 or heparan sulfate by plasminogen activator.70 can release bFGF. Likewise, plasmin released on extracellular matrix71 or decorin cleavage by MMP-2, -3, or -7 releases TGF-β.

**Inflammation Modulation**

ECP can modulate IL and chemokine activity, being agonists of the inflammatory response. This can occur, for example, in IL-1β precursor processing to its active form by MMP-2, MMP-3, and MMP-9.73 ECP, however, can also be inflammatory antagonists. Gelatinase A74 inactivates monocyte chemoattractant protein-3 or similarly IL-1β when degraded by MMPs.73 Whereas theoretical in the cardiovascular system, proteases may also generate immunogenic molecular fragments that stimulate immune or autoimmune responses.75

**The Importance of Shedding**

Many EPCs can cleave the extracellular domain of transmembrane proteins, including membrane-bound cytokines, adhesion molecules, growth factors, enzymes, or receptors, releasing them from the cell surface. Proteases participating in the extracellular cleavage of integral plasma proteins are collectively referred to as sheddases (or secretases). Shedding is a biological pathway by which ECPs regulate many cell functions. By shedding receptor removal, cells often downregulate surface signaling. Cell adhesion receptor shedding also enables cells to modulate cell–cell and cell–extracellular matrix interactions. By shedding, proteases can also convert membrane-anchored molecules or receptors into diffusible factors expanding their effects or, conversely, convert membrane receptors into soluble competitors of their own ligand.

The best known sheddases are the ADAM family, but also some MMPs and serine proteases act as sheddases. One of the best-studied shedding processes is the cytokine TNF-α, being released from its membrane-bound precursor by the ADAM-17 member (also known as TNF-α converting enzyme).76 Other examples important to the vasculature are the shedding of TNF-α,77 FGF receptor-1,78 IL-6 receptor,79 macrophage colony-stimulator factor,79 angiotensin-converting enzyme,80 L-selectin,81 and vascular cell adhesion molecule.82 Interestingly, many nonsteroidal anti-inflammatory drugs such as aspirin exert anti-inflammatory properties by inducing the L-selectin shedding in neutrophils83 in addition to inhibiting prostaglandin synthesis through the cyclooxygenase blockade. ECP cytokine shedding may contribute to systemic inflammation, as in atherosclerotic disease through TNF-α shedding into blood. TNF-α, along with other cytokines, stimulates the liver production of common blood systemic inflammatory atherosclerotic markers such as C-reactive protein, fibrinogen, and serum amyloid A.

**Apoptosis**

Apoptosis contributes to plaque progression, rupture, and thrombus formation in atherosclerosis. Many circumstances involving ECP may trigger programmed cell death. Although the best apoptotic molecules known are the intracellular caspase family of cysteine proteases, extracellular MMPs can also mediate the initiation of apoptotic signaling intervening in Fas-mediated cell apoptosis.84 ECPs also promote apoptosis by cleaving cell–matrix interactions, a curious phenomenon known as “anoikis,” as demonstrated for the plasminogen activation system in vascular smooth muscle cells.85 Smooth muscle cell apoptosis in plaque shoulder regions may contribute to ACS by favoring plaque weakness because smooth muscle cells compete with proteases ECM degradation by secreting ECM and therefore increase fibrous capsule strength. Extracellular proteases, by releasing apoptotic cytokines such TNF-α, also contribute to cell apoptosis. Despite these actions, protease effects on apoptosis are complex and under special circumstances might also decrease apoptosis, as demonstrated by some protease inhibitors that actually promote rather than inhibit apoptosis.82

**Angiogenesis**

Normal coronary arteries have well-developed adventitial vasa vasora. Atheromatous plaque and restenotic lesions also develop intimal neovascularization, apparently necessary for plaque and neoimtimal growth. Many angiogenic growth factors such as bFGF or vascular endothelial growth factor stimulate MMPs,86 serine87 and cysteine88 expression. These proteases are found near neovascularization sites and are likely fundamental for angiogenesis. ECP are implicated in many angiogenic stages, including matrix degradation, endothelial migration and proliferation, and releasing angiogenic growth factors from the extracellular matrix. Vascular endothelial growth factor mobilization by MMP-9 is a typical example.89 The ECPs have similar roles in capillary morphogenesis. Such roles are well-characterized for gelatinase A90 and cathepsin S.88 in which their inhibition reduces tubule formation or, conversely, their overexpression as with gelatinase A88 increases tube-forming activity.

Without neovessels, atheromatous plaque and neointima hyperplasia after stenting may not grow. This concept makes antiprotease treatment a hypothetically attractive strategy for treating atherosclerosis and restenosis. This concept must be tempered through because proteases have dual angiogenic actions and paradoxic results may occur. For example, plasminogen cleavage by MMP-7 or MMP-9 releases angiostatin,91 and collagen XVIII cleavage by elastases92 releases endostatin. Angiostatin and endostatin are 2 fragments with negative angioregulatory activity. Through this effect, protease inhibition might paradoxically promote angiogenesis instead of limiting it.

**Extracellular Proteases in the Diagnosis and Prognosis of Arterial Disease**

Besides protease function and vascular effects, protease detection and quantitation in peripheral blood may help detect atheromatous disease stages and aid in clinical decision-making.
Elevated tPA levels predict coronary artery disease events and stroke in healthy subjects, independent of established risk factors, as well as recurrent coronary events and cardiovascular death in patients with established coronary artery disease.

Serum MMP-2 and MMP-9 are elevated in ACS, but not in stable angina. PAPP-A plasma levels deserve special consideration for detecting ACS. PAPP-A levels identify high-risk patients since they are found elevated in ACS patients with normal troponins and indeterminate C-reactive levels. Such patients might otherwise remain undiagnosed. Plasma PAPP-A has recently been demonstrated as a strong independent predictor of ischemic cardiac events and the need for revascularization in ACS patients with low troponin levels.

Protease shedding may be fundamental for detecting atherosclerotic process molecules and may have value for diagnostic or prognostic information in apparently healthy and asymptomatic populations. Potential candidates are soluble intercellular adhesion molecule-1 or soluble P-selectin, which when detected in peripheral blood shows some clinical usefulness.

ECP detection and measurement in peripheral blood is finding use in other cardiovascular diseases, in which ECP such as MMP-2 and MMP-9 are found in chronic heart failure or patients affected by abdominal aortic aneurysms.

Summary, Conclusions, and Final Considerations

ECPs are a complex and heterogeneous family of enzymes showing important similarities in structure, function, and control. There is consequently much substrate and function overlap. If a member, group, or family is inhibited, other members or families might substitute for them, causing no net biologic effect. This may explain why protease inhibitors just retard, rather than suppress, the desired effect in many atherosclerotic/restenosis animal models. ECPs consequently should not be viewed as individual molecules or families, but instead as a group.

ECP activity is highly regulated at multiple levels. Loss of fine control contributes actively to atherosclerosis/restenosis from their initial stages through a variety of mechanisms. They participate not only in disease through abnormal tissue destruction as in extracellular matrix degrading molecules but also by direct effects on cells such as by modulating cell behavior and leading to cell proliferation, migration and invasion, apoptosis, and morphogenesis. In addition, ECP by acting on other proteins (modulating the inflammatory response, growth factors availability, or transmembrane proteins) can indirectly modulate cell behavior. ECP modes of action are autocrine, paracrine, and endocrine. In addition to these complex and extended actions, antagonist effects as seen in inflammation, apoptosis, angiogenesis, or through shedding complicate the pathobiologic complexity of these molecules even more.

Many selective ECP inhibitors have been used in clinical trials for cancer, chronic inflammatory diseases, and restenosis therapies, as with Batimastat (a MMP inhibitor) eluted from phosphorylcholine BioDivysio stents. Unfortunately, many of these trials failed to show benefit. Considering these enzymes as a group, the knowledge of the biological, complex, and sometimes antagonistic effects and their common control may help design and interpret new clinical trials.

Much remains unknown about ECP biology. They appear to have great potential for diagnosis, control, and treatment of many important diseases of the cardiovascular system. Success in understanding proteases at the molecular level is the first step that will benefit new diagnostic and therapeutic strategies in primary and secondary prevention.

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