Metalloproteases cleave proteins and peptides and deregulation of their function leads to pathology. Understanding of their structure and mechanisms of action is necessary to the development of strategies for their regulation. Among metallopeptidases are the metzincins, which are mostly multi-domain proteins with ~200-260-residue globular catalytic domains showing a common core architecture characterized by a long zinc-binding consensus motif, HEXXHXXGXXH/D, and a methionine-containing Met-turn. Metzincins participate in unspecific protein degradation like digestion of intake proteins and tissue development, maintenance, and remodelling. But they are also involved in highly specific cleavage events to activate or inactivate themselves or other (pro)enzymes and bioactive peptides. Metzincins are subdivided into families and seven such families have been analyzed at the structural level: the astacins, ADAMs/adamalysins/reprolysins, serralysins, matrix metalloproteinases, snapalysins, leishmanolysins, and pappalysins. These families are reviewed from a structural point of view.

Cleavage of peptide bonds is essential for life and the factors responsible for peptide cleavage are ubiquitous. Among them are metallopeptidases (MP), which are mostly zinc-dependent peptide-bond hydrolases. They participate in metabolism through both extensive and unspecific protein degradation and controlled hydrolysis of specific peptide bonds (1). Deregulation of such vast degrading potential leads to pathologies and, in addition, MPs may also act as virulence factors during poisoning and microbial infection. Such a wide range of biological functions makes structural studies of these proteins indispensable to any understanding of their function and to the design of novel, highly-specific therapeutic agents to modulate their activity (2).

Most MPs are members of a protease tribe named zcin and they possess a short consensus amino-acid sequence, HEXXH (amino-acid one-letter code). This motif contains two protein ligands of the catalytic zinc and a glutamate that acts as general base/acid during the catalytic process (3,4). A third metal ligand is a solvent molecule, further bound to and polarized by the glutamate. This solvent performs nucleophilic attack on the carbonyl carbon of the scissile bond of a bound substrate leading to a tetrahedral gem-diolate reaction intermediate, which is stabilized by the positively-charged metal ion and neighboring protein residues (5). In a final elimination step catalyzed by the general base/acid, a proton is transferred to the scissile amide-nitrogen atom, thus breaking the bond (5,6).

Zincins are divided into the gluzincin, aspzin cin, and metzin cin clans (4,7). The latter contains mostly multi-domain proteins with an N-terminal pro-domain engaged in latency maintenance, a catalytic protease domain, and further downstream domains engaged in protein-protein and cell-cell interactions, and other regulatory functions. The protease domain is characterized by a C-terminally extended zinc-binding motif, HEXHXXXGXXH/D, with a hallmark glycine and a third zinc-binding histidine or aspartate. In addition, a methionine is present in a conserved downstream turn, the Met-turn (3,7,8). Metzincins split into families, seven of which have been characterized at the structural level for at least one of their members: astacins, ADAMs/adamalysins/reprolysins, serralysins, matrix metalloproteinases, snapalysins, leishmanolysins, and pappalysins. In addition, a series of sequences reported from genome sequencing projects indicate there are further structurally yet uncharacterized families, tentatively referred to as fraglysin s, gametolysins, archaemetzincins, thuringilysins, coelilysins, ascomycolysins, helico lysins, and cholerilysins (for a detailed review, see (7)).

**The metzin cin fold**

To date, more than 200 structures of metzincins, comprising at least the catalytic domain, have been deposited with the Protein Data Bank (see Supplementary Table 1). In the present review, seven lead structures of each of the aforementioned families are discussed: Astacus astacus astacin, Crotalus adamanteus adamalysin II, Pseudomonas aeruginosa...
aeruginolysin, human neutrophil collagenase (alias MMP-8), Streptomyces caesipitous neutral protease (alias ScNP or snapalysin), Leishmania major leishmanolysin, and Methanosarcina acetivorans ulilysin (9-15). These prototypes cover distinct kingdoms of life and represent archaea, bacteria, protozoa, crustaceans, reptiles, and higher mammals. The structures reveal that metzincins share a common scaffold and active-site environment, but each family has distinguishing structural elements. Mature catalytic domains are ~200-260-residue globular moieties that bifurcate into an upper N-terminal and a lower C-terminal subdomain (NSD and CSD, respectively) with respect to a central active-site cleft. Substrates bind horizontally to this cleft from left to right in an approximately extended conformation (Fig. 1a; all topological indications refer to the standard orientation displayed in Fig. 1).

The NSD displays a five-stranded twisted β-sheet at the top (except leishmanolysin, which has four strands; Fig. 1a). All strands (βI to βV) except the fourth are parallel to each other and to any substrate that is bound in the cleft. The antiparallel strand, βIV, forms the lower edge of this subdomain and creates an upper rim or northern wall of the active-site crevice (16). This strand binds a substrate in an antiparallel manner, mainly on its non-primed side. The αC, and the active-site helix, respectively. Both are arranged on the concave side of the β-sheet in identical manner in all metzincin structures (Fig. 1b). Helix αB superimposes well in all seven structures (Fig. 2a) and encompasses the first half of the zinc-binding motif, which includes the first two zinc-binding histidine residues (Figs. 1, 2a). At the end of αB, the polypeptide chain takes a sharp, downward turn, mediated by the glycine of the consensus sequence. The main-chain angles of this residue in the different lead structures indicate that any other residue would be in a high-energy conformation and, thus, disfavored, with the exception of ulilysin (see below).

The CSD starts after this glycine and the chain leads to the second zinc ligand, a histidine or an aspartate, which approaches the metal from below (Fig. 1). This subdomain contains few regular secondary-structure elements, mainly a C-terminal helix αC at the end of the polypeptide chain. Helices αB and αC are connected by structures that vary both in length and conformation. However, all structures coincide at a conserved 1,4-β-turn containing a methionine at position three, the Met-turn, which is separated from the third zinc-binding histidine by connecting segments of six to 53 amino acids in the different structures. The Met-turn is superimposable (including the conformation of the methionine side chain, see Fig. 2a) and is positioned underneath the catalytic Zn$^{2+}$, forming a hydrophobic pillow. However, no direct contact with the metal is observed. Mutation studies indicated a role for this methionine in the folding and stability of the catalytic domains, although the strict conservation of this residue remains to be explained (18-20). The S$_1$' pocket of metzincins is shaped at the top by a protruding bulge made by LβIIIβIV, and at the bottom by a wall-forming segment made up of residues intercalated between the Met-turn and the C-terminal helix αC (16). This segment diverges in structure and length (ranging from 11 to 37 residues between the Met-turn methionine and the first residue of αC), in all seven of the reference structures.

The zinc-binding site

The catalytic zinc ion lies roughly at the center of the bottom of the active-site cleft. It is coordinated by the Nε2 atoms of the three consensus histidines (two histidine Nε2 atoms and an aspartate Oδ2 atom in snapalysin) and the catalytic solvent molecule-substituted by other ligands in the enzyme+inhibitor/product complexes reported (see Supplementary Table 1)-in an approximately tetrahedral or trigonal pyramidal manner. Some metzincins display a further protein ligand at a slightly greater distance from the catalytic cation in the form of a tyrosine Oη1 atom, as seen in unbound astacin and serralysins and as hypothesized in ulilysin (21). This tyrosine residue lies within the Met-turn, two positions ahead of the methionine. In (unbound) snapalysin, a tyrosine lies two positions downstream of the metal-binding aspartate, though no longer within binding distance of the zinc ion. These tyrosine residues flip back and forth during substrate anchoring, cleavage and product release, in a motion referred to as the tyrosine switch. In this, they may play a role in substrate and catalytic-solvent binding and stabilization of the tetrahedral intermediate or the product amino group (7,9,22-24). Such a role is performed by other, non-conserved residues in tyrosine-lacking metzincins.

Structural relatedness among families

A structure-based sequence alignment reveals that, with the exception of the region comprising the
Distinguishing features of each family

Astacin is a 200-residue digestive enzyme from the crayfish, Astacus astacus, and the first member of the astacin family to be structurally analyzed (9). Through protein degradation, growth-factor activation, extracellular matrix turnover and extracellular coat degradation (hatching), astacins participate in diverse biological processes such as digestion, development, and tissue remodelling and differentiation (e.g. promoting cartilage and bone formation and collagen biosynthesis)(27).

The 3D structure of astacin evinces a packman-like spherical shape and two subdomains of approximately equal size (Fig. 1a; (9)). Whilst this proteinase contains only a pro-peptide and a catalytic MP domain, most other astacins display additional C-terminal MATH, MAM, CUB-like, S/T-rich, I-, EGF-like, Tox1, and transmembrane modules (for details, see (8,27,28)). The astacin family has the longest region of the CSD lacking regular secondary structure elements, just a small helix and a short β-ribbon, although this is the sequentially most conserved connecting segment among metzincins (see Table 1 in (7)). The protein scaffold is cross-linked by four conserved cysteine residues forming two disulfide-bridges (see Fig. 1). The first two residues of the mature enzyme are buried in an internal cavity in the CSD and the N-terminal α-amino group establishes an interaction with a conserved glutamate next to the third zinc-binding histidine. The unbound coordination of the catalytic zinc is trigonal-bipyramidal due to the presence of the fourth invariant, though somewhat more distal, tyrosine zinc ligand from the Met-turn (see Fig. 1a). In addition to astacin, the structures of human tollloid-like protease 1 and bone morphogenetic protein 1 have recently been reported (29).

Serralysins are ~50-kDa bacterial virulence factors secreted as autoactivatable zymogens by pathogenic γ-class proteobacteria (30). These organisms are responsible for human diseases like meningitis, endocarditis, pyelonephritis, plague, dermatitis, soft-tissue infections, septicemia, melioidosis, pneumonia and other respiratory and urinary tract infections. They play a major role in hospital-acquired infections due to their capacity to produce surgical-wound infections and to infect neonates. As part of the virulence potential of these bacteria, serralysins are directed against coagulation factors and defense-oriented proteins, protease inhibitors, lysozyme and transferrin, and may cause an anaphylactic response.

The first serralysin to be biochemically and structurally characterized was Pseudomonas aeruginosa aeruginolysin (10). Its mature 220-residue catalytic domain lacks disulfide connections and is flanked on its C-terminal end by a calcium-stabilized β-roll domain. As in astacin, its two subdomains are of similar size. The polypeptide chain starts with an α-helix in the CSD, characteristic for the family, that is anchored to the molecular body by a conserved salt bridge with the C-terminal helix αC (Fig. 1b). The NSD features a flap, made up by an elongated Lβ1αA, and runs across the convex surface of the β-sheet. This flap varies greatly among serralysins (20 structures have been reported; see Supplementary Table 1), distinctly affecting substrate binding. The CSD of aeruginolysin presents an extra α-helix within the segment linking the Met-turn with the wall-forming stretch, and a second flap shaped by residues of the connecting segment. These elements also modulate substrate binding. Comparison of aeruginolysin, which was first solved in complex with a bound tetrapeptide (10), with the closely-related structure of unbound Serratia marcescens serralysin reveals that the unliganded zinc coordination is similar to astacin (bipyramidal-trigonal). It also includes a tyrosine from the Met-turn that undergoes a hinge motion upon substrate binding (31).

Streptomyces caesipitosus snapalysin is a secreted neutral protease, which comprises a 132-residue catalytic domain preceded by an alanine-rich 100-amino acid N-terminal extension comprising a signal-peptide and a pro-domain. Similar sequences have been reported from other Streptomyces species and they have been termed SnpA (alias Prt and snapalysin), Mpra and SnpA, respectively. They show milk-hydrolysing activity.
Snapalysin is the smallest metzincin and the only family member that has been structurally characterized. Its structure recalls a flattened ellipsoid and bifurcates into two asymmetric subdomains (12). It displays all the characteristic metzincin features, connected by short loops. Distinguishing elements are a small LβββIII protruding from the upper sheet within the NSD, a small bulge on top of the primed side of the active-site crevice, a short helix in Lβααβ, and a calcium-binding site (Fig. 1a). In addition, an aspartate is found at the position of the third zinc-binding histidine and, two positions ahead in the sequence, a conserved tyrosine approaches but not binds the metal.

Matrix metalloproteinases (MMPs), are secreted or membrane-bound proteinases discovered 40 years ago participating in tail resorption during tadpole-to-frog metamorphosis. They are mainly found in in higher mammals, although related sequences have been found in fish, amphibians, insects, plants, prokaryotes, and viruses. Through turnover of extracellular matrix proteins, MMPs are involved in tissue resorption, remodelling and repair, as observed during embryogenesis and development, branching and organ morphogenesis, and angiogenesis. However, their potent proteolytic potential or its absence may also lead to pathologies including inflammation, ulcers, rheumatoid and osteoarthritis, periodontitis, heart failure and cardiovascular disease, fibrosis, emphysema, and cancer and metastasis (32). More recently, MMPs have been observed to be engaged in (in)activation events following limited proteolysis, as observed in apoptosis, intestinal defense-protein activation, but also in pathologies including stroke, HIV-associated dementia, atherosclerosis, multiple sclerosis, bacterial meningitis, and Alzheimer’s disease. MMP include extracellular proteins, such as other (pro-)proteinases, inhibitors, clotting factors, antimicrobial peptides, and chemotactic and adhesion molecules. In common with ADAMs (see below), MMPs are also involved in ectodomain shedding of growth factors, growth-factor binding proteins, hormone and hormone receptors, cytokines and cytokine receptors from the cellular surface (33).

Like other metzincin families, MMPs are mosaic proteins constituted by a series of inserts and domains. These may include a ~20-residue secretory signal peptide, an ~80-residue pro-peptide, a 160-to-170-residue zinc- and calcium-dependent catalytic proteinase domain, a linker region, and a fourfold-propeller haemopexin-like C-terminal domain. Further insertions may comprise fibronectin type-II-related domains, a collagen type-V-like and a vitronectin-like insertion domain, a cysteine-rich, a proline-rich and an interleukin-1 receptor-like domain, an immunoglobulin-like domain, a glycosyl phosphatidylinositol linkage signal, a transmembrane domain and a cytoplasmic tail. Naming of MMPs started historically with fibroblast collagenase as MMP-1 and has currently reached MMP-28, with 24 different forms described in humans (34). Those MMPs encompassing a transmembrane anchor gave rise to the MT-MMP subfamily (16,32). Zymogen activation proceeds in MMPs according to a cysteine-switch or velcro mechanism. This removes pro-domain and switches from an inactive state, where the Sγ atom of a cysteine residue within a conserved motif, PRCGVPD, substitutes the catalytic solvent molecule in the zinc coordination sphere, to the fully-accessible active enzyme (35,36). MMPs are the structurally most thoroughly studied metzincin family, with over 120 structures reported (see Supplemental Table 1). The mature catalytic domain of human neutrophil collagenase (MMP-8; (13)) has a shallow active-site cavity, which separates a larger NSD (~120 residues) from a smaller CSD (~40 amino acids), and generally a deep hydrophobic S1 pocket. No disulfide bonds are present in the structure. The N-terminal α-amino group is anchored to the first of two conserved aspartates imbedded in αC. The NSD displays an S-shaped double loop connecting strands βIII and βIV, which embraces a structural zinc cation and a tightly bound calcium ion. The downstream residues of this segment form a prominent bulge that protrudes into the active-site groove. LβIVβV and LβIIβIII contribute to a second calcium-binding site on top of the NSD β-sheet (Fig. 1a,b). In the CSD, the MMP-8 chain displays the shortest and most conserved connecting segment within metzincins.

Adamalysins/ADAMs/reprolysins split into three subgroups, the snake venom MPs, the mammalian ADAMs, and the likewise mammalian ADAMTSs (37-40). The former are responsible for post-envenomational haemorrhage through digestion of extracellular matrix components surrounding capillaries, resulting in tissue necrosis. ADAMs, in turn, were originally described to play a role in fertilisation and sperm function in mammalian reproductive tracts. They are involved in myogenesis, development and neurogenesis, differentiation of osteoblastic cells, cell-migration modulation, and muscle fusion. They are also engaged in human disorders like asthma, cardiac hypertrophy, obesity-associated adipogenesis and cachexia, rheumatoid arthritis, endotoxic shock, inflammation, and Alzheimer’s disease. They also have a major role in protein ectodomain shedding as described previously for MMPs. Finally, some family members lacking the
transmembrane domain and harboring multiple copies of a thrombospondin 1-like repeat and a CUB domain gave rise to a distinct subfamily of soluble extracellular proteases, the ADAMTSs (41). These enzymes disable cell adherence by binding to integrins. They are also involved in gonad formation, embryonic development and angiogenesis, and procollagen activation, as well as in inflammatory processes, cartilage (aggrecan) degradation in arthritic diseases, bleeding disorders, and glioma-tumour invasion.

All adamalysins/ADAMs/reprolysins are extracellular multidomain proteins containing a catalytic zinc- and calcium-dependent MP domain. In addition, they can display a pro-domain, C-terminal disintegrin-like, cysteine-rich, C-type lectin, EGF-like, thrombospondin 1-like, and/or transmembrane domains, as well as a cytoplasmic domain. Latency is maintained by the pro-domain and activation is believed to occur as in MMPs, i.e. by cleavage of the pro-domain according to a cysteine switch-like mechanism (7,36,42). The first catalytic domain structure to be analyzed was that of adamalysin II from *Crotalus adamanteus* snake venom (11). This is a compact 203-residue molecule of oblate ellipsoidal shape, notched at the periphery to render a relatively flat substrate-fixing cleft. This cleft separates a large ~150-residue NSD from a small ~50-residue CSD (Fig. 1a). Both the N- and the C-termini are surface located; the former is linked by a salt bridge to the C-terminal helix αC (7). Adomalysin II deviates most from the metzincin consensus within the conserved regular secondary structure elements, especially at βI, αA and αC (Fig. 2b). Inserted into the common scaffold, two additional helices are found within the NSD. In the CSD, two disulfide-bonds cross-link the irregular connecting segment and attach αC to the NSD, respectively. A calcium ion is located on the surface, opposite the active site and close to the C-terminus (Fig. 1a). The S1’ pocket, characterized by a pronounced bulge-segment LβIVβV, is hydrophobic and deep, reminiscent of some MMPs. In addition to adamalysin II, a number of snake venom MPs, ADAM-17, ADAM-33, ADAMTS-1, -4, and -5 have been structurally analysed to date (see Supplementary Table 1).

Leishmanolysins are cell-surface proteins present in most trypanosomatid, plasmodiid, and sarcocystid protozoans. They constitute the major component of the promastigote surface and are enzymatically active against polypeptide substrates. They cleave CD4 molecules at the surface of human T cells and protect promastigotes from lysis by complement proteins, suggesting a possible role as a virulence factor. Related sequences have been found in mammals (here called invadolysin), fruitfly, thale cress, nematodea, and bacteria (7,43). The only structurally analyzed family member is *Leishmania major* leishmanolysin. It is synthesized as a 602-residue inactive precursor in the endoplasmic reticulum with a signal and a 100-residue pro-peptide, which includes a highly conserved cysteine residue potentially acting as a cysteine switch (see above). Activation liberates a mature MP of ~280 residues, followed by a ~200-residue C-terminal domain. A 63-residue insertion domain is observed between the glycine and the third zinc-binding histidine of the long consensus motif (Fig. 1a). The MP domain is the most asymmetric among *metzincins*, with a 175-residue NSD and just a ~45-amino acid CSD. Its N-terminus is located on the back left surface. The NSD is characterized by a β-sheet, which lacks strand βII (Fig. 1a,b), and by the presence of two unique ~40-amino acid inserted flaps, which account for most of the differences in size with the other proteins of the clan. The NSD is cross-linked by two disulfide bonds. Preceding strand βIV, a slightly prominent bulge segment lies on top of the shallow, medium-sized S1’ pocket, which is delimited by the wall-forming segment and the beginning of active-site αB. At the end of the CSD, αC is followed by a segment in extended conformation, which runs from left to right across the back surface (14).

The most recent family to be structurally characterized are the pappalysins. They were named after human PAPP-A, a heavily-glycosylated 170-kDa multidomain protein specifically cleaving insulin-like growth factor binding proteins (44). Proulilysin is a 38-kDa archaeal protein from *M. acetivorans*, which shares sequence similarity with PAPP-A, but it encompasses only the pro-domain and the catalytic domain (15). The pro-protein may undergo cysteine-switch mediated activation, as suggested by the presence of a conserved cysteine in the pro-domain. Activation occurs autolytically in the presence of calcium. With 261 residues, mature ulilysin is the largest MP of all metzincin catalytic domains. As distinguishing features, it presents in the NSD a loop dividing strand βII into two substrands (βII and βII’), and a β-ribbon inserted within LβIIIβIV that protrudes from the molecular surface and frames the active-site on its primed side. The segment connecting αA with βI is largest among metzincins and covers almost all the back of the molecule from the NSD to the CSD in a cape-like fashion and includes two unique α-helices. The glycine of the zinc-binding motif is replaced in ulilysin and a small subset of pappalysins by an asparagine under slight variation of the main-chain angles, which do not correspond here to a high-energy
conformation but to a left-handed α-helix. Overall, the chain trace is indistinguishable from other metzincins (see Fig. 1 and (7)). The CSD evinces two disulfide bonds and a unique two-calcium site. This site is a molecular switch for activity, as the proteinase can be reversibly inhibited through calcium chelators (15,21,45). Finally, in the absence of an unbound structure, ulilysin may possess a fifth zinc-binding tyrosine ligand provided by the Met-turn that is swung out upon substrate binding.

**Conclusions**

The metzincins constitute a clan of ubiquitous MPs present in all kingdoms of life, which are pivotal for physiology and pathology. So far, seven families have been structurally analyzed. The clan represents a case of divergent evolution from an urmetzincin, which may not look very different from the smallest member, snapalysin. Into such a minimal scaffold, evolution has introduced unique structural elements conserved among each family. Based on the presence of an extended zinc-binding consensus sequence pattern, several more families have been suggested to enlarge the clan, although future structural analysis will be required to confirm their ascription. Structural information on each of the seven families may help in the elucidation of common catalytic and processing mechanisms and to ascribe the function of proteins encoded by newly discovered gene sequences.

**REFERENCES**


**FOOTNOTES**

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The abbreviations used are: 3D, three-dimensional; CSD, C-terminal subdomain; MMP, matrix metalloproteinase; MP, metallopeptidase; NSD, N-terminal subdomain.

**FIGURE LEGENDS**

**Fig. 1** – (A) Richardson plots of the catalytic MP-domains of the structurally characterized *metzincin* prototypes shown in standard orientation, i.e. viewing into the active-site groove, which runs horizontally from left (non-primed side) to right (primed side). This orientation is employed throughout the text to refer to distinct regions of the structures, i.e. left, right, back, front, etc. Depicted are, from left to right and top to bottom, astacin (PDB 1ast), aeruginolysin (PDB 1kap), adamalysin II (PDB 1iag), human neutrophil collagenase (MMP-8; PDB 1jan), *S. caesius* neutral proteinase (snapalysin; PDB 1c7k), leishmanolysin (PDB 1lml), and ulilysin (PDB 2cki). The common β-strands and α-helices are shown in orange and cyan, respectively. The N- and C-termini are labeled and the side chains of the zinc-binding histidines/aspartates (blue), general base (pink), Met-turn methionine and disulfide-bonding cysteines (yellow), and zinc-binding tyrosines (where present; green) are displayed as sticks. Preceding, inserted, and following (sub)domains (in leishmanolysin and aeruginolysin) have been omitted for clarity. Zinc ions are shown as magenta spheres and calcium cations as red spheres. (B) Topology scheme of each of the metzincin representative structures (same order as in (A)), with helices as rods, strands as arrows, and amino acids as ellipses. Common elements are depicted in cyan and orange as in (A) and are labeled (α-helices, from A to C, β-strands, from I to V, amino acids as dark ellipses with white lettering).
Disulfide bonds are shown as orange connections. Distinguishing regular secondary structure elements of each structure are shown in white.

Fig. 2 – Overlay of structural segments common to the seven prototypes as Cα plots. (A) The active-site helix αB (including the side chains of the zinc-liganding histidines and aspartate, and the general-base/acid) and the Met-turn (with the methionine side chain). Color coding: astacin, blue; adalysin II, cyan; leishmanolysin, red; MMP-8, green; aeruginolysin, white; snapalysin, yellow; and ulilysin, orange. The magenta curved arrows indicate where an extra domain is inserted in leishmanolysin. (B) The upper-domain β-sheet (strands βI-βV; in cyan, blue, green, orange, and yellow, respectively), the posterior helix αA (red) and the C-terminal helix αC (purple) as found in the seven leads. Leishmanolysin lacks strands βII.
Catalytic domain architecture of metzincin metalloproteases

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