FEBS Letters 354 (1994) 1–6

FEBS 14692

Minireview

Families of zinc metalloproteases

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Received 22 August 1994; revised version received 19 September 1994

Abstract A scheme based on the zinc binding site [1992, FEBS Lett. 312, 110–114] has been extended to classify zinc metalloproteases into distinct families. The gluzincins, defined by the HEXXH motif and a glutamic acid as the third zinc ligand, include the thermolysin, endopeptidase-24.11, aminopeptidase, angiotensin converting enzyme, endopeptidase-24.15, and tetanus and botulinum neurotoxin families. The metzincins, defined by the HEXXH motif, a histidine as the third zinc ligand and a Met-turn, include the astacin, serralysin, reprolysin and matrixin families. The inverted zincin motif, HXXEH, defines the inverzincin family of insulin-degrading enzymes, the HXXE motif defines the carboxypeptidase family, and the HXH motif DD-carboxypeptidase.

Key words: Metalloproteinase; Peptide hydrolase; Zinc ligand; Endopeptidase-24.11; Aminopeptidases; Angiotensin converting enzyme

1. Introduction

In recent years the number of identified zinc metalloproteases/peptidases has increased dramatically. Members of this superfamily of enzymes are involved in processes as diverse as embryonic development and bone formation, tetanus and botulism toxins, reproduction, arthritis and cancer. Several papers have appeared over the last five years identifying unique signatures within the amino acid sequences of the zinc metalloproteases, and placing the enzymes into distinct family groups on the basis of sequence and, more recently, structural similarities [1–6]. Jiang and Bond [3] compared the sequences around the HEXXH motif to classify zinc metalloproteases into five distinct families: thermolysin, astacin, serratia, matrixin, and reprolysin metalloproteases. The latter four families have an extended zinc binding site, HEXXHXXGXXH, where the third histidine acts as the third zinc ligand instead of the more distant glutamic acid in thermolysin. Following the determination of the crystal structures of members of two of these families (astacin from crayfish and adamalysin II from snake venom), Bode et al. [4] further classified these latter four families into a superfamily, the 'metzincins', as they all possess a methionine containing turn of similar conformation (the Met-turn). The same authors also suggested that the larger superfamily of zinc metalloproteases possessing the HEXXH motif be termed the 'zincins'.

From recent data it is obvious that this classification into five families is a gross over simplification as the 'thermolysin-like' zinc metalloproteases can be grouped, like the metzincins, into distinct families. Although the HEXXH motif has been used extensively to identify zinc binding sites in metalloproteases when new amino acid sequences are obtained, at least three other zinc binding motifs have been identified in zinc metalloproteases. In this article I have attempted to present an overview of the relationships both between and within the families of zinc metalloproteases by summarising these observations and hypotheses, and extending them to include other known zinc metalloproteases/peptidases. What follows is a brief description of the distinguishing features of the various families of zinc metalloproteases which have not been dealt with elsewhere [3,4].

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2. Zincins

The zincins are those zinc metalloproteases which contain the ***H***EXX***H*** short zinc binding consensus sequence [4] (see Fig. 1). From herein italicised bold letters represent positively identified zinc ligands; underlined letters represent putative zinc ligands; bold letters represent residues involved in catalysis; B stands for bulky, apolar residue; X stands for any amino acid; and the numbering scheme used is arbitrary with #1 being placed on the first zinc ligand in the short zinc binding motif, i.e. the most N-terminal ligand except in the case of DD-carboxypeptidase (after [3]).

2.1. Gluzincins

A number of zinc metalloproteases have the ***H***EXX***H*** short zinc binding consensus sequence containing the first two zinc ligands and a glutamic acid as the third zinc binding ligand, e.g. thermolysin, endopeptidase-24.11, leukotriene A_4 hydrolase, etc. To distinguish these from the metzincins (section 2.2) I propose the name 'gluzincins' for this subset of zinc metalloproteases.

2.1.1. Thermolysin family. Thermolysin and several related bacterial metalloproteases, including *Bacillus sp.* neutral proteases, *Pseudomonas aeruginosa* elastase and *Legionella pneumophila* protease, have two well-conserved regions involved in zinc binding (Fig. 1). The short zinc binding motif is contained within the longer consensus sequence ***H***EXX***H***XBT, while the glutamic acid third zinc ligand lies 25 residues C-terminal to the zincin motif in the consensus sequence GXBN***E***XBS**D** [3].

2.1.2 Endopeptidase-24.11 family. In mammalian endopeptidase-24.11 (neprilysin; EC 3.4.24.11) the glutamic acid third zinc ligand has been identified as lying 64 residues on the

SSDI 0014-5793(94)01079-X

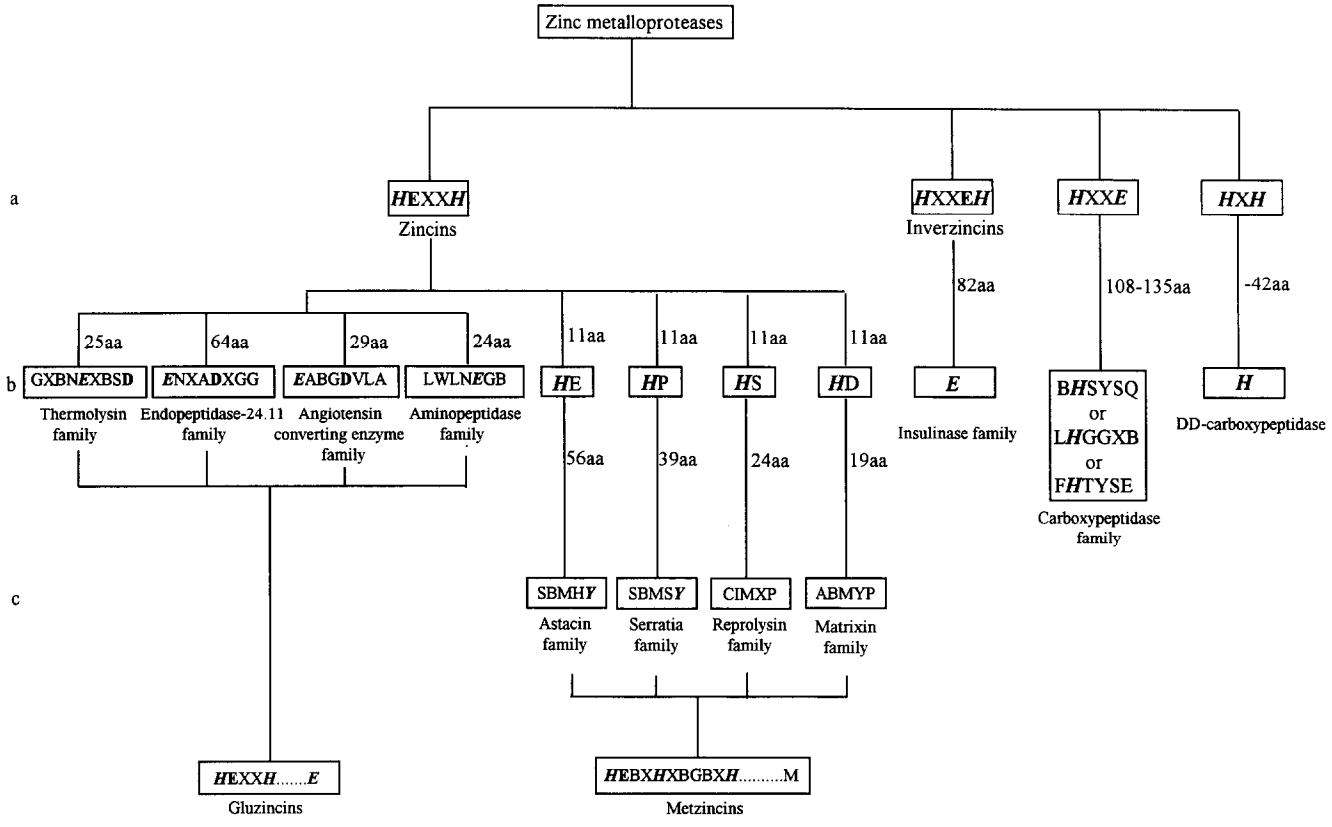

Fig. 1. Families of zinc metalloproteases. The families of the zinc metalloproteases and their inter-relationships based on the sequence around the zinc binding residues. Italicised bold letters represent positively identified zinc ligands; underlined letters represent putative zinc ligands; bold letters represent residues involved in catalysis; B stands for bulky, apolar residue; X stands for any amino acid; and the numbering scheme used is arbitrary with #1 being placed on the first zinc ligand in the short zinc binding motif, i.e. the most N-terminal ligand except in the case of DD-carboxypeptidase. The number of amino acids (aa) represent the distances between the ligands and the first histidine in the short zinc binding motif (i.e. HEXXH, HXXEH, HXXE, or DHTHV). Residues on line (a) correspond to the two ligands in the short zinc binding consensus sequence; residues in line (b) to the third ligand; and where applicable (astacin and serratia families) residues in line (c) to the fifth ligand. See the text for more detail.

N-terminal side of the zincin motif in the sequence ***E***NIADNGG [7]. Recently, by comparison with the sequence of thermolysin, Le Moual et al. [8] have shown that the aspartic acid four residues C-terminal to the glutamic acid is crucial for the catalytic activity of endopeptidase-24.11, presumably as it is involved in a carboxylate-histidine-zinc interaction as shown for thermolysin. Three other proteins have significant sequence identity to endopeptidase-24.11, especially around the two zinc binding sites (Fig. 2a). These are rat and bovine endothelin-converting enzyme, the human Kell blood group antigen and an endopeptidase encoded by the *pepO* gene of *Lactococcus lactis*. A comparison of the sequences around the two zinc binding sites indicate the following consensus sequences for this family of zinc metallopeptidases: BBX***H***EBX***H***XF and BX***E***NXADXGG.

2.1.3. Angiotensin converting enzyme. Mammalian angiotensin converting enzyme (EC 3.4.15.1) exists in two isoforms as a result of differential mRNA expression by tissue-specific promoters. The larger endothelial or somatic isoform contains two ***H***EXX***H*** motifs both of which are catalytically active, whilst the smaller testicular or germinal isoform corresponding to the C-terminal domain of the endothelial form has just one ***H***EXX***H*** motif. By comparison with thermolysin and endopeptidase-24.11 a putative glutamic acid third zinc ligand, which is conserved in all species, can be identified lying 29 residues C-terminal to the zincin motif in both domains (Fig. 2b). Both these putative zinc ligands have an aspartic acid four residues on the C-terminal side [8]. Recently, site directed mutagenesis and expression have been used to positively identify both the glutamic acid and the aspartic acid residues in the C-terminal domain of human angiotensin converting enzyme (Williams, T.A., personal communication). Comparison of the mammalian sequences with each other and with a putative angiotensin converting enzyme from *Drosophila* indicates the following consensus sequences for this family of zinc metallopeptidases: H***H***EBG***H***BQYB and GFH***E***ABGDVLA.

2.1.4. Aminopeptidase family. This family includes mammalian aminopeptidases A and N and leukotriene A_4 hydrolase, *E. coli* aminopeptidase N and an alanine/arginine aminopeptidase encoded by the *AAP1* gene in *Saccharomyces cerevisiae* (Fig. 2c). In this family the short zincin motif lies in the consensus sequence VBX***H***EBX***H***XWFG. The glutamic acid third zinc ligand, which has only been positively identified in leukotriene A_4 hydrolase but for which comparable sequences are present in the other aminopeptidases, is present in the consensus sequence LWLN***E***GB which lies a similar distance on the C-terminal side of the zincin motif as in the thermolysin family [9,10] (Fig. 2c). Unlike the thermolysin, endopeptidase-24.11

a)

```
No.              1   5              64
                 |   |              |
EP-24.11         VIGHEITHGF.........LGENIADNGG
PepO             VIAHEISHAF.........VSENIADQGG
Kell             IMAHELLHIF.........FLENAADVGG
ECE              VVGHELTHAF.........LGENIADNGG

Consensus        BBXHEBXHXF.........BXENXADXGG
```

b)

```
No.              1   5              29
                 |   |              |
ACE (N)          TVHHEMGHBQYY.......GFHEAIGDVLA
ACE (C)          BAHHEMGHIQYF.......GFHEAIGDVLA
Dros             TEHHELGHIQYF.......GFHEAVGDVLA

Consensus        XXHHEBGHBQYB.......GFHEABGDVLA
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c)

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No.              1   5                  24
                 |   |                  |
LTA4             VIAHEISHSWTG..........FWLNEGH
APN              VIAHELAHQWFG..........LWLNEGF
APA              VVAHELVHQWFG..........LWLNEGF
E. coli APN      VIGHEYFHNWTG..........LSLKEGL
AAP1             VIQHELAHQWFG..........LWLNEGF
APE2             VVQHELAHQWFG..........LWLNEGF
lap              VIAHELAHQWFG..........LWLNESF
pepN             VIAHELAHQWFG..........LWLNESF

Consensus        VBXHEBXHXWFG..........LWLNEGB
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Fig. 2. Consensus sequences for the gluzincins. Sequences are aligned starting from the HEXXH motif. See legend to Fig. 1 for detail. (a) Comparison of the zinc binding sites in members of the endopeptidase- 24.11 family. EP-24.11, endopeptidase-24.11 (CALLA) from human, rabbit and rat; PepO, *Lactococcus lactis* endopeptidase; Kell, human Kell blood group antigen; ECE, rat and bovine endothelin-converting enzyme [19–22]. (b) Comparison of the zinc binding sites in members of the angiotensin converting enzyme family. ACE, angiotensin converting enzyme from human, bovine, rabbit and mouse; (N), N-terminal active site; (C), C-terminal active site; Dros, putative *Drosophila* angiotensin converting enzyme [23–25]. (c) Comparison of the zinc binding sites in members of the aminopeptidase family.LTA4, leukotriene A4 hydrolase from human and mouse; APN, aminopeptidase N from human and rat; APA, aminopeptidase A from human and mouse; E. coli APN, aminopeptidase N from *E. coli*; AAP1, alanine/arginine aminopeptidase from *S. cerevisiae* encoded by the *AAP1* gene; APE2, aminopeptidase from *S. cerevisiae* encoded by the *APE2* (*LAP1*) gene; lap, aminopeptidase from *Lactococcus lactis* encoded by the lap gene; pepN, lysyl aminopeptidase from *L. delbruckii* encoded by the *pepN* gene [10,26–32].

and angiotensin converting enzyme families there is no aspartic acid four residues C-terminal to the glutamic acid, thus implying a different active site geometry for the aminopeptidase family.

2.1.5. Endopeptidase-24.15 family. The prototype of this family is rat endopeptidase-24.15 or thimet oligopeptidase (EC 3.4.24.15) which has substantial sequence similarity to a number of other proteins including pig liver soluble angiotensin II-binding protein, rabbit liver microsomal endopeptidase, rat mitochondrial intermediate peptidase, yeast saccharolysin and bacterial oligopeptidases and dipeptidyl carboxypeptidases (Fig. 3a). In this family the zincin motif falls within the longer consensus sequence F*H*EBG*H*XBH. Analysis of the available amino acid sequences of the members of this family suggest that the third zinc ligand may be one of two conserved glutamic acid residues C-terminal to the zincin motif in the consensus sequence DXVEXPSXBBEXB. It should be noted that neither glutamic acid is followed by an aspartic acid four residues on the C-terminal side, thus this family of zinc proteases may be closer to the aminopeptidase family than the thermolysin family.

2.1.6. Tetanus and botulism neurotoxins. A number of tetanus and botulism toxin serotypes contain the short zinc binding motif within the longer consensus sequence LM*H*ELX*H*-XXHXLYG (Fig. 3b). To date there is no information on the identity of the third zinc ligand, although the most likely possibility from the known amino acid sequences [11] is a conserved glutamic acid 39 residues C-terminal to the zincin motif which lies in the consensus sequence EEBXTFGGXDXXBI.

2.2. Metzincins

In contrast to the gluzincins, the metzincins have a longer zinc binding consensus sequence ***H***EBX***H***XBGBX***H*** which contains three of the zinc ligands (Fig. 1). In addition this superfamily has a methionine-containing turn of similar conformation (the Met-turn) [4]. The individual families are distinguished by (i) the residue following the third histidine zinc ligand in the above motif, and (ii) the residues surrounding the methionine in the Met-turn (Fig. 1).

2.2.1. Astacin family. The astacin family, typified by astacin, a digestive enzyme from the crayfish *Astacus astacus* L., consists of several proteins from diverse sources including mammalian metalloendoproteases, such as meprin (EC 3.4.24.18), and developmentally regulated proteins of man, fruitfly, frog and sea urchin. As with the other families constituting the superfamily of the metzincins three of the zinc ligands are contained within the metzincin consensus sequence which lies within the longer family signature sequence ***H***EBX***H***XBGFX-***H***EXXRXDRD. One of the distinguishing features of the astacin family is the glutamic acid residue following the third zinc ligating histidine (Fig. 1). In addition, in this family, there is a somewhat distant fifth zinc ligand a tyrosine (a bound water molecule being the fourth) in a second highly conserved region which also contains the Met- turn, SBMH***Y*** [4], thus the zinc is pentaco-ordinated with a novel trigonal-bipyramidal geometry [12].

2.2.2. Serratia family. This family, which contains several plant pathogen bacterial extracellular proteases including a protease from *Serratia* sp. and protease B and C from *Erwinia chrysanthemi* [13,14], also contains the longer metzincin consensus sequence for the three histidine ligands but in this case the third histidine is followed by a conserved proline (Fig. 1). As

a)

```
No.              1   5                30      37
                 |   |                |       |
EP-24.15         FHEFGHVMH.....DFVEAPSQMLENW
AII              FHEFGHVMH.....DFVEVPSQMLENW
MEP              FHEFGHVMH.....DFVEVPSQMLENW
MIP              FHEMGHAMH.....DFAEVPSILMEYF
Saccharolysin    FHELGHGIH.....DFVEAPSQMLEFW
OpdA             FHEFGHGLH.....DAVELPSQFMENW
E. coli Dcp      FHEFGHTLH.....DFVEFPSQINEHW
S. commune       FHEMGHAMH.....DFVELPSILMEHF
Oligo A          FHEFGHGLH.....DAVELPSQFMENW
S. typhimurium   FHEFGHTLH.....DFVEFPSQINEHW

Consensus        FHEBGHXBH.....DXVEXPSXBBEXB
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b)

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No.                    1   5            40
                       |   |            |
BoNT/A           FATDPAVTLAHELIHAGHRLYG....EELRTFGGHDAKFI
BoNT/B           YFSDPALILMHELIHVLHGLYG....EELYTFGGQDPSII
BoNT/C           FCMDPILILMHELNHAMHNLYG....AEIYAFGGPTIDLI
BoNT/D           FCMDPVIALMHELTHSLHQLYG....EELYTFGGLDVEII
BoNT/E           FIQDPALTLMHELIHSLHGLYG....EEFLTFGGTDLNII
BoNT/F           FIADPAISLAHELIHALHGLYG....EEFLTFGGQDLNII
TeTx             YFQDPALLLMHELIHVLHGLYG....EELFTFGGQDANLI

Consensus        BXXDPXBXLMHELXHXXHXLYG....EEBXTFGGXDXXBI
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Fig. 3. Consensus sequences for the proposed gluzincins. Sequences are aligned starting from the HEXXH motif. See legend to Fig. 1 for detail. (a) Comparison of the zinc binding sites in members of the endopeptidase-24.15 family.The two possibilities for the third zinc ligand are underlined. EP-24.15, rat endopeptidase-24.15; AII, pig liver soluble angiotensin II binding protein; MEP, rabbit liver microsomal endopeptidase; MIP, rat mitochondrial intermediate peptidase; Saccharolysin, *S. cerevisiae* EC 3.4.24.37, open reading frame YCL57w; OpdA, *Salmonella typhimurium* OpdA endo-oligopeptidase EC 3.4.22.19; E. coli Dcp, dipeptidyl carboxypeptidase; S. commune, *Schizophyllum commune* putative metalloendopeptidase; Oligo A, *E. coli* oligopeptidase A; S. typhimurium, *S. typhimurium* dipeptidyl carboxypeptidase [33–35]. (b) Comparison of the zinc binding sites in members of the tetanus and botulism neurotoxins. The possible third zinc ligand is underlined. BoNT, botulism neurotoxin serotypes A, B, C, D, E, or F; TeTx, tetanus neurotoxin [11,36].

with the astacin family there is a potential tyrosine fifth zinc ligand in the conserved Met- turn consensus region of SBMS*Y*.

2.2.3. Reprolysin family. The reprolysin family consists of several snake venom proteases, including haemorrhagic toxin and non-haemorrhagic proteins and a number of mammalian reproductive proteins. In this family the third histidine in the consensus sequence containing the three zinc ligands is followed by a conserved aspartic acid (Fig. 1). Unlike the astacin and serratia families the reprolysin family lacks a fifth zinc ligand, leaving the zinc tetrahedrally co-ordinated [4,15]. In place of the tyrosine in the Met- turn is a conserved proline in the consensus sequence CIMXP.

2.2.4. Matrixin family. The matrixin family consists of mammalian collagenases, gelatinases, and stromelysins. In this family the metzincin superfamily consensus sequence for the three histidines is followed by a conserved serine (Fig. 1). As with the reprolysin family the Met-turn lacks a tyrosine which is replaced by a conserved proline in the consensus sequence ABMYP.

3. Inverzincins

A small group of zinc metalloproteases are characterized by an inverted zinc binding motif HXXEH for which I propose the name 'inverzincins'. This family, which includes the human, rat and *Drosophila* insulin-degrading enzymes, *Escherichia coli* protease III (pitrilysin) and a yeast processing-enhancing protein, possess an inverted zincin motif lying in the consensus sequence GXX*H*BXE*H*BXBXG (Fig. 4). Recently the third zinc ligand has been identified as a glutamic acid lying some 82 amino acid residues C-terminal to this motif but not in any consensus sequence [16].

4. Carboxypeptidases

The carboxypeptidase family, typified by carboxypeptidases A and B but including carboxypeptidases H, M, N, U, mast cell carboxypeptidase A, carboxypeptidase T from *Thermoactinomyces vulgaris* and a carboxypeptidase from *Streptomyces griseus* have a unique short zinc binding motif containing the first two ligands, histidine and glutamic acid, with the third zinc ligand, a histidine, located some distance (108–135 amino acid residues) C-terminal to this motif (Fig. 5). This family can be further subdivided into three distinct groups on the basis of the sequence around the zinc binding ligands. The first group including carboxypeptidases A and B has the zinc ligands located in the consensus sequences DXGB*H*XR*E*WBXXA and B*H*SYSQ. The second group (carboxypeptidase T and the *Streptomyces* carboxypeptidase) are similar in sequence to the above group with the consensus sequences TAXX*H*AR*E*HLTVE and F*H*TYSE. In contrast the third group (carboxypeptidases H, M and N) has somewhat different consensus sequences BXNM*H*GX*E*XBGRE and L*H*GGXB.

5. DD-Carboxypeptidase

D-alanyl-D-alanine-cleaving carboxypeptidase (DD-carboxypeptidase) from *Streptomyces albus* has been sequenced [17]

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No.              1   5                          82
                 |   |                          |
hIDE        GLSHFCEHMLFLG.............VDSEHEK
rIDE        GLSHFCEHMLFLG.............VDSEHEK
dIDE        GLAHFCEHMLFLG.............VNSEHEK
yPEP        GTAHFLEHLAFKG.............IIRESEE
PTR         GLAHYLEHMSLMG.............VNAELTM
yddC        GVAHFVEHMMFNG.............VDAERGV

Consensus   GXXHBXEHBXBXG.............BXXEXXX
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Fig. 4. Consensus sequence for the inverzincins. Comparison of the zinc binding sites in members of the inverzincin family. Sequences are aligned starting from the HXXEH motif. See legend to Fig. 1 for detail. hIDE, human insulin-degrading enzyme; rIDE, rat insulin-degrading enzyme; dIDE, *Drosophila* insulin-degrading enzyme; yPEP, yeast processing-enhancing protein; PTR, *E. coli* protease III (pitrilysin); yddC, hypothetical protease from *E. coli* [16].

```
No.              1  4                    108-135
                 |  |                    |
CPA1         DTGIHSREWVTQA.............IHSYSQ
CPA2         DAGIHAREWVTQA.............LHSYSQ
mcCPA        DCGIHAREWISPA.............FHSYSQ
CPB          DCGFHAREWISPA.............IHSYSQ
cCPB         DGGIHAREWIAPS.............FHSYSQ
CPU          DTGIHAREWISPA.............MHSYSQ

Consensus    DXGBHXREWBXXA.............BHSYSQ


CPT          TALHHAREHLTVE.............FHTYSE
CPSG         TAHQHAREHLTVE.............FHTYSE

Consensus    TAXXHAREHLTVE.............FHTYSE


CPH          IGNMHGNEAVGRE.............LHGGDL
CPM          VANMHGDETVGRE.............LHGGAL
CPN          VGNMHGNEALGRE.............LHGGAV

Consensus    BXNMHGXEXBGRE.............LHGGXB
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Fig. 5. Consensus sequences for the carboxypeptidases. Comparison of the zinc binding sites in members of the carboxypeptidase family. Sequences are aligned starting from the HXXE motif. See legend to Fig. 1 for detail. CPA1, carboxypeptidase A1; CPA2, carboxypeptidase A2; mcCPA, mast cell carboxypeptidase A; CPB, carboxypeptidase B; cCPB, crayfish carboxypeptidase B; CPU, carboxypeptidase U; CPT, carboxypeptidase T; CPSG, carboxpeptidase from *Streptomyces griseus*; CPH, carboxypeptidase H; CPM, carboxypeptidase M; CPN, carboxypeptidase N [37–39].

and crystallized [18]. From the crystal structure the zinc ligands were identified as three histidines, two of which occur in the short sequence D*HXH*V. In contrast to all the other zinc metalloproteases the third zinc ligand, a histidine, is located 42 residues on the N-terminal side of this motif in the sequence SR*H*MY (Fig. 1).

6. Conclusion

This review both highlights the fact that the HEXXH motif is not the only zinc binding motif in zinc metalloproteases/peptidases, and summarises information for the classification of new zinc metalloproteases based on sequence and structural data. Even now several identified zinc metalloproteases exist which do not immediately fit into any of the above families. For example, mycolysin (EC 3.4.24.31) from *Streptomyces cacaoi* has the zinc binding sequences TTV*H*EAG*H*SLM and WT*E*GFADAVA [40] which bear slight similarity to the consensus sequences for the endopeptidase-24.11 family (Fig. 2a). Whilst leishmanolysin (EC 3.4.24.36) the GP63 cell surface protease from Leishmania has the zinc binding sequences VVT*H*EMA*H*ALGFS and MFCN*E*NEVT [41] which show similarity to the consensus sequences for the aminopeptidase family (Fig. 2c).

The above classification not only aids in the elucidation of common catalytic and biosynthetic processing mechanisms, but also is invaluable in elucidating the function of newly identified proteins which possess similar zinc binding motifs. The continued determination of the three-dimensional structures of members of families for which no structural data is currently available and the use of molecular biological techniques to identify residues involved either in co-ordinating the zinc or in catalysis will further aid in the classification of the various members of this biologically important superfamily of enzymes.

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