THE METZINCIN-SUPERFAMILY OF ZINC-PEPTIDASES

INTRODUCTION

Over the past three years, the three-dimensional structures of a number of zinc proteinases that share the zinc-binding motif HEXXHXXGXXH have been elucidated. These proteinases comprise astacin, a digestive enzyme from crayfish [1,2,3], adamalysin II [4,5] and atrolysin C [6] from snake venom, the *Pseudomonas aeruginosa* alkaline proteinase [7] and serralysin from *Serratia marcescens* proteinase [8], the collagenases from human neutrophils [9,10,11] and fibroblasts [12,13,14,15], human stromelysin 1 [16; K. Appelt, personal communication] and matrilysin [M. Browner, Keystone Symposia, March 5-12, 1994]. These enzymes represent four different families of zinc peptidases: the astacins [3,17], the bacterial serralysins [18], the adamalysins/reprolysin [19,20], and the matrixins (matrix metalloproteinases, MMPs) [21,22].

On the level of the amino acid sequences there is only very low similarity between these families [23]. However, a quantitative comparison of the three dimensional structures has uncovered the striking topological equivalence of their catalytic modules [24,25,26]. A sequence alignment based on topological constraints has revealed significant similarities indicating that these proteinases have evolved from a common ancestor. The designation “metzincins” has been coined for this superfamily of zinc peptidases [24,25,26].
This chapter points out the common structural and functional features of the met-zincins as well as their more distant relationship with the thermolysin-like enzymes.

OVERALL THREE-DIMENSIONAL STRUCTURES

Astacin [1,2], adamalysin II [4,5], and the catalytic modules of neutrophil collagenase [9] and Pseudomonas alkaline proteinase [7] are globular entities, subdivided into two domains by the substrate binding cleft, with the zinc at its bottom. In the standard orientation the cleft lies horizontally in the paper plane (Fig.1).

Figure 1. MOLSCRIPT [49] ribbon plots of astacin (A), adamalysin II (B), human neutrophil collagenase (C) and Pseudomonas alkaline protease (D). Zinc and calcium ions are shown as small and large spheres, respectively. The zinc ligands, the methionine of the Met-turn, and the catalytic glutamic acid are labeled.