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Proteolytic Enzymes and Proteinaceous Substrates : a Case of Transient Interactions

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The increase in the number of proteolytic enzymes, and more particularly of metallocarboxypeptidases (MCPs), evidenced in the last decade that their not fully understood simultaneous action on substrates as well their restrictions by natural modulators and inhibitors probably require, in regulated cases, a high complementation and tuning in their binding interactions. The fact that such substrates, as well the efectors, generally are of proteinaceous nature, add extra degrees of sophistication in these interactions (i.e. at the chemo-physical, discrimination capability and kinetic levels). Not to forget that, to achieve full specificity, the help of other factors (compartimentation, temporal expression and localization, degradation ...etc) from living organisms is required (1,2).

Nowadays we could count between 25 and 30 the number of variants of such MCP enzymes, classified between the M14A, B and C forms, to which we should add the recently emerging cytosolic ones (CCPs or Nna-likes) for the M14D subfamily in the MEROPS database (3,4). Giving that all of them seems to keep the "canonical" metallo-carboxypeptidase domain and equivalent recognition sites, it is a real challenge to understand the complex interplay between them, their discriminative interaction with natural substrates (peptidic or proteic, since are proteases), and with the environmental proteinaceous inhibitors. It is also a challenge for drug-designers to generate synthetic ligands that specifically control them (2).

Coincidentally, MCPs (as other proteases, in general) have another characteristic interactomics feature: they act transiently on proteinaceous substrates, promoting cleavages on them which severely effects their conformation and functionality. How to detect such transient interactions is not always an easy task by using standard interactomics approaches or addapted variants of them (5-7), in spite that frequently the promoted changes are very large (i.e. in size and other properties). We shall discuss several recent study cases of MCPs to clarify their interactomics with natural substrates and inhibitors and the strategies followed for their characterization.

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