Comparative structural analysis of active site clefts in pancreatic-like ribonucleases

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Merlino Antonello[1], Filomena Sica[1,2], Lelio Mazzarella[1,2]
[1]Department of Chemistry, University of Naples 'Federico II', Napoli, Italy
[2]Bioimagine and Biostructure Institute, CNR, Napoli, Italy

Motivation

Pancreatic-like ribonucleases (RNases) constitute a highly heterogeneous group of enzymes that catalyses the cleavage of phosphodiester bonds in RNA. Although RNases share the same fold and similar sequences, their ribonucleolytic activity is somewhat different. Furthermore, several members of this protein superfamily individually perform different biological functions in connection with their intrinsic ribonucleolytic activities, including antitumor, embryotoxic and bactericidal properties. However, despite the voluminous research activity on RNases, the precise structural pecularities crucial in determining the enzymatic features of these enzymes are still lacking.

Methods

In a continuing effort to understand the structure-function relationship of these enzymes, we have carried out a comparative structural analysis, using more than 200 X-ray structures of RNases, that reveals specific, previously unidentified, differences in the ribonucleolytic active site cleft among homologues. To validate our results homology modelling and multiple sequence alignments have been also performed.

Results

Subtle structural changes, which appear due to accumulating mutations in the protein core, have lead to distinct packings of the two arms constituting the b-sheet of RNases, and thus to slightly different active site clefts. Interestingly, the members of the family that present larger active site clefts than RNase A have enzymatic activity, toward most RNA substrates, significantly lower than that of the bovine pancreatic enzyme. These data underline the importance of the protein scaffold in the enzyme activity and support recent hypothesis on the role played by core residues in differentiate structural-related protein families.

Email: antonello.merlino@unina.it