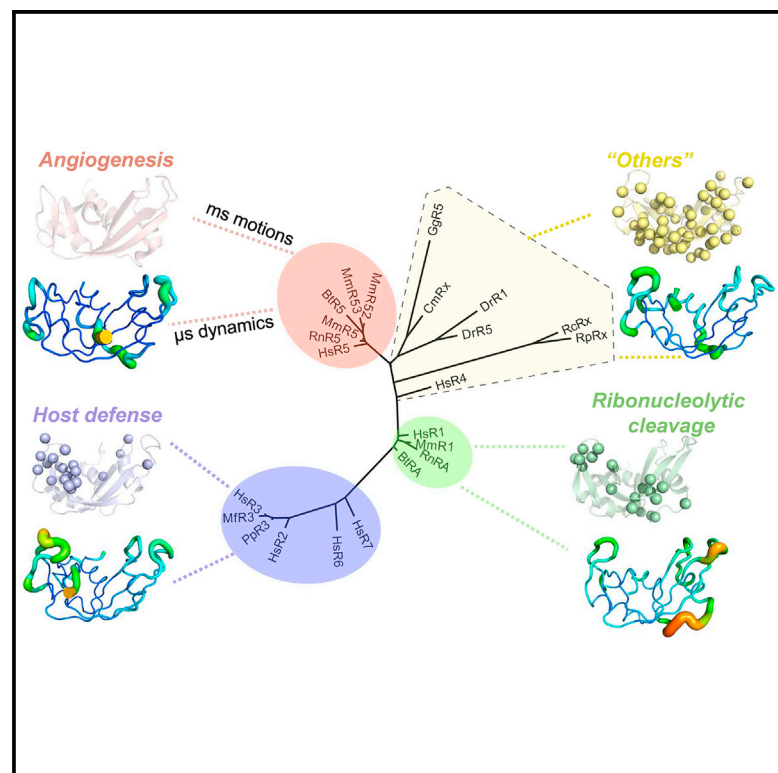


Structure

Conservation of Dynamics Associated with Biological Function in an Enzyme Superfamily

Graphical Abstract



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In Brief

The pancreatic-type RNase enzyme superfamily contains enzymes with diverse biological functions including angiogenesis, host defense, and ribonucleolytic activity. Narayanan, Bernard et al. demonstrate that members of the family can be classified into functionally distinct subfamilies with conserved dynamical traits, which may be linked to their specific functions.

Highlights

- Structurally similar enzymes display diverse dynamics and biological functions
- Phylogenetic classification shows subfamilies with distinct biological function
- Dynamics is conserved within subfamilies indicating potential role in function
- Loop swapping switches dynamical profile of chimera from one subfamily to another

Conservation of Dynamics Associated with Biological Function in an Enzyme Superfamily

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SUMMARY

Enzyme superfamily members that share common chemical and/or biological functions also share common features. While the role of structure is well characterized, the link between enzyme function and dynamics is not well understood. We present a systematic characterization of intrinsic dynamics of over 20 members of the pancreatic-type RNase superfamily, which share a common structural fold. This study is motivated by the fact that the range of chemical activity as well as molecular motions of RNase homologs spans over 10^5 folds. Dynamics was characterized using a combination of nuclear magnetic resonance experiments and computer simulations. Phylogenetic clustering led to the grouping of sequences into functionally distinct subfamilies. Detailed characterization of the diverse RNases showed conserved dynamical traits for enzymes within subfamilies. These results suggest that selective pressure for the conservation of dynamical behavior, among other factors, may be linked to the distinct chemical and biological functions in an enzyme superfamily.

INTRODUCTION

The linkage between dynamics and enzyme catalysis has been intensely debated (Kohen, 2015). Enzymes, like other molecules, experience internal motions over a wide range of timescales. These motions are driven by temperature and surrounding environment, including the solvent (Agarwal, 2005; Frauenfelder et al., 2006). Evidence continues to emerge from an increasing

number of systems emphasizing the involvement of dynamics in enzyme function (Boehr et al., 2006; Eisenmesser et al., 2005; Holliday et al., 2017; Nashine et al., 2010). However, the presence of motions even near/in the active site, or their occurrence at timescales that coincide with rate-limiting events in enzyme mechanisms, does not automatically imply that these motions play a role in enzyme function (Gobeil et al., 2014). One of the challenges associated with investigating enzyme dynamics is that structure and dynamics are inter-related, thus making it difficult to decouple their individual contributions to enzyme catalysis.

The enzyme fold has been proposed to serve as a scaffold that enables optimal positioning of the catalytic residues to provide a unique environment, which is very different from solvent, and provides structural and electrostatic features necessary for transition state stabilization (Warshel et al., 2006). Catalytically important residues are conserved across enzymes that share the same fold and catalyze the same (or similar) chemical reaction (Ojha et al., 2007). It has been suggested that if dynamics plays a functional role in enzyme catalysis, then it must also be subjected to evolutionary pressure and be conserved as a part of the enzyme fold topology (Ramanathan and Agarwal, 2011). Therefore, characterization of dynamics of enzymes within a superfamily could provide vital information on the evolutionary conservation of dynamics (or lack thereof) among structural and functional homologs that catalyze the same chemical reaction. This approach could provide much needed information for teasing apart the role of structure and dynamics in enzyme catalysis.

Pancreatic-type ribonucleases (RNases) are a superfamily of enzymes found mostly in vertebrates that catalyze the hydrolysis and transphosphorylation of RNA substrates (Batot et al., 2017; Singhania et al., 1999; Sorrentino, 2010). Nearly 650 sequences corresponding to members of this superfamily are found in the Pfam database (Finn et al., 2016). Eight catalytically active canonical RNases (and five supplemental pseudo-genes that

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