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MINIREVIEW

# Structural and functional importance of local and global conformational fluctuations in the RNase A superfamily

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Understanding the relationship between protein structure and flexibility is of utmost importance for deciphering the tremendous rates of reactions catalyzed by enzyme biocatalysts. It has been postulated that protein homologs have evolved similar dynamic fluctuations to promote catalytic function, a property that would presumably be encoded in their structural fold. Using one of the best-characterized enzyme systems of the past century, we explore this hypothesis by comparing the numerous and diverse flexibility reports available for a number of structural and functional homologs of the pancreatic-like RNase A superfamily. Using examples from the literature and from our own work, we cover recent and historical evidence pertaining to the highly dynamic nature of this important structural fold, as well as the presumed importance of local and global concerted motions on the ribonucleolytic function. This minireview does not pretend to cover the overwhelming RNase A literature in a comprehensive manner; rather, efforts have been made to focus on the characterization of multiple timescale motions observed in the free and/or ligand-bound structural homologs as they proceed along the reaction coordinates. Although each characterized enzyme of this architectural fold shows unique motional features on a local scale, accumulating evidence from X-ray crystallography, NMR spectroscopy and molecular dynamics simulations suggests that global dynamic fluctuations, such as the functionally relevant