Structural and Dynamic Studies of Onconase Mutants

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Onconase (ONC), a member of the RNase A superfamily extracted from oocytes of Rana pipiens is used in treatment of various forms of cancer. ONC antitumor properties depend on its ribonucleolytic activity that is three-five order of magnitude lower than RNase A. The structural reasons for this very low ribonucleolityc activity are not yet clearly understood. The most damaging side effect from ONC treatment is renal toxicity, probably linked to the enzyme stability, which is unusually high for a protein isolated from a mesophilic source. In this context, we have prepared and determined the crystal structures of two ONC mutants (M23L and C87S,des103-104), and performed molecular dynamics simulations of ONC and C87S,des103-104 with the aim of explaining on structural grounds the modifications of the activity and thermal stability of these mutants. Despite the strict similarity in the β-sheet architecture, ONC does not possess the β-sheet breathing motion characteristic of other RNase-like molecules and considered to be functionally important. The decreased flexibility provides a basis to explain the low affinity of ONC towards nucleotides and, more generally, its lower catalytic activity. The results also suggest the basis of the unusually high thermal stability of the enzyme.[1]

[1] Merlino A., *et al., J. Biol. Chem., accepted for publication*.

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