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Structural aspects of specie specific moonlighting functions of dUTPases

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dUTPases constitute an enzyme family which has a sanitizing role by preventing the incorporation of noncanonical bases in the DNA. The catalytic mechanism of action of these enzymes has been revealed for a number of representatives in clear structural and kinetic detail.

However there are several specie specific moonlighting functions, which allow a fine tuned drug design on different malignant cases, dUTPases being a preferred drug target.

One of our well studied protein is the *Mycobacterium tuberculosis* dUTPase.

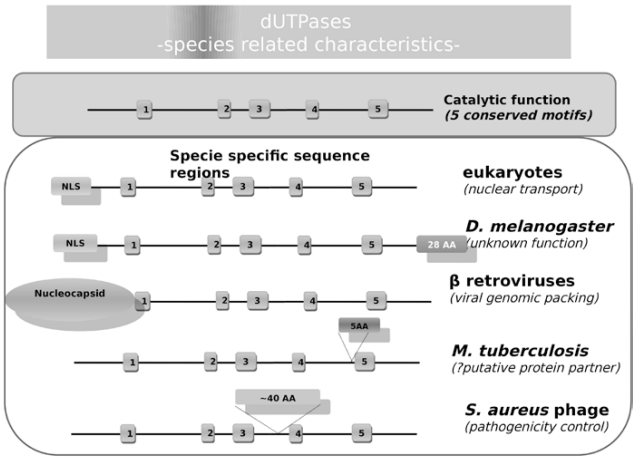
The main catalytic function has been detailed by clear structural proof of a conserved aromatic stacking interaction between dUTPase and its nucleotide substrate which largely contributes to the stabilization of the associative type transition state of the nucleotide hydrolysis reaction.

Further, X-ray structures of mutant proteins revealed the importance of the five amino acids long extra loop, specific to mycobacteria, that is proven to be a target in anti-tuberculotical drug design.

In *Staphylococcus*, phage dUTPases are also suggested to be involved in a moonlighting function regulating the expression of pathogenicity-island genes. Staphylococcal phage trimeric dUTPase sequences include a specific insertion that is not found in other organisms. The phage-specific insert segment of Phi11 phage dUTPase folds into a beta-pleated mini-domain resembling a distorted Greek-key motif. This small structural motif is very common in protein-folding cores. Comparison of the presently available sequences of staphylococcal phages encoding trimeric dUTPases reveals

that the presence of such inserts seems to be general and that subgroups of phages can be distinguished based on the segment characteristics.

The binding partner staphylococcal repressor protein $Stl_{SaPI\text{-}Bov1}$ (Stl) forms strong complex with both staphyllococcal and human dUTPase. Recent structural, functional analysis studies reveal that this interaction results in significant reduction of both dUTPase enzymatic activity and DNA binding capability of Stl.



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