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Structural Characterization of *Mycobacterium Tuberculosis* Truncated Hemoglobin N from Molecular Dynamics Simulations and its Interactions with Free Ligands

Prof. Patrick Lague

Département de Biochimie et de Microbiologie, Université Laval

In *Mycobacterium tuberculosis* the glbN gene encodes the truncated hemoglobin N (trHbN). Inactivation of the glbN gene impairs the ability of stationary phase cells to protect aerobic respiration from NO inhibition, suggesting that trHbN may protect *Mycobacterium tuberculosis* from NO toxicity in vivo. The cystallographic structure of oxygenated trHbN shows an extended heme distal hydrogen-bond network that includes Y(B10), Q(E11) and the bound O2. Besides, trHbN structure shows a network of hydrophobic cavities organized in two orthogonal branches.

The structure and the dynamics of oxygenated and deoxygenated trHbN in explicit water was investigated from 100 nanoseconds of classical molecular dynamics (MD) simulations. The results show that depending on the presence or the absence of a coordinated O_2, the Y(B10) and Q(E11) side chains adopt two different configurations in concert with hydrogen bond network rearrangement. Our data indicate that Y(B10) and Q(E11) influence the dynamics of F(E15). In deoxy-trHbN, F(E15) is restricted to one conformation. Upon O_2 binding, the conformation of Q(E11) changes and residue F(E15) fluctuates between two conformations. Altogether, the dynamics of Y(B10), Q(E11) and F(E15) alter the formation of trHbN tunnels. In addition to the long and the short tunnels reported in the cystallographic structure, two previously unrecognized tunnels that join the protein surface to the buried distal heme pocket were observed. Finally, molecular dynamic simulations revealed that by facilitating the docking and concentration of small apolar ligands over its water-free entrance, the short tunnel may constitute the main pathway for ligands entry into trHbN.

Dr. Patrick Lague received his bachelor and M.Sc. degrees in biophysics from Université du Québec à Trois-Rivières. He then pursued graduate studies in theoretical chemistry at Université de Montréal where he received his Ph.D. in 2001. During his Ph.D., under the supervision of Dr. Martin Zuckermann and Dr. Benoît Roux, he developped an innovative theory for describing the molecular interactions in a homogenous 2-dimensional liquid to model biological membranes. In 2001, he joined the Laboratory of Biophysics of the FDA, in the research group of Dr. Richard W. Pastor, as a Postdoctoral Fellow. He joined the Département de Biochimie et de Microbiologie de l'Université Laval in 2004 as an Assistant Professor. He is implicated in various research projects involving molecular modeling of biologically relevant systems.