Molecular modeling of protein-carbohydrate systems: Preliminary molecular dynamics study of Cholera Toxin B-subunit (CTB) / G_{M1} pentasaccharide complexes

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Cholera[1] is a life-threatening diarrhea- and dehydration-inducing infection caused by the *Vibrio cholerae* bacteria, primarily due to the consumption of contaminated water and/or food. It is worldwide-spread since two centuries and did not show any sign of decrease in recent times. On the contrary, environmental factors correlated to climate change are expected to escalate the threat[2], as demonstrated by the occurring Haiti outbreak.

One of the key steps in cholera human infection is the internalization of a well structurally-described toxin of the AB_5 family, the Cholera Toxin (CT), which starts with the binding of its B-subunit pentamer (CTB) to G_{M1} gangliosides lining the surface of intestinal cells. The first results of a molecular modeling study targeting this protein-carbohydrate system are presented here.

Structural glycobiology is a young discipline in the biochemistry field that has raised great interest in recent years. Its molecular modeling division is significantly less mature than the modeling of other kinds of biomolecules, but its developments are promising.[3] Polysaccharides such as G_{M1} are especially challenging due to their significantly greater conformational fluctuations compared to short peptides. Starting from good quality crystallographic data, 8 structures corresponding to the CTB genotypes of current active toxic strains were modeled in explicit solvent, then submitted to extensive molecular dynamics simulations.

The results provide more precise knowledge on the properties of the CTB/G_{M1} systems, and constitute reference data for further computer-aided investigations. Recent experimental findings reinforced the hypothesis of a molecular origin of the blood group dependence that is observed for cholera[2]. We hope that molecular modeling works will improve the significance of ongoing experimental structural biology investigations.

[1] D.A. Sack *et al.*, *Lancet*, **363**, 223 (2004).
[2] Å. Holmner, A. Mackenzie, U. Krengel, *FEBS Lett.*, **584**, 2548 (2010).
[3] E. Fadda and R.J. Woods, *Drug Discov. Today*, **15**, 596 (2010).