Study of interactions between LPS-derivatives and the dimeric TLR4/MD-2 receptor complex by Molecular Dynamics simulations

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Abstract

Septic shock is a health problem of unknown and underestimated incidence in Mexico. Despite this, it is a prevalent health problem with severe social, occupational and economic implications. Fortunately, sepsis is a rare clinical complication for patients. But, once developed, it shows an extremely unfavorable prognostic aspect with mortal outcome of highest probability. The purpose of this research is to study the interactions of septic agent lipopolysaccharides (LPS) and derivatives with their biomolecular targets: the TLR4/MD-2 receptor complex by means of Molecular Dynamics (MD) simulations and other computational technics. Particularly, the phosphate group interactions of LPS and derivatives, and the binding site electrostatic properties are studied. Elucidating the action mechanism of this kind of ligands is fundamental to develop new drugs for sepsis treatment, because actually there in not a specific therapy. Previous to the MD analysis, a docking study has been carried out between lipid IVa (L4a), a LPS precursor which has dual species-dependent activity, and the TLR4/MD-2 complex receptor in a triangular place inside the complex called the "*Wedge*" for its three interaction interfaces. In the *Wedge* the amino acid residues interacting with phosphate groups of LPS or derivatives, have been mapped for three mammalian species (human, mouse, horse). Through MD, the positional preference of phosphate groups within the *Wedge* were tracked. The phosphate anions are known as the signaling functional groups. So their interaction with certain amino acids directly triggers the biological activity of LPS or its derivatives, which can lead to sepsis in an intercellular biochemical pathway. The results about the phosphate positional preferences obtained by MD were phosphate group interaction potential maps and the *Wedge* electrostatic properties analysis, they show that the species-specificity assumption for the phosphate groups is not correct. It showed a random-determined behavior, no related with the amino acid sequence species supported by a net charge analysis of the *Wedge*. The species-dependent effects of LPS-like molecules is due to other unknown factors not considered in this work, probably bulk steric effects. The acylation state of LPS-like ligands could be also an aspect to consider in the future. By the other hand, the MD simulation times were large in comparison with other studies, however it seems that larger periods of time are necessary. It is save to say that the dynamical behavior of the phosphates cannot reflect the reported activity for all species during 100 ns of simulation time, the phosphate anion did not show a realistic site preference under the influence of the other phosphate. It means that longer observation times are necessary or the MD technique could be combined with other methods to accelerate the dynamics of the system.