Dynamics on human Toll-Like Receptor 4 complexation to MD-2

Aguiar, C.C.¹; Verli, H.¹

¹Centro de Biotecnologia, UFRGS, RS, Brazil.

INTRODUCTION. Toll-like receptors (TLRs) are involved in innate immune response by recognizing pathogen-associated molecular patterns. They present a characteristic leucine-rich-repeat extracellular domain and a TIR (Toll/IL-1 receptor) intracellular domain. Human Toll-Like Receptor 4 (hTLR4) and its co-receptor, myeloid differentiation factor-2 (MD-2), as a heterodimer, is a well-known complex of Gram-negative bacteria lipopolysaccharide (LPS) recognition. In this process, MD-2 recognizes LPS and promotes the dimerization of the complex hTLR4-MD-2-LPS, initiating an intracellular immune signaling. Moreover, it has been reported that hTLR4 can also act in the absence of MD-2, in the case of other ligands recognition and, in these cases, little is known about the structural and conformational changes that hTLR4 structure underwent. The present work aims to explore the structural properties of the hTLR4-MD-2 complex and investigate the implications of the co-receptor complexation to the dynamics of hTLR4.

MATERIALS AND METHODS. Five systems were prepared: 1)(hTLR4-MD-2)¹; 2)(hTLR4)¹; 3)(hTLR4-MD-2)²; 4)(hTLR4)² and 5)(MD-2)¹. Each system was simulated in duplicates, using GROMACS package and GROMOS 53a6 force field. RESULTS AND DISCUSSION. Results show that hTLR4 presents a tweezers-like movement, which seems to be not directly dependent of MD-2, once occurring in all systems simulated. On the other hand, the presence of MD-2 leads to differences in systems that have this molecule in which they present a different correlation between residues in comparison to the systems that lack this molecule. Also, network analysis shows that terminal regions, despite its similar predisposition to major flexibility, belong to different communities of movement. Regarding the MD-2, this molecule showed a tendency of pocket closure, which was less pronounced in the (hTLR4-MD-2)² system, pointing to the importance of this oligomerization for MD-2 stability. CONCLUSIONS. Despite the differences in the composition of the systems studied, the overall changes in the hTLR4 structure was sustained regardless the presence of co-receptor.

Word Keys: TLR4, structural biology, molecular dynamics, immune response.

Supported by: CNPq, CAPES and FAPERGS.