Dynamics of the Complete Membrane Soaked hTLR4

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INTRODUCTION. Human Toll-Like Receptor 4 (hTLR4) is a protein of the immune system. Together with MD-2, hTLR4 can recognize bacterial lipopolysaccharide. hTLR4 posses three domains: an extracellular (ECD), for ligand recognition; a transmembrane helix (TM); and an intracellular domain (TIR), for signaling. In a previous work, we described the influence of MD-2, over the hTLR4 ECD dynamics. **OBJECTIVE:** The present work aims to study the relation of hTLR4 and MD-2 within membranes, searching for clues to the receptor conformational activation. **MATERIALS AND METHODS:** Comparative modeling (Modeller v.9) was employed to produce a model of the complete hTLR4, inserted in a POPC membrane as a single (i, hTLR4), heterodimeric (ii, hTLR4-MD-2) and heterotetrameric (iii, (hTLR4-MD-2)$_2$) systems. These were submitted to molecular dynamics using GROMACS and GROMOS 53A6. **RESULTS AND DISCUSSION:** hTLR4 oligomerization, so far, were able to interfere in its conformational space, whereas it does not seems to be related to the principal movement of ECD. LEU661 of TM appears to be involved in the conformational connection between TM-TIR through different regions of TIR, depending on hTLR4 complexation. GLN742 and ARG780, in (iii), seems to behave as bottlenecks between TIR monomers, communicating these. Furthermore, dynamical network analysis shows that MD-2 induced the formation of a more adherent community of conformational connected residues in TIR, and that oligomerization in (iii) conferred greater movement correlation in TIR than other domains. **CONCLUSIONS:** We had inferred, previously, a main movement of ECD in solution that now we identify without the bias of the absence of other domains or membrane. Furthermore, LEU661 could have influence in TM-TIR dynamics in an oligomerization-dependent manner. Also, oligomerization seems to alter hTLR4 response by changing TIR dynamics and rearranging hTLR4 domains, to major consistency in movement correlation from ECD in (i) and (ii), to TIR portion, in (iii).

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