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A Multiscale Study on the Mechanisms of Spatial Organization in Ligand-receptor Interactions on Cell Surfaces.[1]

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The binding of cell surface receptors with extracellular ligands triggers distinctive signaling pathways, leading into the corresponding phenotypic variation of cells. After ligands and receptors form complexes through trans-interactions, they can further oligomerize into higher-order structures with additional cis-interactions. This ligand-receptor oligomerization on cell surfaces plays a functional role in regulating cell signaling. The underlying mechanism, however, is not well understood. One typical example is proteins that belong to the tumor necrosis factor receptor (TNFR) superfamily. Using a new multiscale simulation platform that spans from atomic to subcellular levels, we compared the detailed physical process of ligand-receptor oligomerization for two specific members in the TNFR superfamily. Interestingly, although these two systems share high similarity on the tertiary and quaternary structural levels, our results indicate that their oligomers are formed with very different dynamic properties and spatial patterns. We demonstrated that the changes of receptor's conformational fluctuations due to the membrane confinements are closely related to such difference. This study, therefore, provides the molecular basis to TNFR oligomerization and reveals new insights to TNFR-mediated signal transduction. Moreover, our multiscale simulation framework serves as a prototype that paves the way to study higher-order assembly of cell surface receptors in many other bio-systems.

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