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## Studying the two-domain fragments of single-pass membrane proteins by NMR in solution

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Single-pass membrane proteins include numerous cell receptors that regulate the cell cycle and immunity and take part in the development of many severe diseases such as cancer and neurodegeneration. These proteins have large extramembrane domains and a single transmembrane (TM) helix. Such architecture hinders the crystallization of single-pass proteins and the increased mobility complicates their high-resolution studies with Cryo-electron microscopy. Spatial structure of single-pass proteins is commonly studied using the so called "divide and conquer" approach. This results in the loss of information concerning the mutual arrangement of protein domains and their interaction. We propose to study two-domain constructs of TM and intracellular or extracellular domains of single-pass membrane proteins in order to reconstruct the architecture of the full-size protein. In the present study, we implemented this "add and conquer" approach to the Toll-like receptor 4, neurotrophin receptor p75NTR and its co-receptor NRADD. We studied the structure of p75NTR construct with the deleted extracellular domain in both monomeric and dimeric states. Our data reveal that TM and intracellular domains of the protein are moving independently, which opposes the previously suggested model of p75NTR activation. We determined the structure of full-length NRADD or p45 protein in bicelles, which is the first high-resolution spatial structure of full-length single-pass membrane protein. Last, we studied the TM domain of TLR4 with juxtamembrane regions and found that the TM domain was initially annotated incorrectly and toll-like receptors have very long TM helices, which could explain the specific localization of the receptors on cell membrane.

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