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Diversity of structural-dynamic properties of transmembrane domains among the insulin receptor family

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Motivation and Aim: Receptor tyrosine kinases (RTKs) are ubiquitous receptors in the human organism which include the insulin receptor subfamily three highly homologous receptors: the Insulin receptor (IR), the Insulin-like growth factor-1 receptor (IGF1R) and an orphanic the insulin receptor-related receptor (IRR) [1]. The receptors of the insulin receptor subfamily are involved in fundamental physiological processes such as growth, division, differentiation and survival. Disruption of the receptors function has been associated with a wide range of diseases including diabetes, cancer and Alzheimer's disease. Although TMDs of receptors do not interact with ligands directly, they are an important part of the molecular mechanism of receptor activation. Due to the lack of information, the process of signal transduction across the plasmatic membrane via TMD remains poorly understood at the molecular scale.
Methods and Algorithms: For characterising the structure and dynamics of all TMDs of the insulin receptor family we assembled genetic constructs, expressed them in CF and purified the recombinant InsRtm, IGF1Rtm and IRRtm. The peptides contained a hydrophobic TM segment flanked by short polar N-terminal and C-terminal regions. InsRtm, IGF1Rtm and IRRtm were solubilised in the aqueous suspension of DPC micelles. We used a detergent/peptide (D/P) molar ratio of 120 to shift the predominant dynamic equilibrium state of the peptides into monomer form. The prepared samples were explored with a conventional $^{15}N/^{13}C$ heteronuclear NMR technique.
Results: We conducted TMDs structural and dynamycs studies in membranes mimicking micelles using NMR spectroscopy (Fig. 1). Each of three obtained structures of TMDs has some distinguishing features. Both InsR and IGF1Rtm structures form slightly curved along the entire length α-helices with a kinks in the proline region. Moreover, IGF1Rtm has increased flexibility in comparison to InsRtm. A distinctive feature of IRRtm is to form two short α-helices connected through a flexible linker.

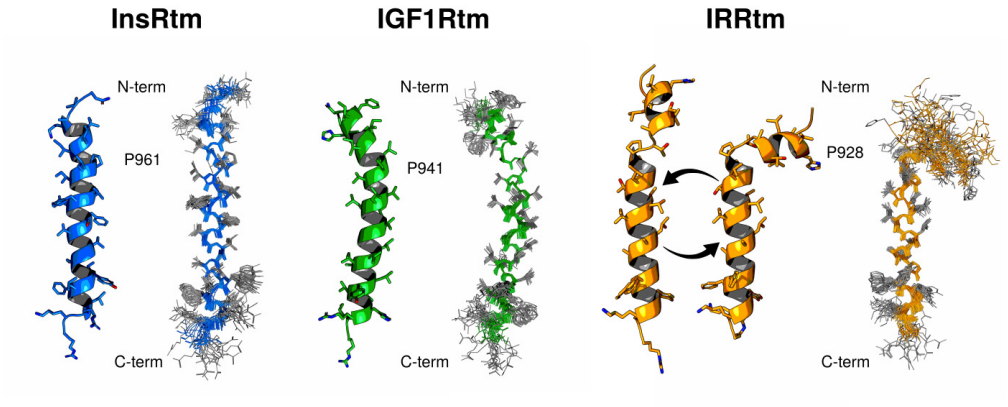

Fig. 1. Spatial structure of the InsRtm (blue; PDB 7PHT), IGF1Rtm (green; PDB 7PH8) and IRRtm (yellow; PDB 7PL4) monomers obtained in micellar membrane mimicking environments. (Left) The ribbon diagrams and (right) the ensemble of 20 NMR-derived structures after alignment of the backbone atoms monomers of the TMDs. Heavy atom bonds are depicted. Hydrogen atom bonds are shown only for polar groups

Conclusion: The structures of InsRtm and IGF1Rtm are similar. They have aproximetly same length of the TM helices. The high similarity of the structures of InsRtm and IGF1Rtm is consistent with the previously obtained MD, structural and biochemical data. IRRtm is significantly different from the other two family members. The IRRtm structure is represented by two helices. The proline sequence, as well as the TATP motif in front of it, locally increase the mobility to such an extent that one turn of the helix disintegrates. This differences of structures probably indicates a different mechanism of signal transduction across the membrane.

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References

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