Mapping the protein binding site of the (pro)renin receptor using *in silico* 3D structural analysis

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Abstract

We have reported that monoclonal antibodies against the (pro)renin receptor [(P)RR] reduce the Wnt/β-catenin-dependent development of pancreatic ductal adenocarcinoma (PDAC), the most common pancreatic cancer. Antibodies against two (P)RR regions (residues 47–60 and 200–213) located in the extracellular domain (ECD) reduced the proliferation of human PDAC cells *in vitro.* Although these regions probably play a role in the activation of Wnt/β-catenin signaling, their functional significance remains unclear. Moreover, the (P)RR ECD is predicted to possess an intrinsically disordered region (IDR), which allows for multiple protein interactions because of its conformational flexibility. In this study, we investigated the significance of the two regions and the IDR by *in silico* 3D structural analysis using the AlphaFold2 program and evolutionary sequence conservation profile. The model showed that ECD adopts a folded domain (residues 17–269) and has an IDR (residues 270–296). The two regions mapped onto the structural model formed a continuous surface patch comprising of evolutionarily conserved hydrophobic residues. The dimer structure predicted by AlphaFold2 showed that full-length (P)RR comprising the ECD, single-span transmembrane, and cytoplasmic domains formed a two-fold symmetric dimer via the ECD, which explains the experimentally proven dimer formation. The dimer model possesses two hand-shaped grooves with residues 47–60 and 200–213 in their palms and the IDR as their fingers. Based on these findings, we propose that the IDR-containing hydrophobic grooves act as a binding site for (P)RR and exerts multiple functions, including Wnt signaling activation.