Structural characterization of the viral E5 oncoprotein and its interaction with the PDGF receptor

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The platelet-derived growth factor receptor (PDGFR) is a receptor tyrosine kinase that gets constitutively activated by the oncogenic E5 protein from papillomavirus, leading to uncontrolled proliferation and cancer. Bovine E5 with a length of only 44 amino acids consists largely of a transmembrane helix that can engage in specific helix-helix interactions with the transmembrane segment of PDGFR [1,2]. Our aim is to elucidate the structural criteria by which these transmembrane segments recognize each other, and to describe the oligomeric bundle formed in the lipid bilayer. We reconstituted each of the two recombinantly expressed polypeptides in lipid bilayers with different acyl chain lengths, in order to (i) confirm their intact helical conformation, to (ii) determine their molecular alignment in the lipid membrane, to (iii) monitor any changes in response to bilayer thickness, and to (iv) observe the structural effect of one partner on the other. Complementary spectroscopic measurements were carried out using solid-state NMR and synchrotron-radiation circular dichroism on macroscopically oriented membrane samples [3,4,5,6]. We observed that, when reconstituted alone in lipid bilayers, the E5 helix is inserted almost upright in thick membranes, it starts to tilt and gets slightly deformed in moderately thinner bilayers and becomes aggregated in very thin membranes because of hydrophobic mismatch. On the other hand, when reconstituted together with the receptor, the E5 protein can compensate the hydrophobic mismatch by binding to the transmembrane segment of the receptor. The observed tilt angle dependence of E5 is the similar to that one observed for the PDGFR transmembrane segment. This hydrophobic mismatch behaviour may be responsible for driving the two different interacting partners together within the thin membrane of the Golgi compartment. They can recognize each other by forming a closely packed bundle transmembrane aligned helices, which is further stabilized by a specific pair of hydrogen-bonding residues.

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