Structural analysis of the PDZ domain of MEG in a complex with a viral protein E6

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High-risk human papillomaviruses (HPVs) cause a variety of cellular hyperproliferation-involved diseases, which include cervical cancer. E6, one of the two HPV-encoded oncoproteins, is known to recruit p53, the master regulator of cell cycle, and induce its degradation. E6 also provokes tumorigenesis in a p53-independent pathway through its C-terminal tail region that recognizes a PDZ domain of diverse host proteins. Herein, we determined the crystal structure of the PDZ domain of MEG in a complex with a peptide derived from the C-terminal region of HPV16 E6, which interact with each other with a dissociation constant of 18.8 μM. Structural analysis exhibited that the complex formation between the two proteins depend on hydrophobic interaction mainly mediated by Leu158 of HPV16 E6 and also on a number of intermolecular hydrogen bonds. Introduction of structure-based mutation and modification into the C-terminal region of HPV16 E6, including L158A, phosphorylation of Thr156, and amidation of the C-terminal end region, disrupted the complex formation, supporting the relevance of our crystal structure. Our study therefore provides a structural and biochemical basis for elucidating an additional target of HPV E6 in causing cell transformation and tumorigenesis.