

HUMAN PAPILOMAVIRUS AND CANCER: PROTEIN-LIGAND INTERACTIONS

We want to understand the molecular principles that govern human papillomavirus (HPV) infection, since this will probably improve the chances of rapid pharmaceutical intervention.

The implication of HPV in cancers of the uterine cervix has been firmly established biologically and experimentally. Most cancers of the vagina and anus are caused by HPV as are a number of cancers of the vulva, penis and oropharynx. HPV's are classically divided into two groups: "low" and "high risk". The mucosal HPV's are considered "low risk" while the "high risk" is based on their prevalence ratio in cervical cancer and its precursors. About 99% of the cervical cancers contain DNA of the high-risk types with HPV16 being the most prevalent, followed by types 18, 45, 13 and 33.

HPV utilises a number of ways to establish its pathogenic potential; one of them includes targeting the tumour suppressor p53 and SAP97 (synapse associated protein 97) for degradation. A lot has been done in trying to understand the mechanism of p53 interaction with HPV. However, little is known about the molecular mechanism with SAP97. During pathogenesis, it is known that an early protein known as E6 is secreted, which binds to the PDZ2 domain of SAP97. Other early proteins such as E4 and E7 are also implicated in the pathogenesis through their interactions with cell cycle proteins cyclin A/E, retinoblastoma tumour suppressor and cdk's.

We are looking at the molecular mechanisms of the interactions between HPV E6 and SAP97, and between HPV E7 and the retinoblastoma tumour suppressor. We are expressing and purifying wild-type and mutant proteins. Their interactions are studied by time-resolved and equilibrium spectroscopic techniques. In collaboration with Maria Selmer at the department of cell and molecular biology, Uppsala University, we also try to solve structures of protein complexes.

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