

The role of ubiquitination of capsid protein L1 in HPV infection

Human Papillomaviruses (HPVs) are small DNA viruses which infect epithelial cells and can cause nearly 5% of all human malignancies, with cervical cancer being the most important.

It is important to note that HPV doesn't cause only cervical cancer and doesn't only affect women. Nearly 4 out of every 10 cases of cancer caused by HPV occur among men. HPV is thought to be responsible for more than 90% of cervical and anal cancers, about 70% of vaginal and vulvar cancers, and 60% of penile cancers.

Although a vaccine against certain HPV types is available, it has some limitations. It is prophylactic and hence has no therapeutic activity; it does not protect from all HPV types and is very expensive.

So far, there is also no direct treatment for HPV infection; therefore, there is an urgent need to understand the cellular processes driving the HPV life cycle - and to identify new targets for the treatment of HPV infection and prevention of HPV-associated malignancies.

This project aims to elucidate **the role of ubiquitination of L1 capsid protein in HPV infection.** This is based on our recent proteomic analysis showed multiple potential ubiquitin acceptor sites in the L1 HPV protein sequence. Moreover, we observed that mutations in ubiquitin acceptor site(s) in the L1 protein affect virus assembly and significantly inhibit HPV PsVs infection. We also confirmed the presence of L1 post-translational modification using the ubiquitination assay.

A major goal of this study will be to answer the below questions:

1. What is the specific ubiquitin chain linked to the L1 protein?
2. What is the function of L1 ubiquitination in HPV infection?
3. Which Ubiquitin protein ligase(s) is (are) involved in L1ubiquitination?
4. Can E3-ubiquitin inhibitors reduce HPV infection?

Unravelling the above questions will help us to have deeper mechanistic insights into the crosstalk between HPV capsid proteins and the ubiquitin-conjugative system. This will provide a better understanding of the HPV infection cycle and potentially identify novel routes for blocking viral infection and release. The ubiquitin-conjugating system plays an important role in the regulation of many cellular pathways and the infection of different viruses. **Targeting components of the ubiquitin-conjugating system by small molecular regulators could provide a unique opportunity for the development of therapeutics for the treatment of HPV infection, which is currently dismal.**