Commentary

Human papillomavirus E2 protein: a potential key regulator of viral cell pathogenesis

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Invited Commentary on 'Large scale genotype comparison of human papillomavirus E2-host interaction networks provides new insights for E2 molecular functions', Muller et al., PLoS Pathogens 2012

The disease burden due to oncogenic forms of human papillomavirus (HPV) has risen significantly over the last decades. HPV-related mortality has become the second most prevalent cause of death due to cancer in women. Concomitantly, there is a noticeable steady increase in the incidence of oropharyngeal squamous cell carcinoma in individuals infected with HPV. Despite the establishment of extensive medical surveillance, the emergence of improved molecular detection methods, the establishment of educational campaigns in the general population and the recent licensure of vaccines to prevent the consequences of HPV infection, it is estimated that the worldwide trend of its devastating effect will not undergo a significant change in the immediate future.

Persistence of viral infection in mucosal and skin tissues is a central pathogenic feature of HPV. Moreover, the progress and severity of the lesions that develop are related to the low or high risk forms of HPV. The targeted selectivity of HPV for epithelial tissues, and its association with viral invasiveness, highlights the importance of the study of the molecular mechanisms involved in viral-cellular interactions and their relation with cell dysregulation. The recent data published by Mandy Muller and colleagues¹ on the protein-protein interactions established by HPV E2, with proteins associated with central cellular functional processes, bring us a step forward in uncovering key similarities and differences across different HPV genotypes and, thus, their role in viral pathology.

Central to the success of the authors' analysis was the validation of the methodological approach used. The study was primarily based on the use of the yeast two-hybrid (Y2H) screening system and a high-throughput *Gaussia princeps* luciferase-based complementation assay (HT-GPCA) to assess protein-protein interactions between 12 E2 proteins, spanning some of the most

prominent high-risk (HR) and low-risk (LR) HPV genotypes, against a human keratinocyte cDNA library. Despite some differences found, mostly due to intrinsic features of the methodologies, the data showed high sensitivity and also robustness in the identification of protein-protein interactions, also called *interactome*. Notably, the authors described diverse interactome profiles for both HR and LR HPV genotypes, suggesting distinct regulation of proteome expression profiles associated with E2 at cutaneous and mucosal levels.

The identification of protein-protein interactions provides an important, but still limited, view of their impact on cell metabolism and overall viral pathogenesis. One of the major contributions of this manuscript was the topological mapping and functional analysis of HPV E2 interactions at the subcellular level. Interestingly, E2 was found associated with activation and repression transcription factors as well as with proteins belonging to signaling pathways controlling cell death and survival which are fundamental processes implicated in viral replication and persistence. Also, some of the proteins identified participate in associated processes, including RNA splicing and ubiquitination, implying a direct role of E2 in protein synthesis and degradation. Remarkably, the analyses also suggest a potential role of E2 in immunoregulation through the interaction with proteins linked to intracellular vesicular trafficking which are known to participate in cell antigen presentation. Altogether, these results shed new light and also pave the way to carrying out a more systematic study on the early molecular mechanisms related to viral infectivity and protein-mediated control of cell regulation that impact HPV pathogenesis.

Nevertheless, it remains to be elucidated whether HPV E2 is a true central viral regulator and what are the most important interactions established during the different stages of disease development. Most importantly, from a therapeutic point of view, it will be important to elucidate the mechanisms in which E2 is involved that makes HPV more susceptible to treatment. Finally, a study of the above described mechanisms in the context of disease epidemiology will also provide clues on susceptibility to infection. Answers to these questions will contribute to designing better targets to prevent and treat HPV infections.

Reference

- 1 Muller M, Jacob Y, Jones L, Weiss A, Brino L, Chantier T, *et al.* Large scale genotype comparison of human papillomavirus E2-host interaction networks provides new insights for E2 molecular functions. *PLoS Pathogens* June 2012;8(6):e1002761.

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