Advancing Human Papillomavirus Research With a Rhesus Monkey Model

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Human papillomavirus (HPV) is the etiological agent of several human cancers. Three decades of basic science and epidemiological research has definitively linked cervical, anal, vulvar, and vaginal cancers to an infection with onecogenic types of this virus, especially HPV types 16 and 18, which together cause approximately 70% of all cervical cancers worldwide (1). More recent research has linked HPV infection to certain head and neck cancers (2). Scientists pursuing HPV research have confronted substantial obstacles over the past three decades. Perhaps, the most daunting of these obstacles is the lack of a practical culture system to produce infectious virions, although certain models such as the athymic mouse xenograft system, the severe combined immunodeficiency mouse system, and raft cultures have permitted the growth and purification of a few papillomavirus types for use in important studies of papillomavirus transmission, infectivity, gene expression, and immunology (3).

A related issue in HPV research is the scarcity of animal models. Species-specific papillomaviruses do infect many animals, but assays related to these animal models (mainly the bovine papillomavirus, canine oral papillomavirus, and cottontail rabbit papillomavirus) are technically challenging and expensive to perform. Only a few studies of papillomavirus natural history and immunology have used nonhuman primates because of these difficulties (3). Development of pseudovirion-based assays has permitted in vitro studies that do not require truly infectious papillomavirus particles; that is, infectious particles that contain the genetic material of the virus and can complete the replication cycle.

In this issue of the Journal, Roberts et al. (4) have advanced HPV research in several key areas. Application of the pseudovirion-based assay system to a primate model is indeed a step forward. Their findings provide insight into some very important questions related both to HPV biology and to the clinical care of women. What factors influence infection of cervical cells with HPV? What can be done, in addition to what is already known, to help reduce the risk of HPV infection? As the authors point out, previous research in this area has reported conflicting data. Conventional wisdom has held that microtrauma from sexual intercourse allows HPV access to the metabolically active basal layer of the genital tract epithelium. This team of researchers induced microtrauma in nonhuman primates via a plastic spatula that is routinely used for collection of cervical cytology specimens. In the cytology group, the cervical epithelium was traumatized, and infectious events, defined by uptake of pseudovirions into cervical cells, were dramatically increased above baseline (4).

The development of a rhesus macaque model in the area of HPV research is yet another important development described by Roberts et al. (4). Several advantages of this model are discussed within the article, including histological similarities and similar levels of HPV susceptibility between the macaque and human cervix. Another potential advantage of this model is the numerous reagents available for simian research.

At present, clinicians have two options to prevent cervical infection with HPV: consistent condom usage and vaccination (1,5). The second major finding of the current study is that an inexpensive microbicide (carrageenan) may prevent the initial events of HPV attachment (2). The search for a vaginal microbicide to prevent HPV and other sexually transmitted infections has been problematic. In the rhesus monkey model described by Roberts et al. (4), application of carrageenan to the cervix after the cytology specimen collection reduced the mean number of HPV16 infectious events to 3.5 (95% confidence interval = 1.8 to 6.9) compared with a mean of 84 infectious events (95% confidence interval = 45 to 158), when surgilube was applied to the cervix after the cytology specimen collection. The authors have previously described similar results of the potential preventative activity of carrageenan in a murine model (6). We await the results of clinical trials investigating the ability of carrageenan to prevent incident infection with HPV in humans.

We believe that the authors are correct in their conclusion that cervical cytology sampling may not play a biologically significant role in increasing the susceptibility of the human cervix to HPV infection (2). The readers should not take home a message that Pap smears increase the risk of HPV infections and subsequent clinical disease. We look forward to future studies from this group.

References


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