HPVs and Kinetochore Functions in Cervical Cancers

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The human papilloma virus (HPV) is one of the most common virus group in the world to affect the skin and mucosal areas of the body. HPV has been found to be associated with several types of cancer: cervical, vulvar, vaginal, penile and oropharyngeal. The vast majority of HPV-positive cervical cancers are associated with HPV16 and HPV18 which called high-risk type HPVs. Condyloma acuminate, or genital warts were caused by the infection of HPV6 and HPV11 which called low-risk type HPVs. Our research interest is focussed on the difference between the high-risk type HPVs and low-risk type HPVs. The low-risk type HPVs were caused benign tumor, but the high-risk type HPVs were caused malignant tumors. Previously we demonstrated that HPV18 E7 interacts with CENP-C as shown in Figure1(1). CENP-C is a component of the inner kinetochore, and is part of the CENP-A, CENP-B, CENP-C complex that associates with centromere α-satellite DNA, thus playing an essential role in centromere formation (2). Targeted disruption of CENP-C causes mitotic delay, chromosome missegregation, and apoptosis (3).

Recent evidence has further demonstrated that conditional knockout of CENP-C results in a loss of expression of the spindle checkpoint protein Mad2 in centromeres, suggesting that the loss of CENP-C in the inner kinetochore disrupts the assembly of other kinetochore components and impairs all centromere functions (4). Furthermore, disruption of CENP-C function has also been suggested as a cause of some human cancers.

We demonstrated that E7 binds CENP-C in HPV18 infected cells, but not in cells infected with HPV11 which is low-risk type HPV. The differences between high- and low-risk HPVs are not fully understood, and only a few details have been reported. We cleared that interaction of HPV18 E7 with CENP-C can cause aneuploidy, the ability of high-risk and low-risk HPVs to induce aneuploidy must differ significantly (Figure2). Aneuploidy is a common characteristic of cancer cells, differences in binding between E7 and CENP-C may therefore partially explain the different oncogenic potential of high- and low-risk HPVs.

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**Figure 1** HPV18 E7 disturbs the function of kinetochore.
We discovered that the conserved region 2 (CR2) domain of high-risk HPV18 E7 binds the C-terminal region of CENP-C and postulate that this interaction may be an important mechanism leading to HPV-induced aneuploidy. Our hypotheses are summarized in Figure 1, 2.

We speculate that the binding between HPV18 E7 and CENP-C inhibits the interaction of CENP-C and α-satellite DNA, then the kinetochore function is destroyed, and finally that leads to aneuploidy. Because aneuploidy is sufficient in and of itself to cause cancer over an extended period, HPV-induced aneuploidy may be associated with oncogenesis. Future research efforts in our laboratory will focus on elucidating the amino acids in the HPV18 E7 CR2 domain and CENP-C C-terminus that are involved in binding, analyzing the ability of other HPV E7s to bind CENP-C, and investigating the interactions between HPV18 E7 and CENP-C that promote aneuploidy.

In summary, we discovered that low-risk HPV E7s could not bind to CENP-C and the PxDLLCxExE in the CR2 of HPV18 E7 were important for E7 binding to CENP-C (5). CENP-C is a component of the inner kinetochore and plays an essential role in proper chromosome segregation, mitotic checkpoint function, and kinetochore assembly. Therefore we speculate that the different binding ability between E7s and CENP-C reflect the different oncogenic potential between these high and low-risk type HPVs.

REFERENCES
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