Short Communication

Journal of Bacteriology and Infectious diseases

2020
Vol. 4, Iss. 2

Bacteriology and Infectious Diseases 2018 - Role of human papillomavirus, estrogen and Apobec3B axis in breast cancer initiation

Pei Pei Chong

Universiti Putra Malaysia, Malaysia

Keywords: Human Papillomaviruses, Oncogenes, Cancer

Human Papillomaviruses (HPVs) are known to cause cancer by altering multiple signaling pathways through integration of their oncogenes into the human host genome. It has been well established that infection with HPVs causes cervical cancer and head and neck cancer; and some forms of genital cancers. The HPV viral oncogenes E6 and E7 play a big role in carcinogenesis. HPV E6 proteins bind to p53 to inhibit and degrade this tumor suppressor to abolish its cancer prevention effects. Consequences of an inactivated p53 also include accumulation of gene mutations and inappropriate response to DNA damage, which cooperate with other cellular changes, eventually leading to carcinogenesis. The APOBEC (apolipoprotein B editing enzyme catalytic polypeptide-like) proteins function in innate immunity by deaminating single-stranded DNA (ssDNA) replication intermediates of viral pathogens (retro-, hepadna-, papilloma-viruses), inhibiting the retrotransposition of L1 and Alu elements and mediating the clearance of foreign DNA through deamination-dependent mechanisms. APOBEC enzymes have also been implicated in cancer pathogenesis. In HPV-positive cancers of the head/neck and cervix, the HPV E6/E7 oncoprotein causes up-regulation of APOBEC3B both at the mRNA and enzymatic activity level. As such, we decided to investigate the prevalence of HPV in breast cancer and whether APOBEC3B is overexpressed in breast cancer samples. Detection of HPV DNA via the Toshiba DNA chip platform technology found 31% of breast cancer samples were positive for high-risk HPV especially HPV16 and HPV18. HPV prevalence was significantly correlated with estrogen receptor, pathological features of the cancer, and age of patients. A significantly higher proportion of ER-positive BC samples were HPV-positive than ER-negative samples. Interestingly, HPV-positive tumors showed better prognosis than HPV-negative tumors. Our in vitro study of normal breast epithelial cells transfected with HPV18 showed enhanced apobec3B expression, which led to γH2AX focus formation, a classic sign of genomic instability and DNA degradation. These A3B induction effects were abrogated when E6, E7 and A3B gene expression was knocked down using shRNA. Finally, we also checked if A3B induction is correlated with HPV status in breast cancer patients. A3B expression level seems to be correlated with HPV infection although statistical significance could not be obtained. In summary, we propose a putative mechanism of breast cancer development whereby Apobec3B induction due to HPV infection in mostly estrogen-receptor positive cells leads to aberrant DNA mutations that initiate carcinogenesis. Indeed, it is highly likely that a synergy between estrogen and p53 insufficiency caused by HPV E6 oncoprotein induces Apobec3B expression which leads to initiation of breast carcinogenesis. The apolipoprotein B messenger RNA-editing, enzyme-catalytic, polypeptide-like 3 (APOBEC3) family of cytidine deaminases plays an important role in the innate immune response to viral infections by editing viral genomes. However, the cytidine deaminase activity of APOBEC3 enzymes also induces somatic mutations in host genomes, which may drive cancer progression. Recent studies of human papillomavirus (HPV) infection and disease outcome highlight this duality. HPV infection is potently inhibited by one family member, APOBEC3A. Expression of APOBEC3A and APOBEC3B is highly elevated by the HPV oncoproteins E6 and E7 during persistent virus infec-

Note: This work is partly presented at 7th International Conference on Bacteriology and Infectious Diseases June 04-05, 2018 Osaka, Japan

tion and disease progression. Furthermore, there is a high prevalence of APOBEC3A and APOBEC3B mutation signatures in HPV-associated cancers. These findings suggest that induction of an APOBEC3-mediated antiviral response during HPV infection may inadvertently contribute to cancer mutagenesis and virus evolution. Here, we discuss current understanding of APOBEC3A and APOBEC3B biology in HPV restriction, evolution, and associated cancer mutagenesis. Despite numerous antiviral roles for A3A, the precise mechanisms of A3A-mediated restriction are unknown. For instance, transgenic mice expressing human A3A are capable of restricting several murine retroviruses such as mouse mammary tumor virus and murine leukemia virus, yet very minimal DNA deamination was observed . In the context of HPV infection, overexpression of A3A during HPV virion production markedly reduced infectivity. Unexpectedly, despite their restriction being dependent on a functional A3A catalytic domain, no A3A-induced mutations were found in the HPV16 long control region or E2 gene, which were previously identified as A3A mutation hotspots . While it is still possible that other regions of the HPV genome may be edited by A3A, RNA editing may provide an alternative mechanism by which A3A restricts HPV infection in lieu of DNA editing. For example, deamination of the transcripts encoding L1 and L2 capsid proteins would likely have a dramatic effect on HPV virion infectivity. Supporting this idea, previous studies have revealed that virus restriction by A3A can occur in a deaminase-dependent mechanism without DNA sequence editing, or by a deaminase-independent mechanism . A study from the Malim group further supports this concept by showing that cytidine deamination and DNA editing is not sufficient for antiviral activity during HIV-1 infection. These results suggest alternative mechanisms by which A3A restricts virus infections beyond editing viral DNA sequences. Editing of viral transcripts may provide a novel mechanism by which A3A inhibits virus infection through cytidine deamination. The inactivation of tumor suppressors by HPV oncoproteins is robust and quick. For example, p53 and pRB are degraded in host cells in which high-risk HPV E6 and E7 are expressed. Nevertheless, HPV-associated cancer progression is a slow process, typically taking two to three decades. A growing number of studies have shown that the continuous expression of E6 and E7 is required through the full process of cancer progression and maintenance. Our CxCa progression study has shown that many HPV-specific gene expression changes occur in a later stage or continuously throughout decades of cancer progression . In this regard, the roles of A3A and A3B in HPV-associated cancer progression are particularly interesting. However, most of these new findings have generated more questions than answers, particularly due to the causal relations and the need for defining the mechanistic elements of these interactions. Now, most studies on A3-induced cancer mutagenesis have been limited to using highly biased sequencing approaches or are based on correlations between expression levels and preferred target sequence changes. Since A3-induced somatic mutations probably accumulate over decades, it would be technically challenging to recapitulate and confirm this process in experimental models. To overcome these barriers, developing transgenic animal models expressing human A3s along with HPV oncoproteins may provide useful tools to track cancer mutagenesis. Additionally, further work is needed to elucidate the mechanisms of A3A restriction of HPV infection, which are distinct from A3B and A3C. It would also be interesting to further investigate whether A3A and A3B restrict other small DNA tumor viruses and contribute to somatic mutagenesis of their associated cancers. Future studies may provide great insights into how virus-host interactions drive the evolution of viruses and host cells, and how these interactions may lead to unexpected consequences such as cancer development.

Note: This work is partly presented at 7th International Conference on Bacteriology and Infectious Diseases June 04-05, 2018 Osaka, Japan