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Role of human papillomavirus, estrogen and Apobec3B axis in breast cancer initiation

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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.

Biography

Pei Pei Chong is a Molecular Biologist with expertise in both infectious diseases and cancer biology. She has special interest in host-pathogen interaction particularly in candidiasis, HPV-associated pathologies, as well as drug resistance and strain typing in MRSA. She is fascinated by the vast repertoire of the Human Papillomaviruses (HPVs) and strongly feels that more studies need to be conducted to unravel at the molecular level, the strategies by which the virus adapts to different sites of infection and cause various diseases.

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