Human Papillomavirus Infection as the Risk Factor to Retinoblastoma

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ABSTRACT

Retinoblastoma (Rb) is the most common malignant tumor of the retina in children. Two main types of retinoblastoma are heritable and non-heritable retinoblastoma. Retinoblastoma can emerge because of loss or inactivation of Rb protein (pRb), RB1 gene product in chromosome 13. HPV infection may play a role as risk factor to non-heritable retinoblastoma.

Keywords: Cancer, Human Papillomavirus, retinoblastoma

ABSTRAK

Retinoblastoma (Rb) merupakan tumor ganas retina yang paling umum terjadi pada anak-anak. Dua tipe retinoblastoma adalah yang diturunkan dan yang tidak diturunkan. Retinoblastoma dapat terjadi akibat inaktivasi protein Rb (pRb) yang merupakan produk gen RB1 pada kromosom 13. Infeksi HPV mungkin berperan sebagai salah satu faktor risiko retinoblastoma. **Albert Tito, Sri Yuliani Iida. Infeksi Human Papillomavirus sebagai Faktor Risiko Retinoblastoma**

Kata kunci: *Human Papillomavirus*, kanker, retinoblastoma

INTRODUCTION

Retinoblastoma is the most common malignant tumor of the retina in children. The incidence is 1 in 18 000-30 000 live birth regardless of sex, race, or geography.[1,2] Two main types of retinoblastoma regarding the genetic factors are heritable and non-heritable retinoblastoma. Heritable retinoblastoma occurs in 40% cases.[3] In heritable retinoblastoma, one pair of alleles of RB1 is mutated in all body cells, and further mutagenic event affects the second allele, trigerring malignant transformation. Because of mutation in all cells, a majority of heritable retinoblastoma develop bilateral and multifocal tumours. In non-heritable retinoblastoma, the tumour is unilateral, non-transmissible and does not predispose to second non-ocular cancers.[3-5] Retinoblastoma can emerge because of loss or inactivation of Rb protein (pRb) - RB1 gene product in chromosome 13. The pRb has an important role in controlling cell activation and block the potential processes to develop cancers in human, including retinoblastoma. pRb binds and inactivates transcription factors, such as E2F group that regulates cell cycle progression. Mutation in retinoblastoma gene (RB1) causes loss of pRb function and leads to the increase of E2F protein release. Most retinoblastoma cases showed a mutation on its RB1, 17%–80% non-heritable retinoblastoma cases have an intact RB1 gene.[3,4]

Some human cancers have a viral etiology. Viral proteins such as the T antigen of SV40, the E1A of adenovirus, and E7 of the human papillomavirus (HPV) are competent to inactivate the function of tumor suppressor proteins.[6,7] HPV is the cause of cervical cancer and also known to be correlated to ocular lesion; HPV is seen as a papilloma, dysplasia, and conjunctival carcinoma, and also can be found in normal mucosa.[5] Some research have shown the association between HPV and retinoblastoma;[4,8] but the results are still contradictory. Studies in Mexican and South American populations have reported high-risk HPV types in 28% and 82% patients with non-heritable retinoblastoma, respectively.[4,8,9] In contrast, none of the 40 cases of non-heritable retinoblastoma showed HPV positive in a North American population.[10] Two studies on Indian population show 0% and 48% of HPV associated retinoblastoma,[11] and a study in Indonesia showed HPV 16 had no role in retinoblastoma.[5] Another study in Korea showed that HPV infection may have no causal relationship with retinoblastoma.[12] HPV role in retinoblastoma is still controversial.

MATERNAL TRANSMISSION OF HPV IN RETINOBLASTOMA

HPV infection is the main etiologic agent for the development of the most cases of cervical cancer.[13] HPV infections might be spread by sexual contact.[13,14] Maternal transmission of mother to fetus is known might be occurred.[13] In up to 80% of neonates born from mother with genital HPV have HPV DNA detectable in nasopharyngeal aspirate or oral mucosa, and may persist for months or years.[13,14] A study in Korea[15] showed that HPV DNA was detected at birth in 5.2% of neonates and was associated with the detection of HPV in mothers during any of three trimesters of pregnancy.

Maternal transmissions are presumed to occur

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during the passage of the fetus through the infected birth canal.[13-15] HPV DNA have been detected in peripheral blood mononuclear cells of pregnant women, cord blood specimens of neonates, oropharyngeal secretions of neonates, amniotic fluid, fetal membrane, placental trophoblastic cells, infants born by elective caesarian section delivery, and in syncitiotrophoblastic cells.[15-18] Based on those findings, HPV transmission from mother to child might be a possible route of HPV infection to the child's eyes and might lead to non-heritable retinoblastoma.[16-22] A study in India showed that HPV DNA were detected in neonates' retinoblastoma samples and correlated to the maternal HPV infection by cervical brushing samples.[22] Maternal transfer of HPV in retinoblastoma could be a possible route of transmission. Another study on the association of maternal health, including sexual behavior, to retinoblastoma showed a negative association of unilateral retinoblastoma with the use of condoms in the year prior to pregnancy, although this study did not directly assess the HPV role in retinoblastoma.[23]

DETECTION OF HPV TYPE ASSOCIATED WITH RETINOBLASTOMA

Based on the tissue tropism there are approximately 200 HPV types which can be divided into mucosal and cutaneous types. Mucosal HPVs are classified into low-risk and high-risk regarding the malignant progression of the lesions that they cause. Approximately 5% human cancers, including >99% cervical carcinomas, penile, vulvar, vaginal and anal carcinomas, and a growing fraction of head and neck squamous cell carcinomas, are caused by high-risk HPV.[24] High-risk HPV associated cancers are generally non-productive infections, viral proteins are produced but no viral progeny is generated. HPV E6 and E7 are the only viral genes that are consistently expressed in the cancers.[6,25]

Some studies showed the geographical distribution of HPV DNA in cervical cancer cases. The DNA of HPV 16 and 18 in United States of America,[8] HPV 16 and HPV 35 in Brazil,[4] and HPV 16 in India.[11] In cervical cancer, HPV 16 often to be found in Europe, while HPV 18 is more common in Asia.[24,26] But there were no enough information of HPV type distribution related to retinoblastoma.[8,27] Mohan, *et al*,[11] studied the detection of HPV DNA in retinoblastoma samples in India by histopathology findings and polymerase chain reaction (PCR), showed that HPV 16 was detected in 57% tumors and HPV 18 was negative at all retinoblastoma samples and the pRb expression was absent in 71% of retinoblastoma which had HPV DNA. Pallazi, *et al*,[4] also studied the presence of HPV DNA with PCR and dot-blot hybridization in samples of paraffin-embedded tumor tissue from 43 children with unilateral retinoblastoma and the results showed a prevalence of HPV DNA in 27.9% of the specimens, mainly 16 and 35 types. Elida, *et al*,[5] have employed PCR in 34 retinoblastoma samples and none with HPV 16 DNA positive. Ryoo, *et al*,[12] study did not detect HPV in any retinoblastoma samples using both high-risk or low-risk HPV probes. Those findings showed the inconsistent results of HPV DNA in retinoblastoma over various studies.

PATHOGENESIS OF HPV ASSOCIATED RETINOBLASTOMA

The role of HPV in retinoblastoma is still unknown regarding the various contradictory results in studies around the world. But some hypotheses are proposed to describe the pathogenesis of HPV to cause retinoblastoma.[25] High-risk HPV is important but not sufficient for progression to cancer. The mutations in cellular genes and chromosomal rearrangements induced by genomic instabilities are the more important factors.[25,27,28] HPV E6 and E7 are the primary transforming viral proteins and E5 enhances proliferation and may contribute to cancer progression. E7 targets the retinoblastoma (Rb) family of proteins that control the activity of E2F transcription factors, which are regulate in S phase genes.[27,28] Inactivation of Rb can cause the differentiation-dependent productive viral lifecycle and for tumor progression. The disruption of Rb function by E7 leads to increased levels of p53 and,consequently, the E6 proteins target p53 for degradation. E6 also induces telomerase expression and modulates the activities of PDZ domain-containing proteins and tumor necrosis factor receptors.[27-30] E7 proteins alter cell cycle through the interactions with histone deacetylases, cyclins, and cyclin-dependent kinase inhibitors. E6 and E7 cause genomic instability through multiple mechanisms, including aberrant centrosome duplication. E6 and E7 also target cytokine expression to modulate cell proliferation and interferon responses, contributing to immune evasion. E5 binds to B cell receptor-associated protein 31 in the endoplasmic reticulum to control trafficking of proteins and to the vacuolar ATPase in endosomes to modulate epidermal growth factor receptor turnover and maintain constitutive signalling.[27-31]

Recent studies suggest that $p16^{INK4A}$ expression in response to high-risk E7 expressionis the main carcinogenic factor, and degradation of RB1 by high-risk HPV E7 proteins has evolved to negate the $p16^{INK4A}$ cytostatic responses.[32]Low-risk HPV E7 proteins do not trigger $p16^{INK4A}$.[32,33] High-risk HPV E7 induces $p16^{INK4A}$ independent of RB1 inactivation through an epigenetic mechanism involving the KDM6B histone demethylase. KDM6B catalyzes removal of trimethyl marks on lysine 27 of histone H3 (H3K27me3), which are important for gene silencing by Polycomb repressive complexes (PRCs). This is reminiscent of RAS oncogene-induced senescence (OIS), a cellular defense response involving $p16^{INK4A}$ - mediated inhibition of CDK4/6 and resulting in RB1 mediated cell cycle arrest and senescence.[33] RB1 binding and E2F activation by E7 is not sufficient to thwart RB1 senescence signaling, high-risk HPV E7 evolved to degrade RB1. High-risk HPV E7 proteins also activate the expression of $p14^{ARF}$, which is normally silenced by PRCs. HPV16 E7 expression causes decreased H3K27me3 marks on the $p14^{ARF}$ promoter.[6,32,33]

Role of HPV in retinoblastoma could be caused by infectious agent exposure or other environmental factors that lead to *in utero* mutation. HPV itself is actually not a carcinogenic agent according to the epidemiology and clinical data.[5,25,31] The malignant HPV transformation in an infected cell is caused by genetic changes.[5,31] The ability of E6 and E7 protein to do transformation depend on the tumor suppressor gene (tumor suppressor gene protein: p53 and pRb) that binds to those proteins. E7 binds several cellular proteins including pRb, p107, p130, and cyclin A. E7 and pRb binding complex causes the release of E2F1 and pRb transcription factors. These processes explain how HPV is able to form retinoblastoma.[5]

CONCLUSION

The role of HPV in retinoblastoma is still


controversial. Based on some studies and hypotheses, there might be a role of HPV infection as one of the risk factors to non-heritable retinoblastoma; although HPV alone is actually not enough to cause carcinoma, there were genetic changes in an infected cell induced by HPV infection. Studies with larger samples are needed.

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