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WARUNYA KOMWACHARAPONG : ROLE OF E6 PROTEIN IN ETOPOSIDE RESISTANCE IN CERVICAL CANCER. THESIS ADVISORS : MATHUROSE PONGLIKITMONGKOL Ph.D., PRAPON WILAIRAT Ph.D., PORNPIMOL RONGNOPARUT Ph.D., MANA ROCHANAWUTANON M.D. 170 P. ISBN 974-662-814-3

Cervical cancer remains the most common type of female cancers in Thailand, causing both morbidity and mortality. Approximately 90 % of cervical cancers are infected with human papillomavirus (HPV) including HPV16 and HPV18.The infection results in an overexpression of viral oncoproteins E6 and E7 following viral integration into host chromosomes. There are 3 forms of E6 mRNA: one full length (E6) and two spliced forms (E6* and E6**). The full length E6 has been shown to act as a transcription factor involved in transformation and drug resistance of host cells.

Etoposide (VP-16), a topoisomerase II inhibitor, has recently been introduced into a new regimen for treatment of cervical cancer. Two etoposide-resistant lines of cervical cancer, HeLa/VP-16 and SiHa/VP-16, were induced in our laboratory and used to study the role of E6 protein in etoposide resistance. HeLa cells are infected with HPV18 while SiHa cells are infected with HPV16. Comparison of gene copy number between HeLa and SiHa cells revealed that HeLa cells contained a higher copy number of E6 gene than SiHa cells. When E6 mRNA levels of all 4 lines (HeLa, SiHa, HeLa/VP-16 and SiHa/VP-16) were quantified using RT-PCR technique, results showed that E6* mRNA level in SiHa/VP-16 was significantly higher than that in its parental SiHa cells. No difference was seen in E6 mRNA levels. There was no apparent change in either E6 and E6* mRNA levels in HeLa/ VP-16 as compared to those in HeLa parental cells. Moreover, RT-PCR products of p53, the target protein of E6 and E6*, remained unchanged in both HeLa/VP-16 and SiHa/VP-16 cells when compared with their parental cells. The effect of E6* in etoposide resistance in SiHa/VP-16 was studied by transfection of E6* gene of SiHa/VP-16 into etoposide-sensitive HeLa cells. E6* transfected Hela cells showed a high level of transient expression of E6* mRNA whereas E6* mRNA was not detected in vector transfected cells. Drug susceptibility tests showed the same LC_{50} value (0.9 μM) between E6* and vector control transfected cells indicating that E6* does not have a role in etoposide resistance.