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Immune-escape Mechanisms of Cervical Carcinomas Induced by HPV Infection: Down Modulation of IL-18 Expression and IL-18-Induced IFN-γ Production via Bindings of HPV Oncoproteins to IL-18 and IL-18 Receptor

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In order to investigate how HPV escape from immune surveillance, E6 and E7 oncogenes of HPV 16 were infected into HaCaT keratinocytes and C33A cervical carcinomas which do not contain HPV genomes. Among proinflammatory cytokines such as IL-1, TNF-α, IL-6 and IL-18, only IL-18 expression was downregulated in C33A and HaCaT cells transfected with E6 oncogenes. Expression of HPV oncogene E6 was reversely correlated to the expression of interleukin-18. The expression of E6 in C33A, independent of E6 splicing, resulted in decreased IL-18 expression and that of IL-18 was also significantly reduced in HaCaT cells expressing E6. The level of p53 was reduced in C33A cells expressing E6 whereas not altered in HaCaT cells expressing E6, suggesting that E6 down-regulated IL-18 expression via independent pathway of p53 degradation in HaCaT cells which have a mutated p53 form. However, E7 did not affect IL-18 expression significantly in both C33A and HaCaT cells. Cotransfection experiments showed that E6 oncogene did not inhibit the activities of IL-18 promoter P1 and P2, suggesting that E6 oncogene indirectly inhibited IL-18 expression. Taken together, E6, E6 mutant and E6/E7 inhibited IL-18 expression with some variation, assuming that cells expressing E6 oncogene can evade immune surveillance by downregulating the expression of immune-stimulating cytokine gene, IL-18, and inhibiting the cascade of downstream effects that follow activation of the IL-18 receptor. In fact, E6 and E7 oncoproteins were competitively bound to IL-18R. However, there were no effects of those oncoproteins on IL-1 receptors. These oncoproteins inhibited IL-18-induced IFN-γ production in NK0 cells and PBMCs. By using IL-18 mutants E42, the effects of oncoproteins on IL-18 binding to IL-18R and on the IL-18 signaling via IL-18R will be discussed.