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Inactivation of IRF-1 Tumor Suppressor Protein by HPV E7 Oncopretin: Implication for the E7-Mediated Immune Escape Mechanism in Cervical Carcinogenesis

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Of HPV oncogene products, E7 protein binds to hypophosphorylated form of pRb tumor suppressor and interferes with its binding to E2F, resulting in release of E2F, which subsequently activates genes essential for progression through late G1 and S phase. Recently, it has been reported that Interferon regulatory factor-1 (IRF-1), a transcription factor, plays multiple roles in the regulation of cell growth including G1 arrest and apoptosis, antiviral response, and immune-promotion, when induced by several stimuli such as interferons, retinoic acids, prolactin, and TNF-α. In a way to study biological roles of IRF-1 in cervical cancer cells, we found that HPV E7 is functionally associated with IRF-1. Yeast and mammalian two-hybrid, and GST pull-down assays indicate a physical interaction between IRF-1 and either HPV-16 or HPV-11 E7 proteins *in vivo* and *in vitro*, respectively. The carboxy-terminal transactivation domain of IRF-1 is found to be absolutely required for the interaction. Transient co-expression of E7 significantly inhibits the IRF-1-mediated activation of IFN β promoter in NIH3T3 cells. Co-transfection of E7 mutants reveals that the pRb-binding portion of E7 is necessary for the E7-mediated inactivation of IRF-1, suggesting that either pRb mediate the E7's repressing activity or more directly the region of E7 is required for interaction with IRF-1. It was next determined whether histone deacetylase (HDAC) is involved in the inactivation mechanism as recently suggested that the carboxy-terminal zinc finger domain of E7 recruits NURD complex containing HDAC through the interaction with Mi2β. When TSA, a inhibitor of HDAC was treated, the repressing activity of E7 was inhibited in a dose-dependent manner. Furthermore, the mutation of zinc finger region abrogates such activity without effect on the interaction with IRF-1. These results suggest that HPV E7 interferes with the tansactivation function of IRF-1 by recruiting HDAC to the promoter. Tet-inducible E7 expressing cell line is under construction to demonstrate the physiology *in vivo*. The immuno-promoting role of IRF-1 evokes that our novel finding might be important for the elucidation of the E7-mediated immune escape mechanism that is frequently found in cervical cancer patient.