

Thesis Abstract

No. _____

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Thesis Title Development of an in vitro carcinogenesis model of human papillomavirus-induced cervical adenocarcinoma (ヒトパピローマウイルス誘発性子宮頸部腺がん in vitro 発がんモデルの構築)			
Thesis Summary Cervical adenocarcinoma is the second most common pathological subtype of cervical cancer after squamous cell carcinoma. It accounts for approximately 20% of cervical cancers, and the incidence has increased in the past few decades, particularly among young patients. The persistent infection of high-risk human papillomavirus (HPV) is responsible for most cervical adenocarcinoma. However, almost all available <i>in vitro</i> models are designed to study the carcinogenesis of cervical squamous cell carcinoma. To gain better insights into molecular background of adenocarcinoma, I aimed to establish an <i>in vitro</i> carcinogenesis model of adenocarcinoma. Our group previously reported previously reported the establishment of an <i>in vitro</i> model for cervical squamous cell carcinoma by introducing defined viral and cellular oncogenes, HPV16 E6 and E7, c-MYC and activated RAS to human cervical keratinocytes (HCKs) immortalized with ectopic TERT expression such as HCK1T. In this study, the expression of potential lineage-specifying factors and/or SMAD4 reduction was introduced into HCK1T in addition to the defined four oncogenes to direct carcinogenesis toward adenocarcinoma and the cell properties associated with the cell lineage were analyzed in monolayer and organoid cultures and the tumors in mouse xenografts. I successfully developed an in vitro model of cervical adenocarcinoma from the same cells as an in vitro cervical squamous cell carcinoma model by introducing expression of E6 and E7 of HPV16 or HPV18, oncogenic KRAS and MYC with ectopic expression of FOXA2 and/or the reduced expression of SMAD4. In the cells expressing FOXA2, apparent changes in the cell property were observed, such as elevated expression of columnar cell markers and decreased expression of squamous cell markers. Strikingly, the histopathology of tumors expressing FOXA2 resembled cervical adenocarcinoma, proposing that FOXA2 plays a vital role in dictating the histopathology of cervical cancers.			