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学位授与の要件	学位規則第４条第１項該当 医学系研究科病態制御医学専攻
学位論文名	Aberrant Expression of Disintegrin-metalloprotease Proteins in the Formation and Progression of the Uterine Cervical Cancer （子宮頸部癌の発生・進展におけるディスインテグリン・メタロプロテアーゼ分子の発現異常）
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論文内容の要旨

〔　目　　的　〕

Dysregulated expressions of disintegrin - metalloprotease proteins (ADAM and ADAMTS) have been reported in many types of cancers, and are believed to play important roles in cancer formation and metastasis. However, little is known about the expression of ADAMs and ADAMTS in the development of human cervical cancer.

〔　方法ならびに成績　〕

Reverse　transcriptase polymerase chain reaction, and immunoblotting were performed to assess the expression of several members of disintegrin-metalloproteases, and tissue inhibitor of metalloproteinases (TIMPs) in squamous-type cervical cancer cells, and oncogenically modified keratinocytes (immortalized human cervical keratinocytes transduced with Human papilloma virus-16 E6/E7 proteins with or without oncogenes). Immunohistochemistry of ADAM-9, ADAM-10 and TIMP-3 was performed on 31 primary human cervical tissue specimens of preinvasive, and invasive cervical carcinoma. mRNA levels of ADAM-9, ADAM-10, ADAM-12, TIMP-2 and TIMP-3 were upregulated as cervical cells progress from dyspalstic to malignant lesions compared to normal cervical cells. These results were corroborated at the protein level by western blot analysis and immunohistochemistry.

〔　総　　括　〕

The expression of disintegrin-metalloprotease and their endogenous regulators were dysregulated during cervical carcinogenesis. The aberrant expressions of ADAMs might contribute to the pathogenesis of cervical cancer formation and progression.

論文審査の結果の要旨

Objective:　Dysregulated expressions of disintegrin - metalloprotease proteins (ADAM and ADAMTS) have been reported in many types of cancers, and are believed to play important roles in cancer formation and metastasis. However, little is known about the expression of ADAMs and ADAMTS in the development of human cervical cancer.

Methods: Reverse　transcriptase polymerase chain reaction, and immunoblotting were performed to assess the expression of several members of disintegrin-metalloproteases, and tissue inhibitor of metalloproteinases (TIMPs) in squamous-type cervical cancer cells, and oncogenically modified keratinocytes (immortalized human cervical keratinocytes transduced with Human papilloma virus-16 E6/E7 proteins with or without oncogenes). Immunohistochemistry of ADAM-9, ADAM-10 and TIMP-3 was performed on 31 primary human cervical tissue specimens of preinvasive, and invasive cervical carcinoma.

Results: mRNA levels of ADAM-9, ADAM-10, ADAM-12, TIMP-2 and TIMP-3 were upregulated as cervical cells progress from dyspalstic to malignant lesions compared to normal cervical cells. These results were corroborated at the protein level by western blot analysis and immunohistochemistry.

Conclusion: The expression of disintegrin-metalloprotease and their endogenous regulators were dysregulated during cervical carcinogenesis. The aberrant expressions of ADAMs might contribute to the pathogenesis of cervical cancer formation and progression.