論 文 の 内 容 の 要 旨

論文提出者氏名	Maureen Tania Widyasaputra
論文審査担当者	主　査　菅野　祐幸 副　査　竹下　敏一　・　藤永　康成　・　岩渕　徳郎（学外）・

論　文　題　目

Increased expression of secreted protein acidic and rich in cysteine and tissue inhibitor of metalloproteinase-3 in epidermotropic melanoma metastasis
(悪性黒色腫の表皮向性転移における、secreted protein acidic and rich in cysteine および tissue inhibitor of metalloproteinase-3 の発現増強)

（論文の内容の要旨）

[Background] Primary cutaneous melanoma generally arises in the epidermis, followed by invasion into the dermis. Next, melanoma can metastasize either by the lymphatic or by the hematogenous route to other organs or distant skin areas. When melanoma cells metastasize to the distant skin area, they will usually arise into the dermal area (common skin metastasis). Although infrequent, the metastases can develop more superficially than usual within the intraepidermal area and form epidermotropic melanoma metastasis (EMM).

[Objective] In this study, we focused on this unique manner of metastasis and tried to identify key molecules which affect EMM. Through this study, we further tried to illuminate invasion mechanism from the epidermis to the dermis.

[Materials and Methods] Gene expression in EMM was compared with that in common skin metastasis (CSM). As an initial screening, mRNA expression was evaluated using PCR arrays for genes affecting the extracellular matrix, cellular adhesion, and tumor metastasis on three EMM and three CSM samples. For molecules showing altered expression in the EMM, expression levels were further verified using real-time quantitative PCR (qPCR) and immunohistochemistry. Next, we also compared the protein expression of EMM and CSM on molecules that were previously known to involve the melanoma metastasis pathway.

[Results] Five molecules showed an expression difference in the initial screening. Among these, SPARC was preferentially expressed in EMM (p=0.01) by real-time qPCR. Another candidate molecule, TIMP3, was not statistically significant (p=0.07), but showed the tendency of higher expression. These results correlated negatively to expression of N-cadherin and β-catenin.

[Conclusion] The upregulation of SPARC and TIMP3 may disrupt the continuity of the canonical Wnt pathway. This pathway regulates adhesion activity of melanoma cells to localize within the dermis, which consequently promotes EMM. Our study highlights the potential role of SPARC and TIMP3 as key molecules in EMM, and analysis of EMM may contribute for understanding melanoma invasion between the epidermis and the dermis.