論 文 審 査 の 結 果 の 要 旨

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（論文審査の結果の要旨）

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: We found the following results:

1. In the human extracellular matrix and adhesion matrix array, secreted protein acidic and rich in cysteine (SPARC), tissue inhibitor of metalloproteinase-3 (TIMP3), collagen type I alpha I chain, collagen type XV alpha I chain, and connective tissue growth factor were higher in EMM samples than CSM samples.
2. Through real-time qPCR and immune staining, the increase of SPARC and TIMP3 in EMM were confirmed in the levels of mRNA and protein.
3. Different from CSM, EMM showed an absence of neural cadherin (N-cadherin) and *β*-catenin upregulation.
4. Most primary melanoma lesions expressed TIMP3 but not SPARC.

Conclusions: The present study showed novel findings of SPARC and TIMP3 expression in EMM and proposed a potential mechanism of melanoma cell invasion. These results correlated negatively to the expression of N-cadherin and *β-catenin.* The upregulation of SPARC and TIMP3 may disrupt the continuity of the canonical *Wnt* pathway. This pathway regulates the adhesion activity of melanoma cells to localize within the dermis, and the disruption consequently promotes EMM. Our study highlights the potential role of SPARC and TIMP3 as key molecules in EMM, and analysis of EMM may contribute to understanding melanoma invasion between the epidermis and the dermis.

よって、主査、副査は一致して本論文を学位論文として価値があるものと認めた。