

IDENTIFIKASI *MIRNA* YANG BERPERAN DALAM PENGATURAN *CDH2* PADA PROSES *EPITHELIAL MESENCHYMAL TRANSITION* DI MELANOMA

INTISARI

Latar Belakang : Melanoma merupakan kanker kulit yang berasal dari melanosit, sel turunan kista neural, dan memiliki tingkat mortalitas tinggi akibat kemampuan metastasis yang agresif. Berbeda dengan kanker epitel, melanoma tidak mengalami EMT klasik, melainkan proses yang dikenal sebagai *phenotype switching*, yaitu perubahan dinamis antara fenotipe proliferasif dan fenotipe invasif. Perubahan ini ditandai dengan peningkatan ekspresi N-cadherin (*CDH2*) yang berkontribusi terhadap peningkatan migrasi, invasi, dan kemampuan metastasis sel tumor. Regulasi perubahan fenotipe ini diduga melibatkan mekanisme epigenetik, termasuk *miRNA*, yang berperan dalam mengatur ekspresi gen-gen kunci pada jalur pertumbuhan dan progresi tumor.

Tujuan : Penelitian ini bertujuan untuk menganalisis hubungan antara kelompok *miRNA* yang secara dominan mengatur ekspresi *CDH2* pada proses EMT di Melanoma.

Metode : Studi observasional analitik dengan desain potong lintang dan pendekatan retrospektif menggunakan data sekunder dari TCGA-SKCM (368 sampel tumor primer dan metastasis melanoma kulit). Sampel dikelompokkan berdasarkan ekspresi *CDH2* tinggi dan rendah. Analisis *miRNA* diekspresikan berbeda (FDR < 0,05), kemudian dipilih 25 *miRNA* teratas untuk dianalisis lebih lanjut. Interaksi *miRNA-mRNA* dilakukan menggunakan miRNet dan analisis jalur biologis menggunakan DAVID.

Hasil : Ditemukan perbedaan profil *miRNA* antara kelompok *CDH2* tinggi dan rendah pada melanoma primer dan metastasis. Pada primer, 10 *miRNA* meningkat pada *CDH2* tinggi. Pada metastasis, 22 *miRNA* meningkat dan 3 *miRNA* menurun pada *CDH2* tinggi. Gen target terutama terlibat dalam jalur MAPK, PI3K-Akt, regulasi siklus sel, dan p53 signaling.

Kesimpulan : Penelitian ini menunjukkan perbedaan regulasi *miRNA* pada melanoma dengan ekspresi *CDH2* tinggi antara fase primer dan metastasis. Pada fase primer, *miRNA* seperti hsa-miR-21-5p, hsa-miR-9-3p, dan hsa-miR-206 memodulasi jalur MAPK dan PI3K-Akt. Pada metastasis, peningkatan hsa-miR-125b-5p, hsa-miR-214-5p, dan hsa-miR-149-3p berkaitan dengan penekanan gen tumor suppressor, sedangkan penurunan hsa-miR-203a-3p dan hsa-miR-211-5p menyebabkan aktivasi siklus sel. Validasi eksperimental dan integrasi data klinis diperlukan untuk memperkuat temuan

Kata Kunci : Melanoma, EMT, *CDH2*, *miRNA*

IDENTIFICATION OF miRNAs INVOLVED IN THE REGULATION OF CDH2 IN THE EPITHELIAL–MESENCHYMAL TRANSITION PROCESS IN MELANOMA

ABSTRACT

Background: Melanoma is a malignant skin cancer derived from melanocytes, neural crest–origin cells, and is associated with high mortality due to its aggressive metastatic potential. Unlike epithelial cancers, melanoma does not undergo classical epithelial–mesenchymal transition (EMT) but instead exhibits a process known as phenotype switching, characterized by dynamic transitions between proliferative and invasive states. This transition is marked by increased N-cadherin (CDH2) expression, which contributes to enhanced migration, invasion, and metastatic capacity. Epigenetic mechanisms, including (miRNAs), are believed to regulate this phenotypic shift by modulating key genes involved in tumor growth and progression.

Objective: This study aimed to analyze the association between miRNA expression profiles and CDH2 expression levels in the context of EMT-related processes in melanoma.

Methods: An analytical observational study with a cross-sectional and retrospective design was conducted using secondary data from TCGA-SKCM (368 primary and metastatic cutaneous melanoma samples). Samples were stratified based on high and low CDH2 expression. Differentially expressed miRNAs were identified using an FDR cutoff < 0.05 , and the top 25 miRNAs were selected for further analysis. miRNA–mRNA interactions were analyzed using miRNet, and biological pathway enrichment was performed using DAVID.

Results: Distinct miRNA expression profiles were observed between CDH2-high and CDH2-low groups in both primary and metastatic melanoma. In primary tumors, 10 miRNAs were upregulated in the CDH2-high group. In metastatic tumors, 22 miRNAs were upregulated and 3 were downregulated in the CDH2-high group. Target genes were predominantly involved in the MAPK pathway, PI3K–Akt pathway, cell cycle regulation, and p53 signaling.

Conclusion: This study demonstrates differential miRNA regulation in CDH2-high melanoma between primary and metastatic stages. In primary melanoma, miRNAs such as hsa-miR-21-5p, hsa-miR-9-3p, and hsa-miR-206 modulate MAPK and PI3K–Akt signaling. In metastatic melanoma, upregulated miRNAs including hsa-miR-125b-5p, hsa-miR-214-5p, and hsa-miR-149-3p are associated with tumor suppressor gene repression, while downregulated miRNAs such as hsa-miR-203a-3p and hsa-miR-211-5p contribute to cell cycle activation. Experimental validation and integration with clinical data are warranted to strengthen these findings.

Keywords: Melanoma, EMT, CDH2, microRNA