MELANOMA AND MELANOCYTIC NAEVI

WHOLE EXOME SEQUENCING AND SINGLE-CELL RNA SEQUENCING OF B16 MELANOMA MODEL REVEAL MECHANISMS FOR DISTANT METASTASIS

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Introduction: Understanding the mechanism for distant metastasis is one of the fundamental issues in controlling metastatic melanoma. Pulmonary metastasis is the frequent complications in patients with melanoma and are associated with dismal prognosis.

Objective: The purpose of our study was to elucidate the mechanisms for distant metastasis of melanoma using whole exome sequencing (WES) and single-cell RNA sequencing (scRNAseq) of B16 melanoma model.

Materials and Methods: We performed WES and scRNAseq of murine melanoma cell line (B16F0) and its highly pulmonary metastatic variant (B16F10). The R package Seurat was used to identify the cluster, and differentially expressed genes between clusters, and cellular heterogeneity in genetic signatures. Gene set enrichment analysis were performed to find significantly enriched pathways in metastasis. To understand the expression kinetics of melanoma metastasis, pseudo-temporal ordering along the single-cell trajectory was constructed by using by the R package Monocle.

Results: WES revealed putative driver mutation, mutational signature, and copy number alteration associated with melanoma metastasis. Unbiased clustering of single-cell transcriptomes of total 4,711 cells found the major two subpopulations representing the identity of the cell lines. Differentially expressed genes and gene set enrichment analysis between clusters revealed gene expression signature related to metastasis. Pseudo-

temporal reconstruction along the single-cell trajectory revealed the expression kinetics and the potential candidate genes with putative role during acquisition of metastasis potential of melanoma. The rare subpopulation with increased metastatic potential in B16F0 cell line was identified.

Conclusions: We identified genetic alternation during the metastasis progression of melanoma using WES and scRNAseq. The result of our study will deepen our understanding of metastasis progression of melanoma and their clinical implications.