

## Original Article

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# RANK Is Expressed in Metastatic Melanoma and Highly Upregulated on Melanoma-Initiating Cells

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## Abstract

Melanoma accounts for ~79% of skin cancer-related deaths, and the receptor activator of NF- $\kappa$ B (RANK)–receptor activator of NF- $\kappa$ B ligand (RANKL) pathway has been shown to be involved in the migration and metastasis of epithelial tumor cells. In this study, we demonstrate that RANK was significantly increased in peripheral circulating melanoma cells, primary melanomas, and metastases from stage IV melanoma patients compared with tumor cells from stage I melanoma patients. However, upregulated RANK expression was not found in stage IV melanoma patients with bone metastases compared with stage IV melanoma patients without bone metastases, providing a possible explanation for the clinical observation that melanoma cells do not preferentially metastasize to bone tissue. Strikingly, RANK-expressing melanoma cells from peripheral blood, primary tumors, or metastases of stage IV patients coexpressed ATP-binding cassette (ABC) B5 and CD133, both markers characteristic of melanoma-initiating cells, suggesting a tumor stem cell–like phenotype. In support of this hypothesis, RANK-expressing melanoma cells showed a reduced Ki67 proliferation index compared with RANK<sup>−</sup> melanoma cells from the same patient and are able to induce tumor growth in immunodeficient mice. Together, our data demonstrate that RANK expression is increased in metastatic melanoma and highly upregulated on melanoma-initiating cells, suggesting that RANK might be involved in the development and maintenance of melanoma-initiating cells and possibly in metastatic spreading.

## Abbreviations:

ABC, ATP-binding cassette; MM, malignant melanoma; mRNA, messenger RNA; RANK, receptor activator of NF- $\kappa$ B; RANKL, receptor activator of NF- $\kappa$ B ligand