Activation of transforming growth factor- β and epithelial-mesenchymal transition enhance regulatory T cells-mediated metastasis

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Background: Even though substantial portion of patients with melanoma diagnosis are present with distant metastases, the underlying oncogenic process remains unclear.

Methods: We have hypothesized that regulatory T cells (Tregs) play a critical role in invasion and metastasis of melanoma cells. Thus, we evaluated whether the administration of exogenous Tregs into melanoma tumor-bearing mice promotes lung metastasis.

Results: Our results demonstrated that cell-to-cell contact between melanoma cells and Tregs increase the invasive and metastatic phenotype of melanoma. Further, interaction of cancer cell and Treg significantly elevated the expression level of transforming growth factor- β (TGF- β) and the subsequent induction of the epithelial-to-mesenchymal transition. B16-BL6 melanoma tumors co-cultured with Tregs showed a larger population of migrating cells compared to B16-BL6 tumors cultured without Tregs. Additionally, the injection of exogenous Tregs into B16-BL6 melanoma tumors led to the recruitment and infiltration of endogenous Tregs into tumor tissues, thus increasing the overall Treg percentage in the tumor infiltrating lymphocyte population.

Conclusions: Collectively, our findings suggest novel mechanisms in which exogenous Treg-dependent upregulation of TGF- β and mesenchymal markers is crucial for augmenting the migration capacity and invasiveness, thereby contributing to the metastasis of melanoma.

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