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# A Novel Strategy to Inhibit Small Cell Lung Cancer Progression and Metastasis by S100A9 Inhibitor of Tumor-Associated Macrophages and Myeloid Derived Suppressor Cells

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Small cell lung cancer (SCLC) treatment is a major clinical challenge at present as it is highly refractory to available drugs. The MDSCs/macrophages are known to help SCLC develop resistant to available therapies. S100A9 (Migration inhibitory factor-related protein 14 (MRP14) is an EF-hand calcium-binding protein that has been involved in cell migration, invasion, proliferation and tumor metastasis in various type of cancers. S100A9 has been shown that increases migration of macrophages *in vitro* and *in vivo.* The relationship between S100A9 and MDSC has not been studied in SCLC. In this study, we found that S100A9 protein is highly up-regulated in various type of pulmonary neuroendocrine carcinomas (NEC) tissues by tissue microarray. We also observed that SCLC patients with higher S100A9 expression have significantly increased the number of macrophage in the stroma. Additionally, furthermore pre-treatment of the cells with S100A9 inhibitor (Tasquinimod) suppressed in-*vitro* cell migration, invasion and colony formation. Furthermore, we analyzed the efficacy of S100A9 inhibitor in SCLC *in vitro* and in *vivo*. By using xenograft mouse model showed S100A9 inhibitor significantly reduces tumor growth and metastasis in SCLC. Here, we reported that S100A9 inhibitor suppressed MDSC populations and TAMs of the M2-polarized phenotype in SCLC. Moreover, we found myeloid cells sequestered from tumors of treated mice expressed higher levels of inducible nitric oxide synthase (iNos) and lower levels of arginase-1 were more immunosuppressive. Molecular analysis revealed that Tasquinimod decreases expression of IL6, IL10 and TGF-β1 in the cancer cells which helps inhibit macrophage activation to TAMs. Reduced proliferation and vascularization were observed in the tumors obtained from animals treated with S100A9 inhibitor. We also observed S100A9 inhibitor suppressed osteolytic bone formation in ex-vivo resorption assay. Overall, our studies, for the first time, we description here a unique immunotherapy Tasquinimod targets S100A9 signaling that decreases the immunosuppressive assets of myeloid cells and angiogenesis in mouse model of SCLC.