S100A9 Inhibitor Tasquinimod: A novel strategy to inhibit small cell lung cancer progression and metastasis

Abstract

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, however not much is known about its role in SCLC. In this study, we found that S100A9 protein is highly up-regulated in various types of pulmonary neuroendocrine carcinomas (NEC) patient tissues compared to normal using tissue microarrays. We also observed that SCLC patients with higher S100A9 expression have significantly increased numbers of macrophage in the stroma. We have also shown that pre-treatment of the cells with S100A9 inhibitor (Tasquinimod) suppressed in-*vitro* cell migration, invasion, and colony formation. In addition, we analyzed the efficacy of S100A9 inhibitor against SCLC using *in vivo* mouse models. S100A9 inhibitor significantly reduces tumor growth and metastasis in SCLC in xenograft mouse models. We further observed that S100A9 inhibitor suppressed myeloid-derived suppressor cells (MDSC) populations and TAMs of the M2-polarized phenotype in SCLC. Moreover, we found myeloid cells sequestered from tumors of treated mice expressed were MI type as they showed higher levels of inducible nitric oxide synthase (iNos), and lower levels of arginase-1. 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, show that Tasquinimod that targets S100A9 signaling could be used as a novel therapeutic strategy against SCLC.