Shuangshen granules attenuate lung metastasis by modulating bone marrow differentiation through mTOR signalling inhibition

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ABSTRACT

ETHNOPHARMACOLOGICAL RELEVANCE: Traditional Chinese medicine Shuangshen granules (SSG) have been used to treat lung cancer patients with Qi deficiency and blood stasis for decades. According to clinical experience, SSG indeed improve the quality of life and prolong the survival time of patients with lung cancer after surgery. Each of the components herbs was proved to be effective in anti-cancer therapy. Both the American ginseng and notoginseng belong to genus Panax of the family Araliaceae. Preclinical and clinical studies demonstrated that ginsenosides of them have anti- or preventive activities to various tumors, including cancers of gastric, breast, liver, lung, ovarian, colon, melanoma and leukemia. PDS, such as ginsenoside Rb1, and PTS, such as ginsenoside Rg1 are the main anticancer compositions. Cordyceps sinensis had also been found effective in inhibiting tumor growth and metastasis, especially on tumor associated immune cells, such as macorphages. However, limited information is available regarding potential mechanisms of SSG. Myeloid-derived suppressor cell (MDSC)-mediated immunosuppression, which is closely associated with poor clinical outcomes in cancer patients, may be the target of SSG, which regulate immune function.

AIM OF THE STUDY: The present study aimed to explore whether SSG attenuate the differentiation of bone marrow cells (BMCs) into MDSCs by blocking the mTOR signalling, leading to the suppression of lung metastasis.

MATERIALS AND METHODS: First, we observed the differentiation of BMCs into MDSCs in vitro and in vivo. BMCs were cultured alone or co-cultured with Lewis lung carcinoma (LLC) cell supernatant in vitro. The effects of different concentrations of SSG, or LLC cell supernatant as a control, on BMC differentiation were detected by flow cytometry and western blotting. Male C57BL/6J mice were subcutaneously implanted with LLC cells, and SSG were administered by gavage twice daily before and after implantation for 7 or 14 days, respectively. The tumour weight, proportion of MDSCs, presence of $CD11b^{+}Ly6C^{+}Ly6G^{-}$ and $CD11b^{+}Ly6C^{+}Ly6G^{+}$ cells in the bone marrow, blood, and lungs, as well as the expression levels of differentiation-related proteins in the bone marrow and lungs were evaluated.

RESULTS: SSG attenuated the differentiation of BMCs into MDSCs, and reduced the fraction of $CD11b^{+}Ly6C^{+}Ly6G^{+}$ cells by inhibiting the mTOR/S6K1/Myc signalling pathway. In vivo, SSG attenuated differentiation-associated protein markers and reduced the

fractions of MDSCs and $CD11b^{+}Ly6C^{+}Ly6G^{+}$ cells in the bone marrow, blood, and lungs. In addition, SSG administration reduced the tumour weight and inhibited lung metastasis.

CONCLUSIONS: SSG may reduce lung metastasis by attenuating BMC differentiation into $CD11b^{+}Ly6C^{+}Ly6G^{+}$ cells by inhibiting mTOR signalling in vitro and in vivo.

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