

Abstract

Osteosarcoma (OS) is the most common malignant tumor of bone in children and adolescents. Although lung metastasis is a major obstacle to improving the prognosis of OS patients, the underlying mechanism of lung metastasis of OS is poorly understood. Tumor-associated macrophages (TAMs) with M2-like characteristics are reportedly associated with lung metastasis and poor prognosis in OS patients. In this study, we investigated the metastasis-associated tumor microenvironment (TME) in orthotopic OS tumor models with non-metastatic and metastatic OS cells. Non-metastatic and metastatic tumor cells derived from mouse OS (Dunn and LM8) and human OS (HOS and 143B) were used to analyze the TME associated with lung metastasis in orthotopic OS tumor models. OS cell-derived secretion factors were identified by cytokine array and enzyme-linked immunosorbent assay (ELISA). Orthotopic tumor models with metastatic LM8 and 143B cells were analyzed to evaluate the therapeutic potential of a neutralizing antibody in the development of primary and metastatic tumors. Metastatic OS cells developed metastatic tumors with infiltration of M2-like TAMs in the lungs. Cytokine array and ELISA demonstrated that metastatic mouse and human OS cells commonly secreted CCL2, which was partially encapsulated in extracellular vesicles. *In vivo* experiments demonstrated that while primary tumor growth was unaffected, administration of CCL2-neutralizing antibody led to a significant suppression of lung metastasis and infiltration of M2-like TAMs in the lung tissue. Our results suggest that CCL2 plays a crucial role in promoting the lung metastasis of OS cells via accumulation of M2-like TAMs.