

Together with brain, liver, and bones, the lungs are frequent targets of tumor metastasis. Although secreted phosphoprotein 1 (SPP1) has been associated with the dissemination of various bodily tumors, its role in lung metastasis remains unknown.

To investigate the mechanism by which SPP1 induces pulmonary metastasis, we employed mouse models of spontaneous (s.c. injection of a million tumor cells) and induced (i.v. injection of half a million tumor cells) lung-targeted metastasis of three cancer cell lines (MC38 colon and LLC lung adenocarcinomas; B16F10 melanoma) in syngeneic C57BL/6 mice competent (Spp1^{+/+}) and deficient (Spp1^{-/-}) in Spp1 alleles. Tumor-derived SPP1 expression was modulated using stable anti-Spp1 shRNA and forced overexpression of intracellular (Spp1is2) and secreted (Spp1is4) Spp1 isoforms.

We determined that lung epithelial cells expressed predominantly SPP1is4, which played no role in pulmonary metastasis, since Spp1^{+/+} and Spp1^{-/-} mice equally developed lung metastases. On the contrary, tumor cells expressing both isoforms, exerted distinct effects: SPP1is2 promoted blood-borne tumor cell survival via suppressing TRP53 expression, whereas SPP1is4 accelerated lung metastasis by enhancing tumor-derived CCL2 secretion. Consistently with the above findings, Ccr2^{-/-} mice were protected from lung metastasis. In addition, SPP1-competent and incompetent tumor cells could equally colonize the lungs of both Ccr2^{+/+} and Ccr2^{-/-} mice, indicating the role of CCL2 to SPP1 mediated effects.

In conclusion, our data indicate that tumor-derived SPP1 promotes pneumotropic metastasis and presents a possible therapeutic target aimed at preventing lung tumor dissemination