**Genetic depletion of the dual specificity protein phosphatase DUSP3 promotes LLC Lung tumour metastasis**

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**Abstract:**

DUSP3, also called *Vaccinia*-H1 Related (VHR) is a small dual specificity phosphatase dephosphorylating both tyrosine and serine/threonine phosphorylated residues. DUSP3 plays an important role in cell cycle regulation and is up-regulated in several human cancers. The physiological role of this phosphatase is, however, poorly understood. We have recently generated a DUSP3 knockout mouse by homologous recombination. The obtained mice have no spontaneous phenotype or pathology. However, DUSP3 deficiency prevented neo-vascularization of subcutaneously transplanted Matrigel plugs and Lung Lewis Carcinoma (LLC) tumours, suggesting an involvement of DUSP3 in tumour angiogenesis.

Considering the importance of angiogenesis in metastatic formation, our study aimed to investigate the role of DUSP3 in metastatic dissemination. To do so, we used the LLC experimental metastasis model that shortcuts the intravasation/extravasation processes by injecting intravenously the LLC and the B16 (metastatic melanoma cell line) cells. Surprisingly, LLC, but not B16, lung metastasis developed twice faster in DUSP3-KO than WT mice. The enhanced LLC metastatic growth in DUSP3-/- mice was transferable to WT mice via DUSP3-/- bone marrow adoptive transfer, suggesting an involvement of the hematopoietic compartment in the observed phenotype. This was confirmed by a higher infiltration of neutrophils and macrophages in the lungs of DUSP3-KO compared to WT mice after LLC injection. This infiltration was correlated with higher expression of the chemokine receptor CCR2 in LLC-bearing DUSP3-KO lungs macrophages. Interestingly, LLC, but not B16 cells, were found to secrete high level of CCL2/MCP1, the CCR ligand chemokine. In line with this observation, we found that DUSP3-/- bone marrow derived-macrophages have a higher migration potential in response to LLC, but not B16, -conditionned medium.

Altogether, our results suggest that DUSP3 plays an important role in metastatic dissemination/growth by a mechanism involving the control of CCR2-CCL2 chemoattraction axis in macrophages.

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