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THYMIC STROMAL LYMPHOPOIETIN PROMOTES INTERPLAY BETWEEN TUMOUR CELLS AND MYELOID CELLS TO REGULATE BREAST TUMOUR PROGRESSION

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The cytokine thymic stromal lymphopoietin (TSLP) has been implicated in controlling various human cancer developments through regulating type-2 inflammation via T cells. However, it is still largely unknown the role of TSLP in other cell types within tumours since TSLP receptor (TSLPR) is widely expressed on many cell types, including hematopoietic cells and epithelial cells under inflammatory conditions. We found that both human and mouse breast tumour cells express functional TSLPR and TSLP signalling is important to maintain their survival through inducing Bcl-2 *in vitro*. By using murine metastatic breast tumour models we found the most important TSLP source for maintaining breast tumour cell survival *in vivo* is not derived from tumour cells but rather from myeloid cells. Furthermore, tumour cell-derived IL-1a is important to increase TSLP expression in myeloid cells. Blocking TSLP systemically after tumour development has reduced primary tumour size in a spontaneous mouse breast cancer model. Constitutive expression of TSLP in lungs of mice that mimicked human asthma enhanced tumour cell survival in lungs that further led to more lung metastases and TSLP blockage only in lungs reduced tumour metastases. Besides tumour cells, we discovered that TSLP signalling in Ly6Chi monocytes is also crucial for promoting tumour progression by regulating monocyte suppressor functions and their ability to differentiate into tumour associated macrophages. Our work is the first to show a tumour-myeloid cell axis, mediated through IL-1a and TSLP, to promote tumour cell survival. We also provided another novel mechanism of the requirement of TSLP signalling in regulating the pro-tumour functions in Ly6Chi monocytes. These studies define a novel TSLP-mediated crosstalk between tumour-infiltrating myeloid cells and tumour cells and provide an effective therapeutic intervention in metastatic breast cancer.

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