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Tumour microenvironment

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BACKGROUND: Cytokines are important players in inflammation, a process highly associated with tumour initiation, tumour growth, angiogenesis and metastasis. Oncostatin M (OSM) is a cytokine belonging to the interleukin 6 (IL6) family and it has been shown to play a role in inflammation, development and hematopoiesis and is increasingly being recognized as an important contributor to cancer progression. In breast cancer it has been associated with the induction of EMT process and metastasis. We investigate the role of OSM signaling in breast cancer progression and its importance in mediating the communication with the tumour microenvironment.

MATERIALS & METHODS: To address this issue we used a wide array of tools including clinical samples, *in vivo* models and *in vitro* cell cultures of breast cancer cell lines together with co-cultures of stromal cells such as cancer-associated fibroblasts and macrophages. The role of OSM in oncogenesis and metastasis was studied by generating a mouse line that expresses the PyMT oncogene after the MMTV promoter and lacks the OSM receptor (OSMR). To address the importance of OSM pathway in the tumour microenvironment context, we injected murine cells in the mammary gland of OSMR KO and control mice.

RESULTS AND DISCUSSION: Analysis of human clinical samples revealed that OSM and OSMR are upregulated in breast cancer stroma compared to normal breast stroma. The receptor OSMR is mainly expressed by breast cancer cells and fibroblasts while the ligand OSM seems to be mainly produced by cancer associated macrophages and neutrophils. Our in vitro 3D cultures show that OSM promotes cancer associated fibroblasts (CAFS) proliferation and activation by inducing expression of α-SMA and fibroblast contractility. Depletion of OSMR delays tumour onset, decreases tumour growth and generation of lung metastasis in MMTV-PYMT mice model. Orthotopic injections of murine cells in OSMR deficient mice shows a decrease in tumour growth compared to control mice, suggesting that OSMR signaling is important in the tumour microenvironment.

CONCLUSIONS: Our results support that OSM pathway has an important role in the initiation and progression of breast cancer and that it is important in preparing the tumour microenvironment to facilitate tumourigenesis. OSM and its receptor could be blocked by antibody based inhibition, strategy that has had a major impact on breast cancer, which makes OSM a promising candidate for therapeutic targeting.

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