Bidirectional crosstalk between uveal melanoma cells and hepatic myofibroblasts promotes inflammation-induced chemokines expression

Narjes BABCHIA[1]; Solange LANDREVILLE[2]; Bruno CLEMENT[1]; Cédric COULOUARN*[1]; Frédéric MOURIAUX*[1, 2].

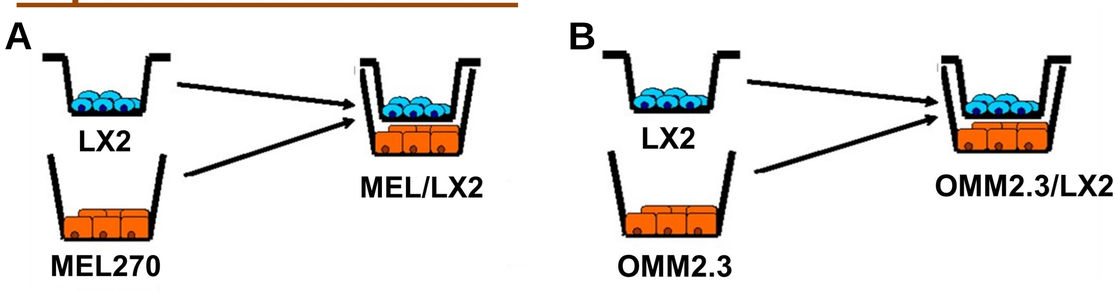
1. UMR 1241 NUMECAN (Nutrition, Métabolisme et Cancer), Université Rennes 1; Site Pontchaillou-Villejean; Rennes, France.

2. Centre de recherche du CHU de Québec-Université Laval ; Québec, Canada,

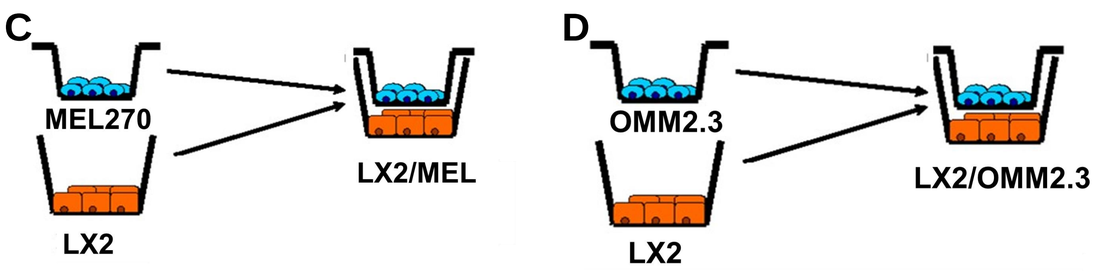
Background

Uveal melanoma (UM) is the most common primary ocular neoplasm in adults. The metastatic disease develops in up to 50% of patients, and usually involves the liver. Treatment rarely extend the survival, because metastases are highly resistant to most chemotherapeutic agents. Tumor cells may modulate the functions of surrounding cells to facilitate their own growth, survival, invasion, and metastasis. This study was conducted to investigate the role of the hepatic microenvironment on UM cells (UMCs) aggressiveness.

Experimental conditions



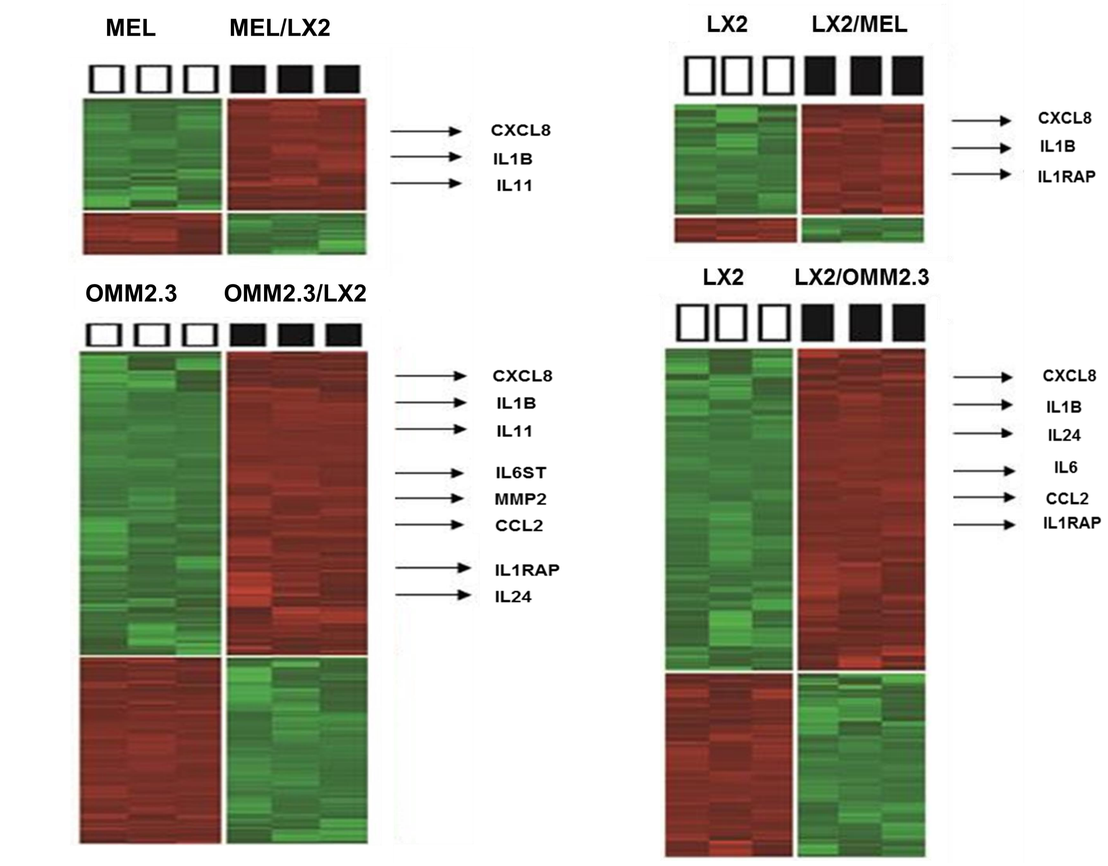
MEL270 (non-metastatic UMCs) and OMM2.3 (metastatic UMCs) were seeded in 6-well plates (lower chamber). Cell culture Inserts were placed in the wells and LX2 (hepatic stellate cells, HSCs) were seeded onto them (upper chamber) (A and B).



LX2 cells were seeded in 6-well plates (lower chamber). Cell culture Inserts were placed in the wells and UMCs were seeded onto them (upper chamber) (C and D).

Results

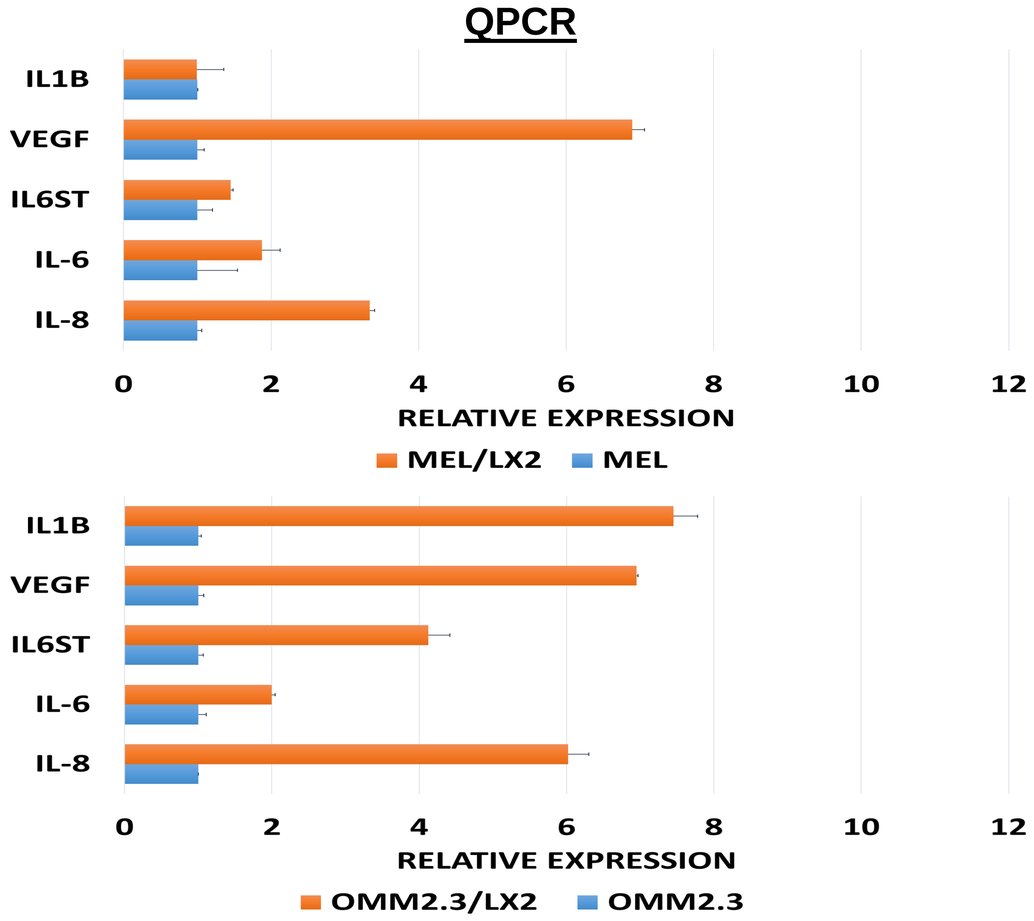
A/ Bidirectional crosstalk between UMCs and activated HSCs

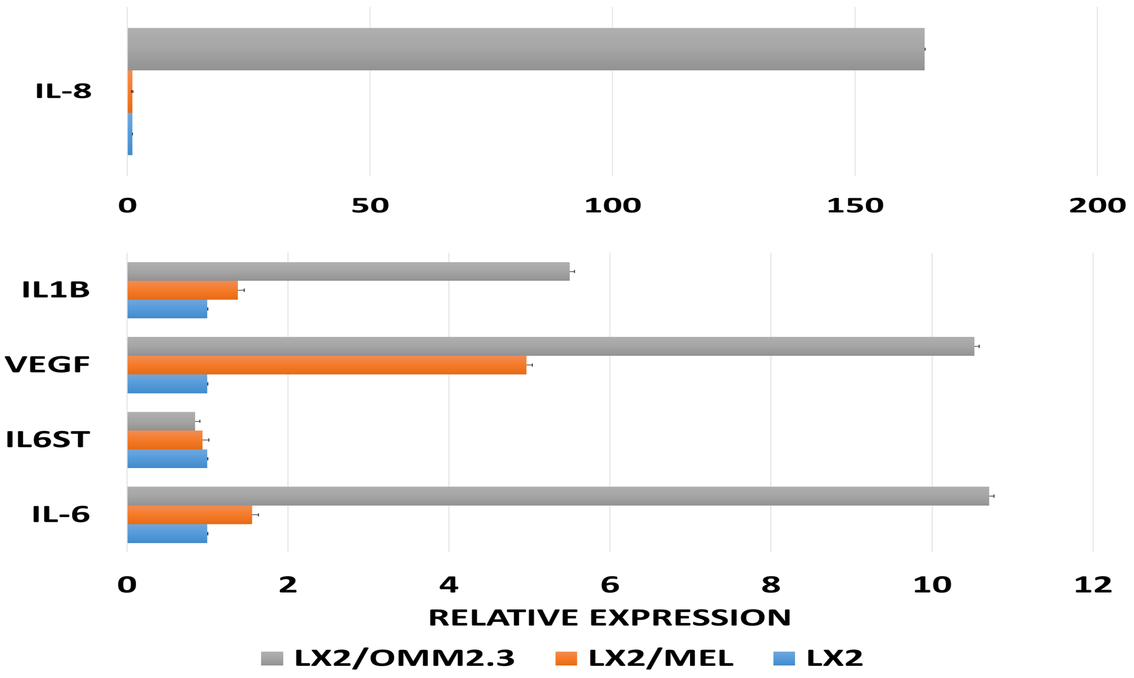


Green, overexpressed genes; Red, underexpressed genes.

B/ UMC-HSC crosstalk promotes inflammation-induced expression of chemokine transcripts

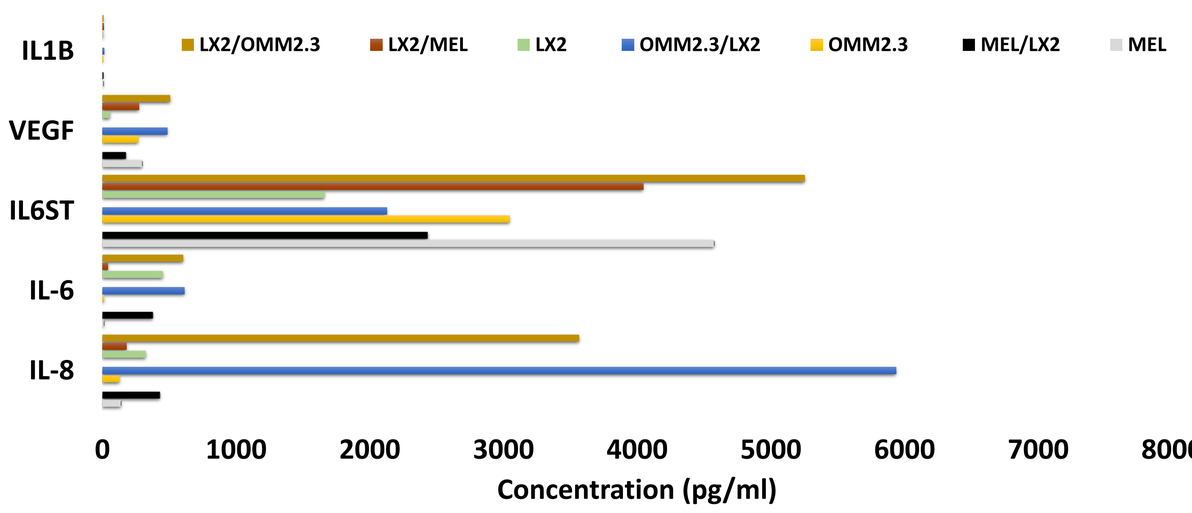
QPCR



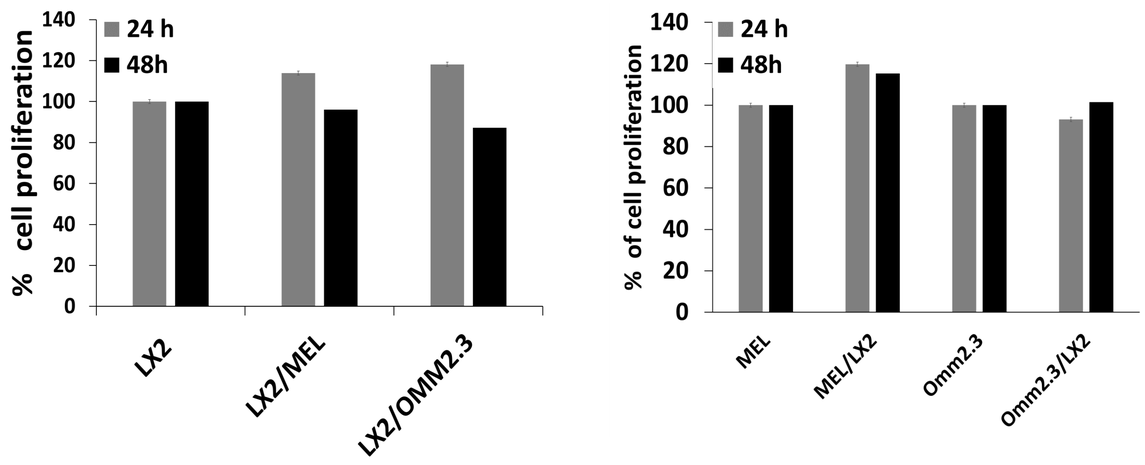


C/ UMC-HSC crosstalk promotes the secretion of chemokines

ELISA

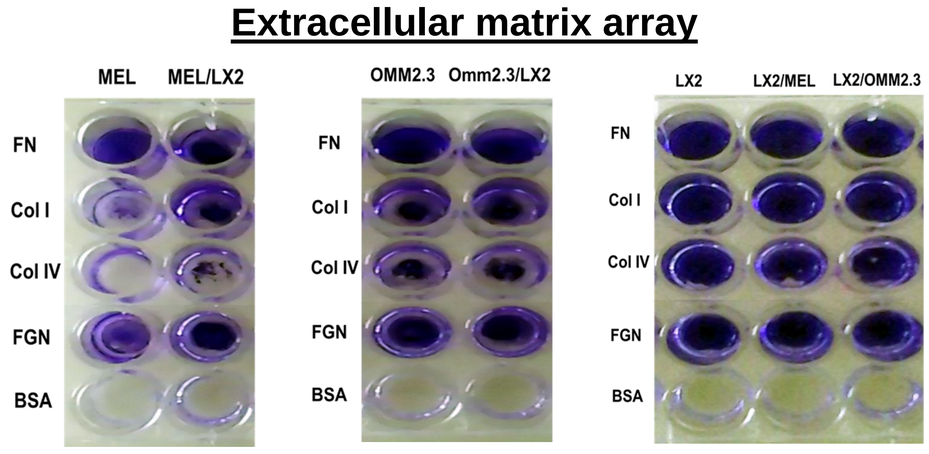


D/ UMC-HSC crosstalk has no effect on cell proliferation



E/ UMC-HSC crosstalk induces the expression of cell adhesion receptors

Extracellular matrix array



Conclusion

The hepatic microenvironment increased the expression of numerous genes.

The number of genes overexpressed in metastatic co-cultures is three times higher than in non-metastatic co-cultures. Overexpressed genes in co-culture were linked to inflammation and included several interleukins. The hepatic microenvironment had no effect on cell proliferation. UMC-HSC crosstalk induced expression of transmembrane receptors such as integrins, and increased particularly the adhesion to fibronectin. Our results provide evidence for an important role of inflammation in the progression of metastatic UM. The inflammatory characteristics of the tumor microenvironment might offer new therapeutic opportunities.

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Corresponding author: Narjes BABCHIA **Email: narjesbabchia@gmail.com**