ONCOSTATIN M RECEPTOR IS A NOVEL THERAPEUTIC TARGET IN TRIPLE NEGATIVE BREAST CANCER

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OSM:OSMR signalling

- gp130
- OSMR
- MAPK pathway
- PI3K pathway

- SOCS
- JAK
- PTP
- Ub
- Proteasome
- STAT
- PIAS
- Transcription
- Nucleus

- Y
- P
- P
- P

11º SIMPOSIO INTERNACIONAL GEICAM
Pro-malignant effects of OSMR signalling

Adapted from Caffarel & Coleman, J Pathol 2014
Aims of the project

- Is OSMR a biomarker in breast cancer?
- Does OSMR signalling promote tumour progression?
- Can we target tumour progression by blocking OSMR signalling?
OSMR is a prognostic factor in ER neg breast cancer

**Overall survival OSMR**

- p.value = 0.006

**Overall survival ER neg OSMR**

- p.value = 0.011

METABRIC dataset (n=1981)

Collaboration with Carlos Caldas, CRUK, Cambridge, UK
OSM is over-expressed in ER negative and basal tumours

- **METABRIC dataset (n=1462)**
  - ANOVA: p < 0.0001
  - Basal, HER2, luminal, luminal B, normal

- **TCGA dataset (n=547)**
  - ANOVA: p = 0.011
  - Basal, HER2, luminal, normal

Collaboration with Arkaitz Carracedo, Biogune
OSMR pathway is over expressed in basal breast cancer cell lines
OSMR is expressed by tumour cells

Normal breast

Infiltrating breast tumours
OSM is expressed by the tumour stroma

**Normal breast**
- Mammary epithelial cells

**Infiltrating breast tumours**
- Tumour cells
- Tumour stroma
OSM expression increases after chemotherapy
The tumour microenvironment has a key role in all the steps of tumour progression.
Do stromal cells contribute to OSMR signalling in cancer cells?

Do CAFs secrete OSM in co-culture with breast cancer cells?  
Do they have an effect in the invasion, migration, pro-angiogenic phenotype of breast cancer cells?

Collaboration with Paloma Bragado, IDIBAPS, Barcelona
Do stromal cells (fibroblasts) contribute to OSMR signalling in cancer cells?

**OSMR**

ANOVA = 0.0019

**OSM**

ANOVA = 0.0020
OSM activates STAT3 and induces the expression of pro-malignant factors in basal breast cancer cells

MDA-MB-231 cells

OSM treatment ng/ml
Does OSMR signalling promote tumour progression?

MDA-MB-231:
+ hOSM (OSM over-expressing cells)
+ hControl (Control cells)
Activation of OSMR induces tumour formation

Tumour onset

Body weight

Control tumour and mammary glands

OSM tumours

p=0.0020
OSMR pathway is activated in OSM-expressing tumours

- OSMR mRNA (fold change): $p = 0.0002$
- STAT3 mRNA (fold change): $p = 0.01$
- IL6 mRNA (fold change): $p = 0.10$
- VEGFA mRNA (fold change): $p = 0.16$
Immunocompetent mouse models

MMTV-PyMT  MMTV-Neu

Lung metastases

Generation of a breast cancer genetic model with OSMR knock out

Study impact of OSMR deletion on:
- Tumour onset
- Tumour growth
- Lung metastasis
- Response to drugs
Conclusions

Estrogen negative breast cancer

Decreased overall survival

Stromal cells

OSM

OSMR

OSM
Conclusions

Biomarker

OSMR

Therapy

Mechanism
Future work

- Study the contribution of the tumour microenvironment to OSMR activation
- Immunocompetent mouse models
- Pre-clinical testing of OSM:OSMR neutralizing antibodies
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Representative tumour

Representative reactive lymph node
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