CCR3: Containing prostate cancer

A drug-repositionning approach integrating obesity factor

November 2018

Context

Prostate cancer (Pca): local and metastasis dissemination at stake

- 85% of patients with localized Pca have an overall survival > 10 years
- But risk of extraprostatic disease remains high (30-60%) and bone metastasis is the most common form (70-90% of cases)
- Prognosis of metastasized Pca is low (survival < 2 years)

Preventing/slowing down the spread of Pca outside the capsule and especially to the bone is a major goal of treatment

Responsibility of adipocytes: a plausible hypothesis

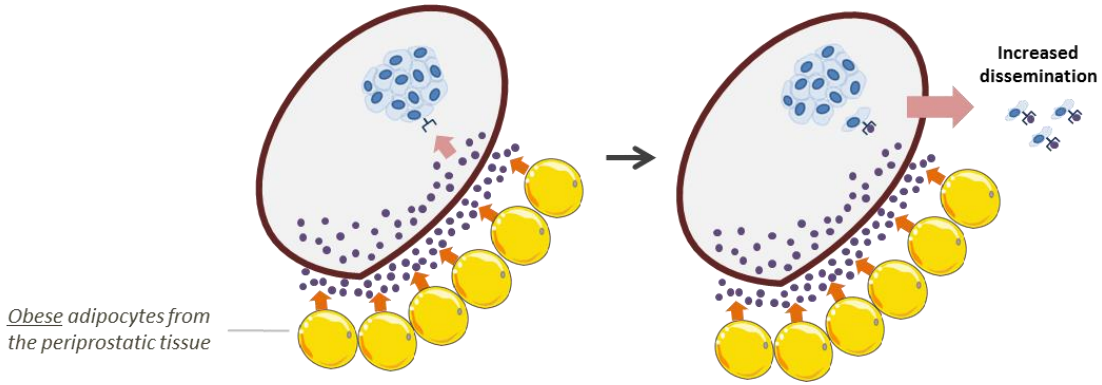
- Adipose tissue is present both at periprostatic tissue and bone
- Its main constituents, adipocytes, display different secretion profiles in lean and obese conditions
- Obesity is a renown risk factor for developing aggressive Pca*

** http://www.wcrf.org/sites/default/files/Prostate-Cancer-2014-Report.pdf*

Value proposition

Offer: a new target…

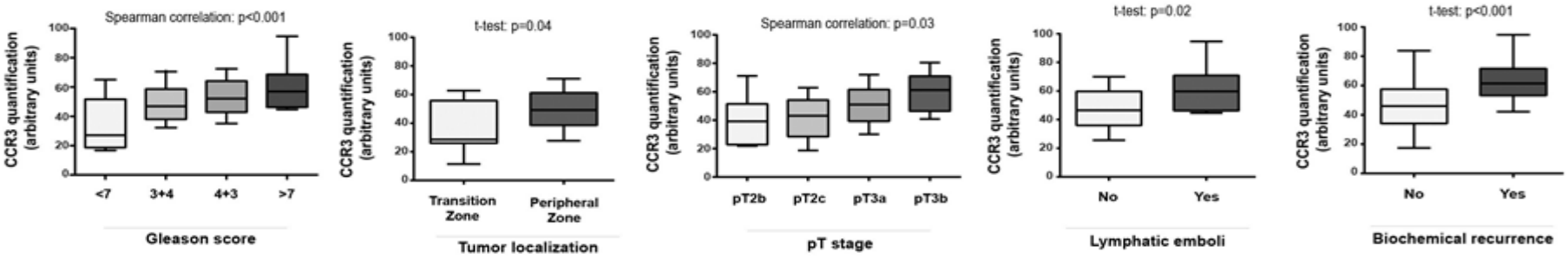
- CCL7, a chemokine secreted by periprostatic adipocytes, interacts with CCR3 receptor of localized tumors, favoring both local dissemination and metastasis of prostate cancer
- Increased effect under obesity condition in periprostatic tissue and medullary adipocytes
- CCR3 inhibition leads to complete tumor control



… with known inhibitors under clinical development

- CCR3 is a target under study in inflammatory diseases (allergic rhinitis, allergic asthma) and infection blocking (HIV)
- Numerous antagonists are available, some have passed phase II trials

Link between CCR3 expression and Pca severity

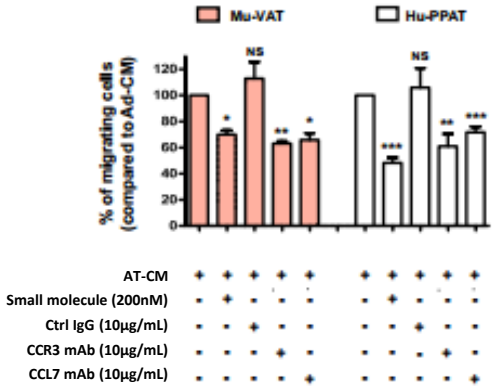


Boxplots of CCR3 values comparing tumors Gleason score, tumor localization, tumor stage, patients with and without lymphatic emboli or biochemical recurrence. CCR3 expression was evaluated by immunohistochemistry on a TMA containing 101 tumors in duplicate

Experimental proof of CCR3 inhibition effect

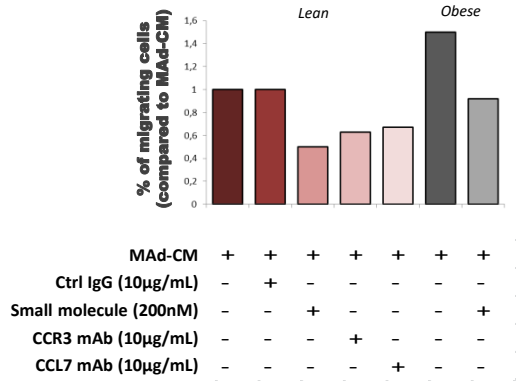
Ex vivo

Local dissemination



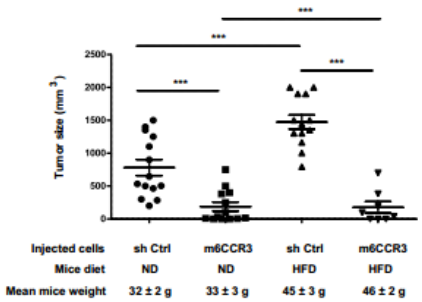
Small molecule and mAb inhibit prostate cancer cell migration toward murine visceral adipose tissue (mu-VAT) and human periprostatic adipose tissue (hu-PPAT) conditioned medium (AT-CM)

Metastasis



Small molecule and mAb inhibit prostate cancer cell migration toward human medullary adipocytes conditioned medium (MAd-CM). Under obese conditions, the increase migration capacity is reversed

In vivo



CCR3 silencing abrogates the differences in size and dorsal invasion observed with the parental cell line in lean and obese mice

Techno ID

IP status

- Patent application pending FR (06/2014), US and EP
- Results published in Nature Communication (2016), DOI: 10.1038/ncomms10230

Research team

- Laboratory « Pharmacology and Structural Biology Institute » (IPBS, UMR 5089, CNRS /UPS)

- Team « Microenvironment, Cancer and Adipocytes » led by Catherine Müller

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