Periprostatic adipose tissue promotes prostate cancer invasion:
role of oxidative stress & regulation by obesity

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Background
The prostate gland is surrounded by periprostatic adipose tissue (PPAT), whose paracrine role in prostate cancer (PCa) progression is more and more suspected. Infiltration of PPAT by tumor cells is a widely acknowledged adverse factor in PCa and an important determinant of PCa recurrence after treatment. Obesity is also associated with an increased risk of aggressive PCa with increased local and distant dissemination. We previously showed that adipocytes favor the homing of PCa cells to PPAT and that this event is strongly upregulated by obesity¹.

Experimental design & Results
We show here that once tumor cells have invaded PPAT (reproduced by an in vitro model of co-culture), a bidirectional crosstalk is established between cancer cells and adipocytes, which leads to cancer cells’ increased invasive abilities. Tumor cells induce lipolysis in adipocytes and the liberated free fatty acid (FFAs) are up-taken and stored in tumor cells. Incubation with exogenous lipid stimulates the invasive ability of tumor cells, suggesting a key role of the lipid transfer in the increase of cancer aggressiveness. However, in opposition to what we previously observed in breast cancer², the increased invasive capacities induced by co-culture were not modified by inhibition of fatty acid β-oxidation, suggesting that an alternate pathway explains the role of these FFAs in prostate cancer aggressiveness.

One of the key factors in PCa progression is oxidative stress and we showed that accumulated FFAs (from co-culture or exogenous lipids treatment) stimulate the expression of pro-oxidants enzymes, especially one isoform of NADPH-oxidase (NOX5). This contributes to increase intra-cellular reactive oxygen species (ROS) that in turns activate a HIF-1/MMP14 pathway leading to increased invasive potential of tumor cells. In obesity, the tumor-surrounding adipocytes are more prone to activate the depicted signaling pathway and to induce tumor invasion. Finally, the expression of NOX5 and MMP14 is upregulated at the invasive front of human tumors and this event is amplified in obese patients, underlining the clinical relevance of our results.

Conclusion
Our work emphasizes the key role of adjacent PPAT in prostate cancer dissemination and proposes new molecular targets in the treatment of obese patients exhibiting aggressive diseases.

References
¹ Laurent V et al, Nature Communications 7:10230, 2016
² Wang YY et al, JCI Insight 2(4):e87489, 2017