

## The adipose tissue that surrounds the prostate gland exhibits traits of hypoxic state that could contribute to its role in prostate cancer progression

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**Introduction & Objectives:** The prostate gland is surrounded by periprostatic adipose tissue (PPAT), whose role in prostate cancer (PCa) progression has been recently revealed by several teams including ours (Laurent et al, Nature Comm, 2016; Mol Cancer Res, 2019). However, this specific adipose depot is poorly described, a lack of characterization that hinders the definition of its role in tumor progression. Our goal was to characterize the tissue and cellular organization of PPAT as well as its functional capacities in comparison to paired perivesical adipose tissue (PVAT), an adipose depot at proximity to the bladder.

**Materials & Methods:** Paired PPAT and PVAT were obtained from patients with PCa who underwent a radical prostatectomy. Using pre-surgical MRI, we measured the volume of PPAT and PVAT with dedicated software in a cohort of 54 patients. Immunohistochemistry, 3D microscopy, flow cytometry, proteomic and nanosight analysis were performed on the collected samples.

**Results:** While the volume of PVAT correlated with BMI ( $R = 0.7957$ ,  $p < 0.00001$ ), PPAT volume was totally dissociated from BMI ( $R = 0.00441$ ,  $p = 0.7470$ ) demonstrating that this fat depot abundance is not increased in obesity. At macroscopic level, the lobules were smaller by 2.9 fold in PPAT than PVAT. PPAT was composed of slightly smaller adipocytes than in PVAT and contained a higher number of stromal cells including early adipose progenitors (CD271-/MSCA1-). Surprisingly, the vascular organization was clearly different between these two fat depots. PPAT exhibit shorter vessels that vascularize group of adipocytes (between 10 and 20 cells) whereas vessels surrounded each adipocyte in PVAT. These results strongly suggest that PPAT exhibit a hypoxic state. Accordingly, we observed in PPAT several hypoxic traits including an increase in: i) the recruitment of pro-inflammatory monocytes-derived macrophages (HLA-DR+/CD206-), ii) extra-cellular matrix deposition as well as iii) extracellular vesicles secretion. Finally, we demonstrated that PPAT-conditioned medium (CM) had more proliferative effect than PVAT-CM on aggressive prostate PCa cells, PC3.

**Conclusions:** Taken together, our results demonstrate a hypoxic environment in PPAT compared to PVAT that could limit its expansion in obesity but also results in features known to favor tumor progression.