Bi-Directional Extracellular Vesicle-Mediated Communication Between Peri-Prostatic Adipose Tissue and Tumour Cells Drives Prostate Cancer Aggressivity

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Prostate Cancer (PC) affects 1-in-8 men in the UK, and obesity 1-in-3. Obesity will shortly overtake smoking as the largest modifiable cancer risk-factor, and is termed an epidemic by the WHO. High-fat diet is linked with increased risk of PC death, and volume of peri-prostatic adipose tissue (PPAT) is associated with increased PC lethality and reduced therapy-response. Furthermore, weight gain and central obesity are major side-effects of androgen-deprivation therapy. Adipose is the largest human endocrine gland and shows altered secretory profiles in obese-*versus*-lean patients. This includes cytokines and extracellular vesicles (EVs), which represent potential pro-tumourigenic communication tools through delivery of proteins, lipids, metabolites and RNAs: PPAT EVs promote melanoma, lung, ovarian and breast cancer progression. **We aim to delineate the unexplored molecular mechanisms underpinning obesity-driven PC using primary PPAT explants and novel immortalised pre-adipocytes.**

Our first-in-field research showed that PPAT EVs from obese patients significantly increase proliferation, migration, EMT, invasion and adhesion of PC cells, but reduce angiogenesis compared to lean patient EVs. RNA-seq revealed dysregulation of Rac/Rho, MAPK, Wnt, EGFR signalling and cytoskeleton dynamics in PC cells treated with PPAT EVs, with differential impacts in the lean-versus-obese context. Top PPAT EV-dysregulated genes are increased in PC *versus* normal tissue, associate with reduced survival and significantly alter PC cell proliferation, migration and invasion. SNP analysis and microRNA profiling reveal the importance of non-RNA EV cargo in driving these effects. Anti-tumourigenic cytokines are decreased in conditioned medium of obese-*versus*-lean PC PPAT.

Furthermore, PC cells reprogramme their surrounding PPAT to promote disease progression: PPAT from genetically-engineered mice (GEMMs) modelling PC natural history, showed dramatic changes in tissue histology, immune response (increased MDSC markers, reduced antigen presentation), lipid metabolism, insulin response and ECM composition in PPAT of aggressive *versus* indolent tumours. Since genetic alterations in GEMMs are prostate-confined, such transcriptomic changes must be mediated by paracrine signalling from PC cells. These data may suggest that PPAT constitutes an immunosuppressive 'barrier' that opposes anti-tumour immune infiltration in advanced PC.

Integrative analysis of these data will elucidate novel, actionable drivers of aggressive PC progression for personalised medicine.

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