Communication between prostate tumours and peri-prostatic adipose drives obesity-associated prostate cancer aggressivity

Grunberg N[1], Qian J[1], Tam J[1], Lorentzen M[1], Akdogan S[2], Lack N[2,3], Campbell M[4], Abate-Shen C[5], Khoubehi B[6], Hellawell G[6], Shah T[6], Winkler M[6], Leach D[1], Ahmed H[1,6], Bevan CL[1] and Fletcher CE[1]

[1] Imperial College London, UK
[2] Koç University, Turkey
[3] Vancouver Prostate Center, Vancouver, Canada
[4] Cedars-Sinai Medical Center
[5] Columbia University, New York, USA
[6] Imperial College NHS Trust, London, UK.

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 from a cohort of PC patients.

We showed that PPAT EVs from obese patients significantly increase proliferation, migration, EMT and invasion of PC cells, but reduce angiogenesis compared to lean patient EVs- consistent with chronic hypoxia observed in obesity. Moreover, anti-tumourigenic cytokines are decreased in conditioned-medium of obese-*versus*-lean PPAT. There was no significant decrease in conditioned-media from non-prostatic fat control.

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 lean-*versus*-obese samples. Top PPAT EV-dysregulated genes are increased in PC-*versus*-normal tissue, associate with reduced survival and significantly alter PC cell proliferation and migration. Our recent data indicates PPAT-driven PC aggressivity could be the result of cell adhesion changes impacting cell migration via alterations in TGFβ/Rho-GTPase pathways. Silencing of one such PPAT-upregulated gene, TBX1, repressed PC cell migration, invasion, proliferation and EMT. SNP analysis of RNA-seq data from PPAT EV-treated PC cells reveals that phenotypic effects of EVs are not attributable to transferred long RNAs, but both lean and obese PPAT EVs contain different microRNA cargo compared to NPAT. We are investigating metabolic, lipid and proteomic cargo of these EVs.

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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