Abstract: 54S

Obesity and Cancer - Metabolic Reprogramming and Prostate Cancer Progression

Renea A. Taylor[1,2], Gio Fidelito[3], Matthew J. Watt[3]

[1] *Department of Physiology, Biomedicine Discovery Institute, Cancer Program, Melbourne Urological Research Alliance (MURAL), Monash University, Melbourne, Victoria, Australia, 3800.*

[2] *Sir Peter MacCallum Department of Oncology, The University of Melbourne, Victoria 3010, Australia.*

[3] *Department of Anatomy and Physiology, The University of Melbourne, Melbourne, Victoria, 3010, Australia.*

Understanding the links between obesity and prostate cancer will have major implications for the health policy for men with prostate cancer and the development of new therapeutic or preventative strategies. Cancer metabolism is a hallmark of cancer pathogenesis and is required to support the malignant properties of cancer cells. This dysregulation is exacerbated in obesity, where patients develop excess adipose tissue with dysfunctional lipid metabolism and endocrine function that promotes cancer cell survival. Studies in cells and mice have highlighted the importance of oxidative metabolism and lipogenesis in prostate cancer, however, the metabolic landscape of human prostate cancer remains unclear. To address this knowledge gap, we performed radiometric (^{14}C) and stable (^{13}C) isotope tracing assays in precision-cut slices of patient-derived xenografts (PDXs) representing different stages of disease. This approach allowed us to assess the utilisation of multiple substrates in parallel, in clinically relevant human tumours. These data indicated variable upregulation of glucose, glutamine, and fatty acid oxidation in prostate cancer PDXs compared to non-malignant prostate PDXs, while lactate oxidation was not different. *De novo* lipogenesis (DNL) and storage of free fatty acids into phospholipids and triacylglycerols was also increased in prostate cancer PDXs. Mechanistically, glucose utilisation was mediated by acetyl-CoA production rather than carboxylation of pyruvate, while glutamine entered the TCA cycle through transaminase reactions before being utilized via oxidative or reductive pathways. One of the important findings was the marked heterogeneity in rates of substrate utilisation across tumour samples, which was previously unappreciated from cell line studies. This heterogeneity leads to inherent difficulties in designing generalised therapies and indicate that personalised approaches may be required. Despite this, our preclinical studies using pharmacological agents showed that blocking fatty acid uptake or oxidation was sufficient to reduce cell viability in a range PDX-derived organoids, whereas blockade of DNL, or glucose or glutamine oxidation induced variable and limited therapeutic efficacy. These findings demonstrate that fatty acid uptake and oxidation are targetable metabolic vulnerabilities in human prostate cancer.