Prostate Specific Membrane Antigen (PSMA) related Neuronal Metabolites in Treatment Resistant Prostate Cancer

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Background: Most men treated with prostate cancer (PC) treated with androgen deprivation therapy (ADT) will relapse, known as castration resistant PC (CRPC) which remains poorly understood. CRPC is clinically associated with glucocorticoid mediated cardiovascular risk factors (obesity and type 2 diabetes). A role for the glucocorticoid receptor (GR) is now emerging in CRPC. N-acetyl aspartate (NAA) is the downstream neuronal metabolite of prostate specific membrane antigen (PSMA). PSMA converts NAAG, a highly prevalent neurotransmitter, to NAA and Glutamate and may be important in radioresistance. We hypothesise that PSMA activity can be determined by NAA/NAAG measurement in urine. These neuronal metabolites may promote survival as a local acetate and glutamate source for sphingolipid dependent survival mechanisms driven by GR activation.

Methods: A combined pre-clinical and clinical approach is being undertaken to investigate NAA/NAAG biology. Urinary NAA/NAAG pre and post radiotherapy may be clinically useful to explain differences in radiosensitivity related to PSMA activity. Surgical explant models of CRPC including bone metastasis will visualise NAA and NAAG within the tissue microenvironment using Mass Spec Imaging (MALDI / DESI). The GR axis will be manipulated using the GR antagonist mifepristone or relacorilant and agonist dexamethasone. The PSMA inhibitor (2-PMPA) and sphingolipid inhibitor (GW4869) will also be assessed. High resolution 7T MRI Spectroscopy (MRS) imaging of NAA/NAAG in ex vivo clinical specimens is also being developed.

Results: NAA and NAAG supplementation at higher doses appear to inhibit growth of CRPC cell line 22Rv1. I will identify the major source of NAA in CRPC using NAT8L and PSMA CRISPR KO and assess downstream metabolite changes. Custom isotope lipidomics will identify whether NAA (N-acetyl-13C2) is incorporated into sphingolipids. KO tumours (PSMA or NAT8L) will be expected to show sensitivity to GR blockade due to impaired NAA synthesis.

Conclusions: An important role for alternative nuclear receptors (GR) and neuronal biology is emerging in CRPC. Urinary NAA/NAAG as a proxy of PSMA activity during radiotherapy may allow for treatment intensification. Direct GR blockade will always suffer from adverse off target clinical side effects. Targeting tissue specific effects of GR hypothesised to be PSMA related neuronal metabolites NAA/NAAG may provide unique therapeutic opportunities currently lacking in CRPC.

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