Anti-androgens regulate amino acid-mTORC1 signalling and extracellular vesicle secretion to modulate prostate cancer progression

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Metastatic prostate cancer (mPCa) is currently incurable, and despite recent improvements in next-generation androgen deprivation therapy (ADT) and chemotherapy most patients develop treatment resistance within a small number of years. A better understanding of the mechanisms underlying treatment resistance is necessary to develop novel therapies. Extracellular vesicles (EVs) are nanosized, membrane-bound carriers of proteins, lipids and nucleic acids, which mediate intercellular communication and have been increasingly implicated in numerous processes involved in PCa progression. The ways in which anti-cancer treatments such as ADT affect EVs released from PCa cells, and whether these EVs influence treatment resistance, remains poorly understood.

We have characterised the effects of the non-steroidal anti-androgen bicalutamide on EV secretion from PCa cells. We find that bicalutamide promotes secretion of EVs carrying the androgen receptor (AR) via a mechanism involving inhibition of the mTORC1 microenvironmental sensor. Our data suggests that anti-androgen treatment inhibits mTORC1 activity by downregulating expression of SLC36A4 (PAT4), a glutamine-sensitive amino acid transporter. Depletion of the PAT4 substrate, glutamine, promotes secretion of AR-containing EVs. Furthermore, we explore the functional effects of these two EV sub-populations with respect to PCa progression and drug resistance. These findings led us to hypothesise that ADT may select for more aggressive PCa tumours that express high levels of PAT4. In support of this theory we further report that mRNA expression and copy number changes in PAT4 are associated with disease progression in PCa patients.

Overall, we propose that anti-androgen therapies promote PCa progression via mechanisms involving altered EV signalling and modulation of the PAT4-mTORC1 regulatory axis. This work highlights novel future therapeutic strategies and defines EV protein signatures that could be used to monitor treatment responsiveness.