Dissecting mechanisms of therapy resistance in lethal prostate cancer

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Androgen deprivation therapy (ADT) through bilateral orchiectomy or gonadotropin releasing hormone agonists alone or in combination with antiandrogen is generally the initial treatment for metastatic prostate cancer. Despite initial response rates as high as 90%, nearly all men eventually develop progressive disease, referred as castration resistant prostate cancer (CRPC). Several agents, such as enzalutamide, abiraterone acetate, radium223, docetaxel, and cabazitaxel have demonstrated improvement in overall survival in this clinical situation. However, to this date, no treatments for CRPC are curative. Several mechanisms account for prostate cancer therapy resistance, including mutations in the AR itself, restoration of signaling downstream of the pharmacological blocking and activation of alternative oncogenic pathways. In addition, lineage plasticity and transdifferentiation towards a cellular state that no longer depends on the therapeutic target is an increasingly recognized mechanism of resistance to molecularly targeted cancer therapy. Our group exploits preclinical models to unravel the molecular mechanisms associated to the acquisition of therapy resistance to identify emerging vulnerabilities and new therapeutic opportunities.