SLC-mediated metabolic reprogramming: A new paradigm for targeting enzalutamide resistance in prostate cancer

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Background

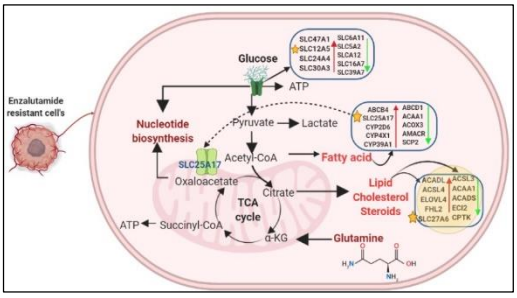
Androgen deprivation therapy (ADT) is standard-of-care for advanced-stage prostate cancer, and enzalutamide (Xtandi®), a second generation antiandrogen, is frequently prescribed for use in clinical setting. Response to this medication is usually temporary, and prolong treatment results in the emergence of drug resistance. Therefore, an understanding of molecular mechanism and its association with enzalutamide resistance will facilitate circumventing this problem.

Methods

We employed next generation sequencing (NGS) and compared the transcriptomic profile of paired enzalutamide-sensitive and resistant in two cell lines of prostate cancer; Lymph Node Carcinoma of the prostate (LNCaP) and C4-2 bone metastatic (C4-2B) for identification of genes involved in drug resistance along with *in silico* analysis. Pathway analysis was performed by IPA/iPathway and subset of differentially expressed genes in both cell lines were validated at transcript and protein level by qRT-PCR and western blot respectively.

Results

NGS data identified 9409 and 7757 genes differentially expressed in LNCaP and C4-2B cells respectively compared to their parental counterparts. Pathway analysis revealed metabolic signaling pathway was overrepresented and membrane transporters including solute carrier proteins, ATP-binding cassette transporters and other metabolizing enzymes as the most prominent genes dysregulated during metabolic reprogramming in resistant cell lines. RNA-Seq data of resistant cells demonstrate predominance of solute carrier genes, in particular, *SLC12A5*, *SLC25A17* and *SLC27A6*, during metabolic reprogramming and in the development of drug resistance as showed in figure. Upregulation of these genes were associated with an increase in stemness; higher uptake of lactic/citric acid and lower glucose intake in resistant cells.



Conclusion

Our data suggest predominance of solute carrier genes (SLCs) during metabolic reprogramming of prostate cancer cells in an androgen-deprived environment. SLCs are important in cellular uptake of nutrients and drug absorption, thus could play a significant role in the emergence of drug-resistant phenotype, designating SLC genes as potentially attractive therapeutic targets.

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