

# Involvement of solute carrier proteins (SLCs) in prostate cancer recurrence

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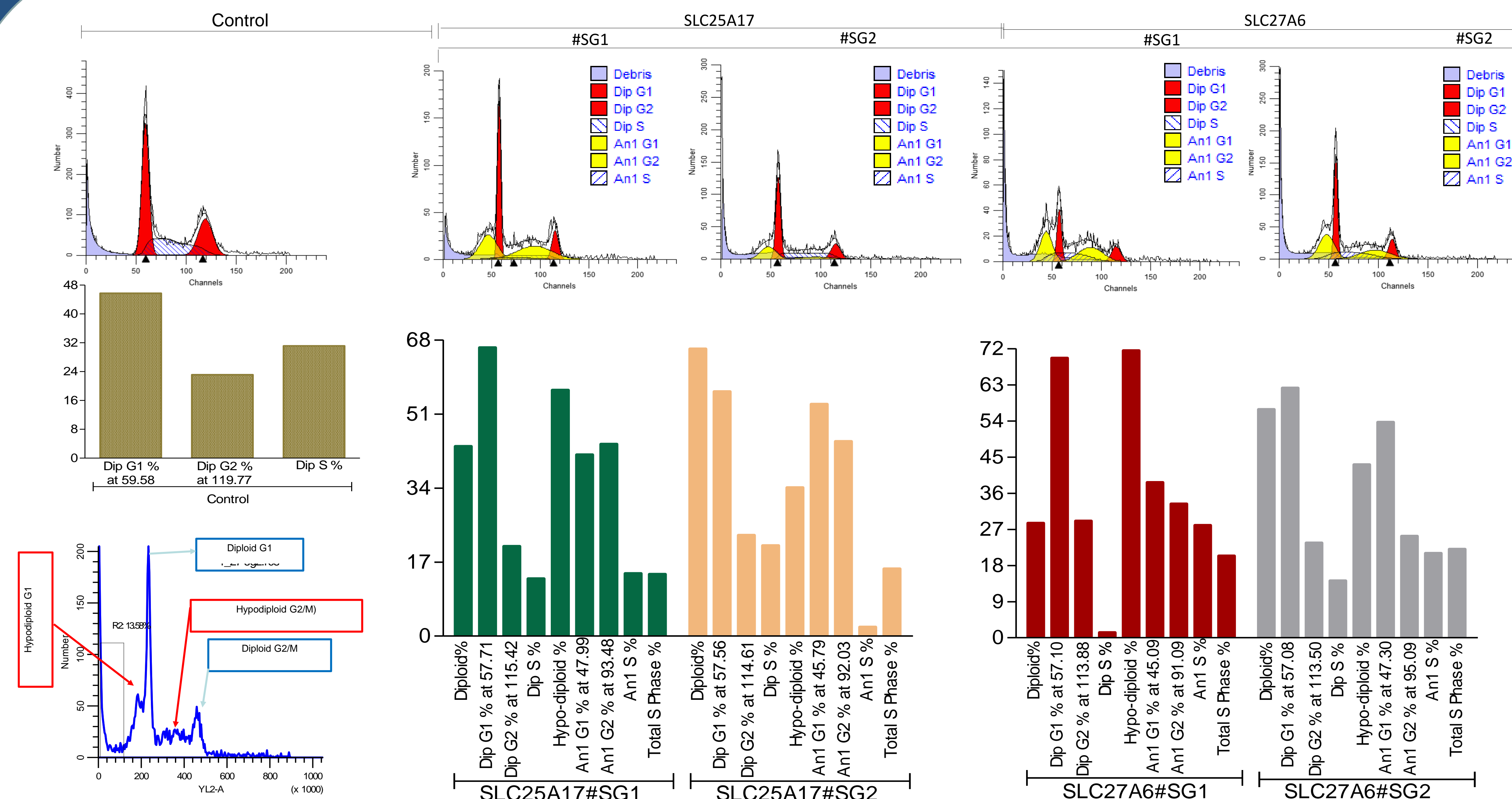
## Abstract

Prostate cancer is the second-leading cause of cancer-related mortality among men in the United States. Androgen deprivation therapy (ADT) therapy (XTANDI® (enzalutamide)) is commonly used treatment for castration-resistant prostate cancer (CRPC) patients. Recently, transcriptome analysis of CRPC cells revealed the aberrant expression of SLCs, involved in CRPC disease progression, however, the molecular understanding was unknown. Based on the above, our current research investigation was to understand the critical role of SLCs in CRPC. To achieve the set objective, we conduct the experiments in CRPC cells and generate C42B-enzalutamide resistant cells (C42B-ENZU), and knockdown cell lines of SLCs (SLC25A17 and SLC27A6) and performed subsequent experiments such as cell cycle, cell proliferation, migration, ELISA, and western blot. The cell cycle assay showed that absence of SLCs, induces cell cycle arrest at G1/S phase. Moreover, the cell-cycle marker genes including Cyclin D1, CDK6, CDK4, and CDK2 proteins levels were highly reduced in SLC25A17 knockdown cells, in comparison to SLC27A6. Knockdown of SLC25A17 and SLC27A6 suppressed cell proliferation and migration in C42B-ENZU cells. In context of apoptosis, absence of SLC25A17 induced more apoptosis (increased RIPK3, BAX, and decreased BCL-XL) in C42B-ENZU cells compared to SLC27A6. Presumed that SLCs modulate the fatty acid biosynthesis pathway, thus we evaluated the end product of TCA cycle. Absence of both the SLCs showed lower protein expression of fatty acid synthase, Acetyl-CoA carboxylase and ACSL5 in C42B-ENZU cells. Indeed, metabolites such as lactic acid, triglyceride and citric acid in the absence of both SLCs were found reduced in C42B-ENZU cells, the result of ELISA further supports that SLCs are involved in metabolic reprogramming which leads to castrate resistant in prostate cancer patients. In terms of clinical implication of our research finding, targeting the downstream of SLCs for e.g. ACSL5 may serve as therapeutic target in management of castrate resistant.

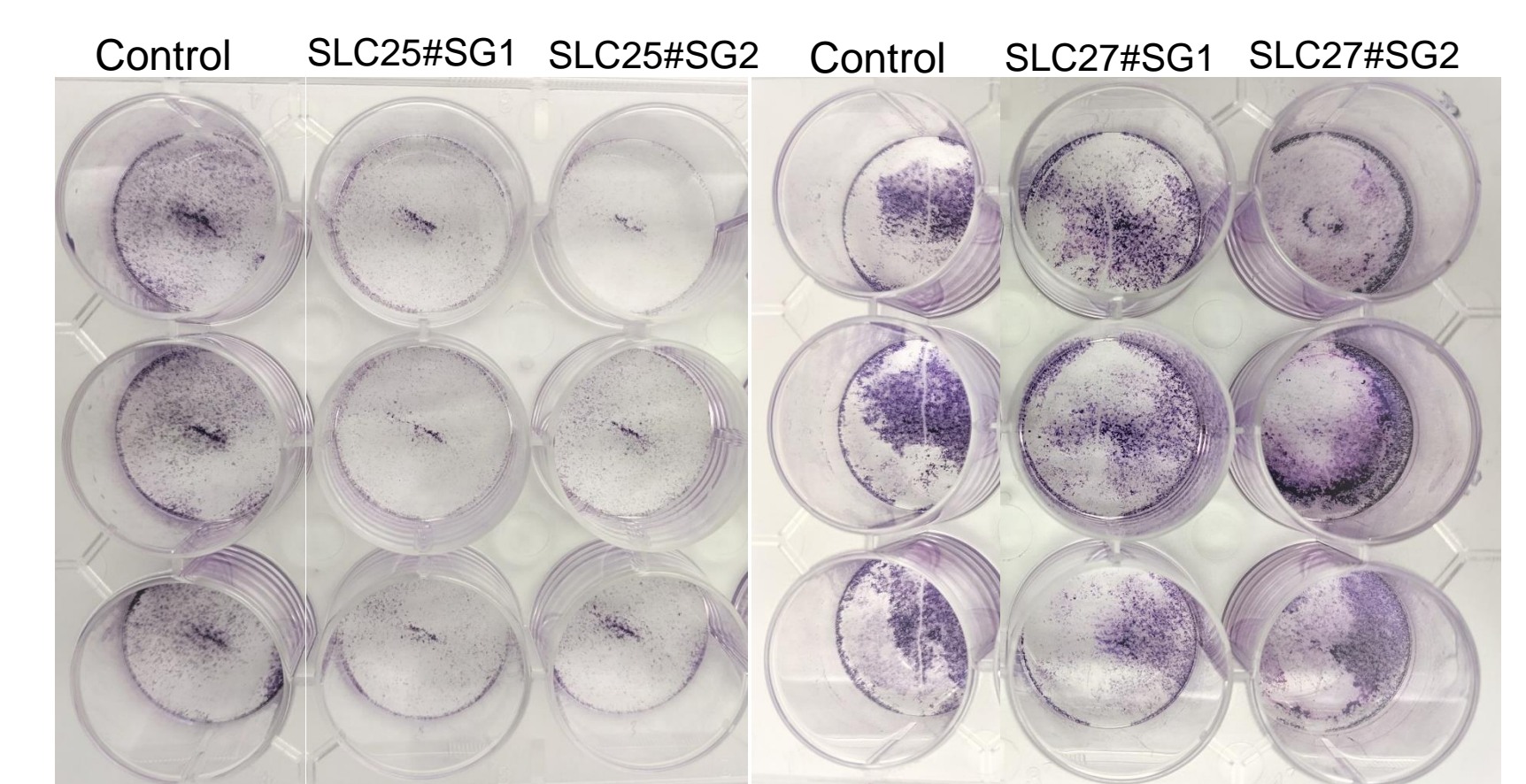
## Methodology

Androgen insensitive C42B cells were grown in the presence of 5uM enzalutamide to develop C42B-enzalutamide resistant cell line, and maintained in the same environment for 60 days. These cells were used for knockdown of SLC25A17 and SLC27A6. Different assays such as cell proliferation, crystal violet assay, cell migration, and cell cycle analysis were performed in SLCs-knockdown in C42B-enzalutamide resistant cells. The protein levels expression of different metabolic associated genes such as fatty acid synthase (FASN), Acetyl-CoA carboxylase (ACC) and Acyl-CoA synthetase Long Chain Family Member 5 (ACSL5); apoptosis markers such as RIPK3, BAX, and BCL-XL; cell cycle markers such as Cyclin D1, CDK6, CDK4, and CDK2 were analyzed by using western blot technique in SLCs-knockdown in C42B-enzalutamide resistant cells. Further, the levels of the metabolites such as lactic acid, triglyceride and citric acid were also analyzed by using ELISA techniques in SLCs-knockdown in C42B-enzalutamide resistant cells.

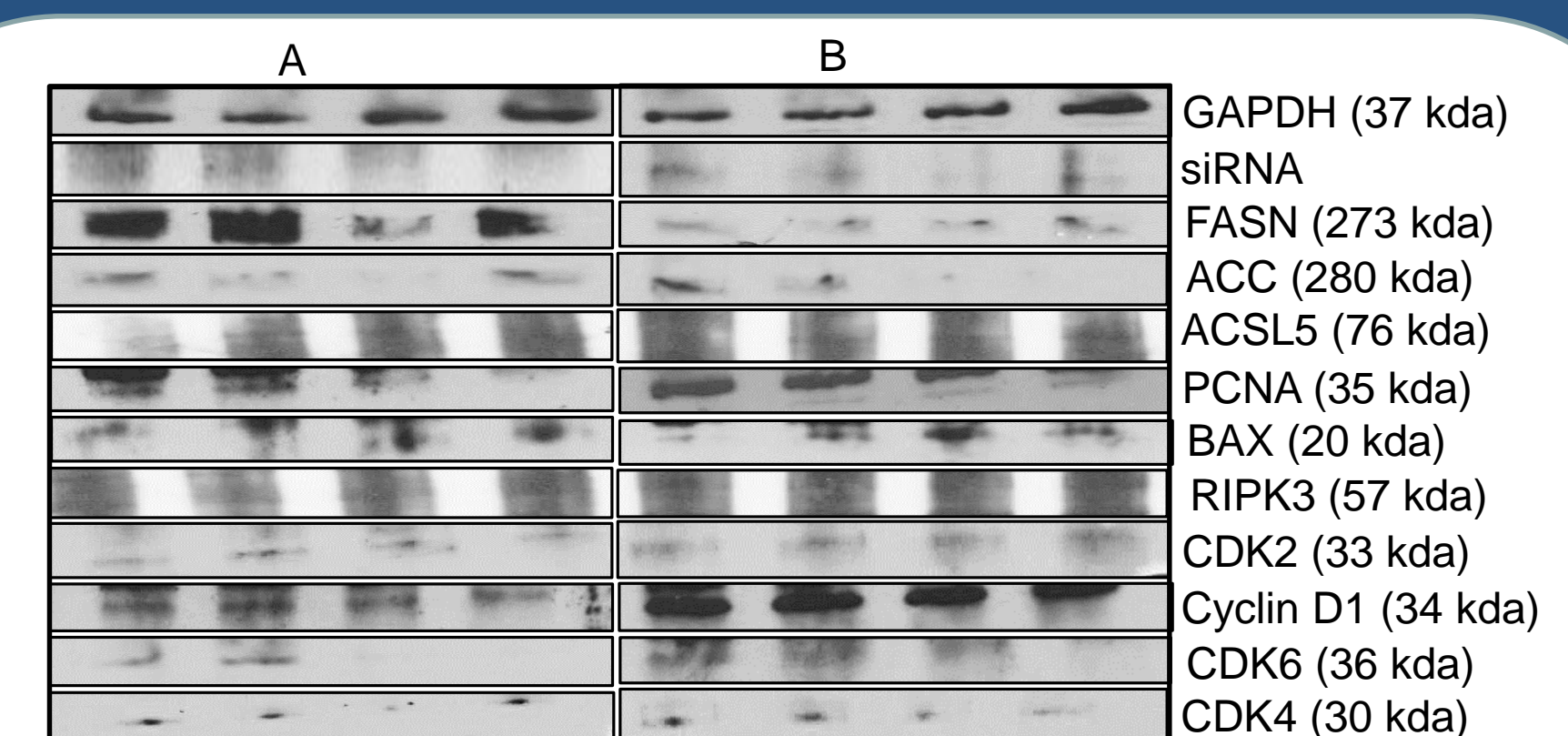
## Results



**Figure 1:**The effect of SLC25A17 and SLC27A6-silencing on cell cycle.



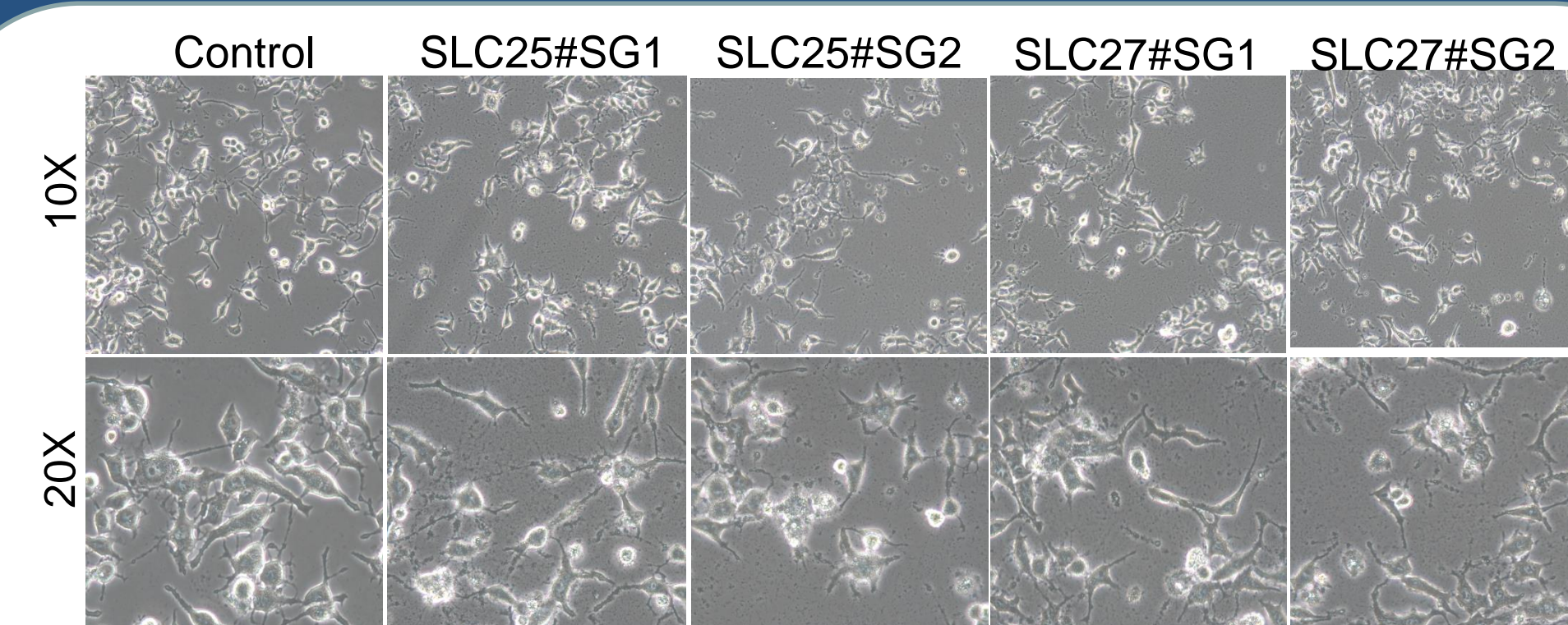
**Figure 2:**The effect of SLC25A17 and SLC27A6-silencing on cell proliferation assessed by using crystal violet staining.



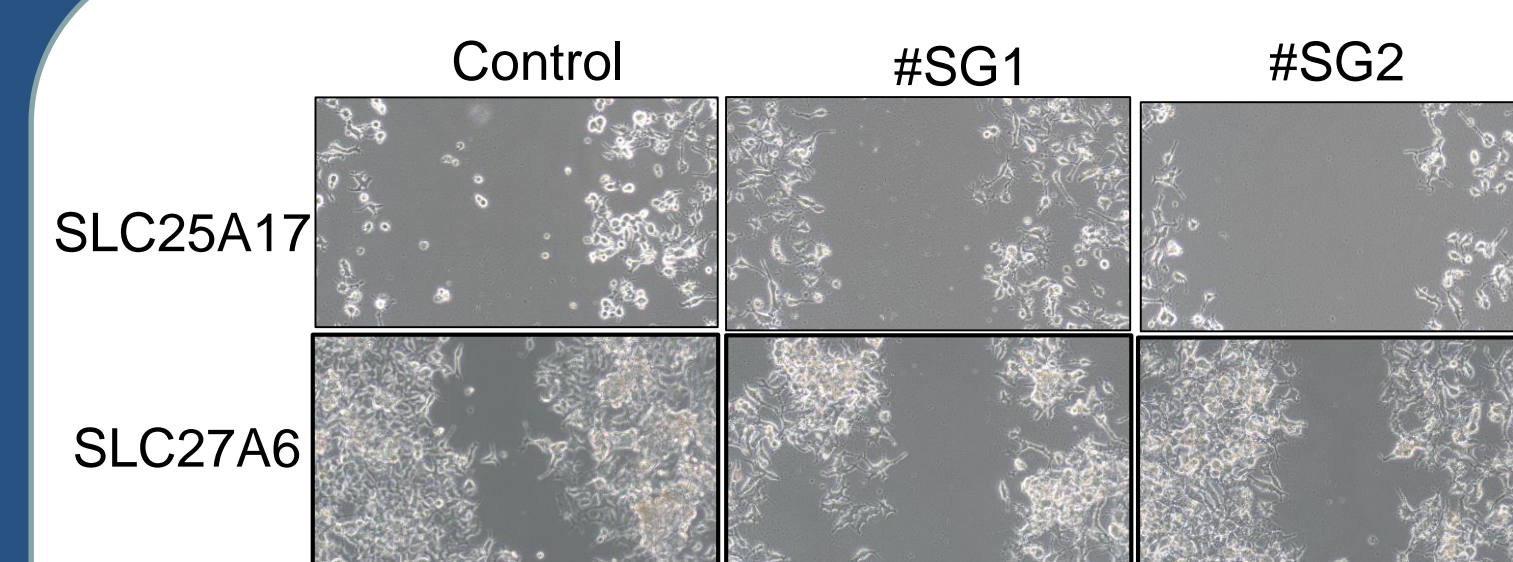
**Figure 3:** Western blot analysis of metabolic pathway genes, apoptosis, cell cycle and proliferation markers in SLC25A17 and SLC27A6-silenced C42B-enzalutamide resistant cells.

## Conclusion

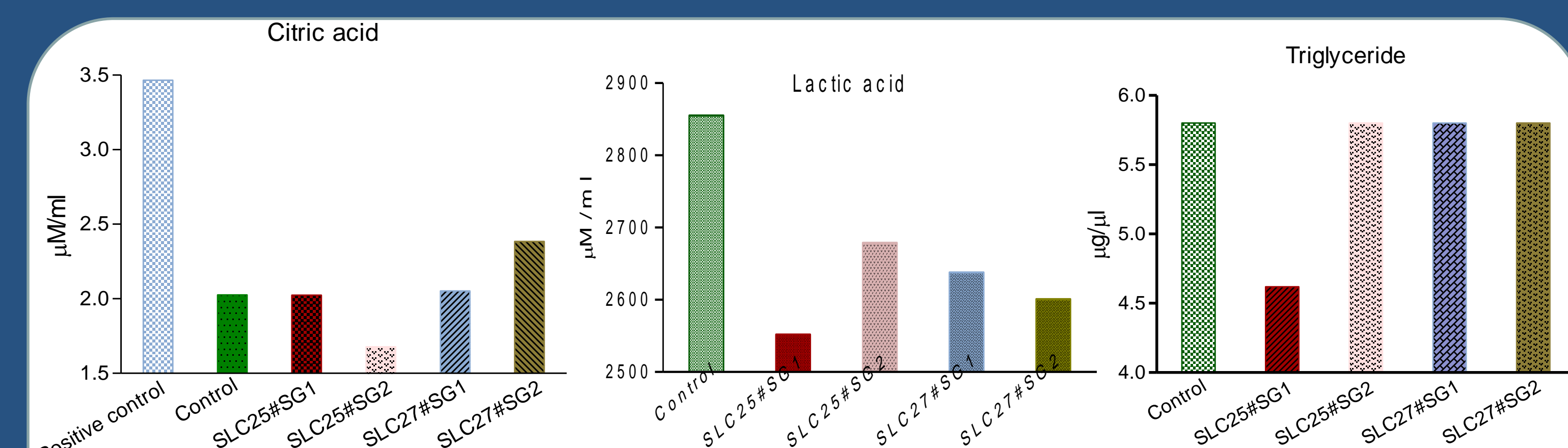
The present study suggests that solute carriers proteins SLC25A17 and SLC27A6 play an important role in enzalutamide resistance development via metabolic reprogramming. The loss of function of SLC25A17 and SLC27A6 also results in cell death. Thus, in terms of clinical implication of our research finding, SLC25A17 and SLC27A6 may serve as a therapeutic target for enzalutamide resistant prostate cancer management.



**Figure 4:**The effect of SLC25A17 and SLC27A6-silencing on cell proliferation.



**Figure 5:**The effect of SLC25A17 and SLC27A6-silencing on cell migration.



**Figure 6:**The effect of SLC25A17 and SLC27A6-silencing on citric acid, lactic acid and triglyceride levels.

## Acknowledgement

Department of Defense grant W81XWH-18-1-0618 and W81XWH-19-1-0720 to SG.

## References

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