SIRT1 and mTOR interplay in bladder cancer: a potential therapeutic target

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INTRODUCTION

Bladder cancer (BC), a tumour with high heterogeneity, has a high incidence and recurrence rate, with frequent alterations in several signalling pathways. The mammalian target of rapamycin (mTOR) pathway is altered in 72% of BC cases. Interestingly, the role of SIRT1 in tumorigenesis has been a matter of controversy since it can act both as a tumour promoter or tumour suppressor, suggesting that it has different roles according to the characteristics of the tumour. In recent studies, mitochondrial functions, metabolic pathways and signalling proteins have been related to both SIRT1 and mTOR pathways. Herein, we hypothesize that SIRT1 has a role in BC progression and that it interacts with mTOR pathway, modulating bioenergetics and metabolic features.

RESULTS

SIRT1 activation upregulated GLUT3 and MCT1 in HT-1376 cells without alteration on metabolites levels. mTOR inhibition alone also upregulated GLUT3, MCT1 and MCT4 expression in HT-1376 cells and increased MCT4 in TCCSUP cells, but with no direct action on metabolites levels.

The combined treatment with SIRT1 and mTOR inhibitors significantly decreased lactate production in TCCSUP cells and alanine was consumed instead of produced.

CONCLUSION

Our data showed that SIRT1 alteration have differential effects on BC cells of both grades, suggesting a possible therapeutic target for BC progression. These studies highlight the need to preselect patients based on metabolic cancer phenotype, since the cells’ behaviour from different stages diverse in metabolic genes, metabolites involved and mitochondrial function. In the context of personalized medicine, these differences in signalling pathways are essential for a specific diagnosis and therapy of each particular tumour. Overall, our data suggest that SIRT1 and mTOR are key players in BC physiology and highlight the need to unveil the interplay of both pathways in BC development.