Targeting BCAT1 is a metabolic vulnerability that impairs cell proliferation and aggressiveness in renal cell carcinoma

Pouria Jandaghi[1]
Daniel Auld[2], Hannah Klimmt[2], Mehdi Mansoor[3], Minjun Kim[2], Jierlui Luo[2], Brian Meehan[4], Fadi Brimo[3], Simon Tanguay[5], Janusz Rak[4] and Yasser Riazalhosseini[2]
[1] McGill University
[2] Department of Human Genetics, McGill Genome Centre, McGill University
[3] Department of Pathology, McGill University
[4] The research institute of the McGill University Health Centre (RI-MUHC)
[5] Division of Urology, McGill University

Background & objectives

Clear cell renal cell carcinoma (ccRCC), the most common type of kidney cancer, is resistant to chemo- and radiotherapies. Agents targeting angiogenesis, or immune checkpoint inhibitors are used for treatment, but resistance to these therapies is common, highlighting the need for novel therapeutic targets. CcRCC is also known as a metabolic disorder.

Methods

Pathway enrichment analysis was applied to differentially expressed genes between tumors and normal samples to identify pathways that are significantly (adjusted p-value 0.05) dysregulated in ccRCC. We used immunohistochemistry (IHC) to quantify BCAT1 protein levels on tissue microarrays (TMAs) that include benign kidney, primary ccRCC, and metastatic ccRCC tumors. We used specific siRNAs and shRNAs to suppress BCAT1 expression in 786-O and A-498 cell line models of ccRCC, and Gabapentin for pharmacological inhibition of BCAT1. Flow cytometry was used for cell cycle analysis.

Results

Our transcriptome analysis of ccRCC has revealed that the top-ranked pathway that separates tumor and normal tissues is the catabolism of branched-chain amino acid. We observed that upregulation of mRNA levels of the Branched Chain Amino Acid Transaminase 1 (BCAT1), a key regulator of the pathway, in tumors is associated with poor survival in patients. Our analysis of BCAT1 protein levels using ccRCC TMAs confirmed that BCAT1 is upregulated in ccRCC tumors compared to normal kidney tissues, with even higher levels in metastatic ccRCC. BCAT1 inhibition (using RNAi or Gabapentin) induced cell cycle arrest, reduced colony formation, and cell migration in 786-O and A-498 cell lines. These effects were paralleled by decreased cellular levels of branched keto acids (BKA), Glutamate (products of BCAT1), and their metabolite, Glutathione (GSH). Furthermore, BCAT1 suppression using RNAi reduced tumor growth in vivo in xenograft models of ccRCC.

Conclusion

Our findings show that BCAT1 plays a key role in ccRCC progression by modulating metabolic pathways that promote cell proliferation. Given the availability of BCAT1 inhibitors, targeting this protein may open a new therapeutic avenue for ccRCC.