BCAT1 overexpression as a poor prognostic factor in patients with urothelial carcinomas of upper urinary tracts and urinary bladders

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Background: Urothelial carcinoma (UC) is the most common histopathological type of urinary tract neoplasm. In spite of the less frequent prevalence and more advanced disease at diagnosis of upper tract urothelial carcinoma (UTUC) compared with urinary bladder urothelial carcinoma (UBUC), tumorigenesis of UC arising from both areas may share a similar pathway. Amino acid biosynthesis is one of the most cardinal events of carcinogenesis that has not been systemically investigated in UC. By data mining from a published transcriptomic database of UBUCs (GSE31684), branched-chain amino acid transaminase 1 (BCAT1) was identified as the most significant gene showing stepwise upregulation from early tumor development to progression among those associated with amino acid biosynthetic process (GO:0008652). BCAT1 is recently researched to be associated with tumor cell proliferation and cancer progression. Accordingly, we analyzed BCAT1 transcript and protein expressions and their associations with clinicopathological parameters and survivals in our well-characterized cohort of UC.

Design: Real time RT-PCR was used to detect BCAT1 messenger RNA (mRNA) level in 20 UTUCs and 20 UBUCs, respectively. Immunohistochemical study was evaluated by H-score method and used to determine BCAT1 protein expression in 340 UTUCs and 295 UBUCs, respectively. The mRNA and protein expression statuses were further correlated with clinicopathological features. The prognostic significance of BCAT1 protein expression was further gauged for disease-specific survival (DSS) and metastasis-free survival (MeFS).

Results: Higher BCAT1 transcript level was associated with higher pT status in both UTUC and UBUC (all p<0.05). BCAT1 protein overexpression was also significantly associated with advanced pT stage (both p<0.001), nodal metastasis (UTUC, p<0.001; UBUC, p=0.004), high histological grade (both p<0.001), vascular invasion (both p<0.001), perineural invasion (UTUC, p=0.009; UBUC, p=0.001) and high mitotic rate (UTUC, p<0.001; UBUC, p=0.023) in both groups of UC. HAS3 overexpression not only predicted worse DSS and MeFS at univariate analysis, but also indicated inferior DSS and MeFS (all p<0.001) in multivariate analysis.

Conclusions: BCAT1 overexpression is associated with advanced tumor status, unfavorable pathological features and implicated adverse clinical outcome for both groups of UTUCs and UBUCs. Our study unclosed that BCAT1 plays a crucial role in tumor progression in UC and may serve as a promising prognostic biomarker and a novel therapeutic target of UC.

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