FROM CILIA TO CANCER: THE TWO SPLICING VARIANTS OF THE HUMAN TBCCD1 GENE

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Almost all human genes that contain multiple exons undergo alternative splicing. Therefore, a single gene can originate multiple mRNA isoforms which causes a dramatic increase in the variability of the expected proteome. Noteworthy, phenotypic variability and disease susceptibility in human populations are related to alternative splicing. Published work from our group identified a new human centrosomal protein, TBCC domain-containing 1 (TBCCD1). Our studies revealed that this gene undergoes alternative splicing producing at least two transcripts encoding proteins. Here we analyze the differential functions of the two splicing variants (TBCCD1v1 and TBCCD1v2). Both variants present distinct cellular localization being TBCCD1v1 essentially centrosomal, whereas TBCCD1v2 is cytoplasmatic. The screening for TBCCD1v2 proximity interactome using BioID identified 19 proteins that functionally group in kinetochore, MT/cilia, and DNA-binding proteins. Striking, the overexpression of TBCCD1v2 decreases the levels of the kinetochore protein CENP-M, a protein upregulated in tumors. On the other hand, the TBCCD1v1 is involved in MT organization and is required to maintain distal structure of the mother centriole. Our BioID screening for TBCCD1v1 interactors revealed 82 distinct proteins including several well-known proteins encoded by ciliopathy genes. A wider analysis of how TBCCD1v1 levels impact in cellular physiological proteome showed that the group of proteins presenting fold changes in their levels vs control cells are enriched in proteins involved in focal adhesions, namely HSPA5/GRP-78/BiP, PDIA3, RPS10, MSN, TGM2 and PPP1R12A. Together our results show that we are still far from having a complete picture of the functional importance of TBCCD1 and how its deregulation may be associated not only with developing of ciliopathies but also with more common diseases like cancer.

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