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The STK4/Hippo-YAP axis promotes metastasis by increasing cancer cell stemness

The STK4-encoded MST1 (mammalian STE20-like kinase 1) and its key intermediate LATS1/2 (large tumor suppressor 1 and 2) are core components of the Hippo pathway in mammalian. The transcriptional co-activator YAP1/WWTR1 (thereof YAP) is a prominent nuclear effector of the Hippo pathway, which restricts organ size and tumorigenesis. The MST1 and LATS1/2 signaling cascade phosphorylates and inhibits YAP. Evidence suggests that activation of YAP is linked to poor cancer prognosis. Our studies have indicated that dysregulation of the MST1-YAP1 axis plays critical role in the etiology of metastatic prostate cancer (PC). However, the mechanism of how the MST1-YAP axis contributes to aggressive PC remains elusive. Here, we tested a novel concept that MST1 low cell variants that share cancer stem-like cells (CSCs) and epithelial-to-mesenchymal transition (EMT) phenotypes leads to metastatic PC through increases in interaction of nuclear YAP1 with androgen receptor (AR), a key oncogene for PC. Using our prior knowledge, we developed a novel method to isolate MST1 low and MST1 high cell variants to test this concept. Our functional and molecular analysis demonstrated that unlike MST1 high, MST1 low cells expressed the high levels of CSCs and EMT markers and were resistant to enzalutamide (ENZ), a direct small molecule inhibitor of AR signaling. In addition, MST1 low cells were highly invasive *ex vivo* and *in vivo* compared with MST1 high cells. Moreover, we demonstrated that nuclear YAP1 interacted with AR and that the interaction between YAP and AR occurred independently of androgen hormone signaling and were resistant to ENZ exposure in castration-resistant PC cells in comparison with castration-sensitive PC cells. Furthermore, we demonstrated that silencing of MST1 increased stem cell characteristics as well augmented androgen-independent YAP-AR interactions and PC cell growth *ex vivo*. In addition, MST1 induction had the opposite effects, validating our above observations. In summary, these findings suggest that the STK4/Hippo-YAP signaling axis plays a critical role in the promotion of metastatic disease and targeting of this pathway could reveal a new approach to fight against invasive cancer.

Speaker Biography

Bekir Cinar has completed his Post-doctoral Fellowship, Boston Children's Hospital, Harvard Medical School (HMS), Boston, MA (2002-2006) and PhD from Department of Biochemistry and Molecular Genetics, School of Medicine University of Virginia, Charlottesville, VA (1995-2002), DVM Veterinary Medical School, Ankara University, Ankara, Turkey (1987-1992). Currently, he is working as Associate Professor, Department of Biological Sciences, Clark Atlanta University (CAU), Atlanta, GA (2015 to present). Presently, he is also member of the Center for Cancer Research and Therapeutic Development at CAU and a member of the NCI-designated Winship Comprehensive Cancer Center at Emory University. Prior to joining CAU, he was Assistant Professor of Medicine-Hematology/Oncology and Biomedical Sciences at Cedars-Sinai Medical Center, where he was a member of Samuel Oschin Comprehensive Cancer Institute.

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