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Targeting cancer stem cells in urothelial cancer enhances chemotherapeutic response

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A large body of evidence indicates that cancer stem cells (CSCs) is the driving force of tumorigenesis, metastases and treatment resistance. However, the underlying mechanisms responsible for the urothelial CSC traits remain elusive. Here, we show that COX2/PGE2 and YAP1 signaling pathways are required to accelerate SOX2 that acts not only as a critical oncogene linked with malignant stemness properties, but also as a master regulator to govern and maintain urothelial CSCs. Moreover, we identify $CD133^{+}/CD24^{+}$ as a potent marker to enrich SOX2-expressing CSCs. Mechanistically, COX2/PGE2 signaling induces promoter methylation of let-7 host gene via promoting DNA methyltransferases, resulting in downregulated let-7 expression and subsequent SOX2 expression. YAP1 also activates COX2/PGE2 signaling-independent of SOX2 expression, and these signaling mutually compensate via negative feedback mechanism of SOX2, indicating that dual blockade of these signaling is indispensable to eradicate urothelial CSCs. Combined treatment with COX2 and YAP1 inhibitors elicits long-lasting therapeutic response by subverting CSCs expansion following chemotherapy or EGFR inhibitor for basal type urothelial carcinoma (UC) cells. Thus, our findings provide a rationale to concurrently target these pathways as an effective therapeutic strategy.

Significance

Improvement in survival of UCB has been stagnant over two decades and none of molecular-targeted agents has been approved to date. Here, we show that COX2/PGE2 and YAP1 signaling promotes urothelial CSCs generation via activating SOX2, leading to acquired resistance to systemic therapy such as chemotherapy or EGFR-targeted therapy for basal type UC. Concurrent inhibition of these signaling together with systemic therapy elicits robust therapeutic response by eradicating both the urothelial CSC pool and bulk of tumor, shedding light on progress in an effective therapeutic strategy for UC of bladder, including EGFR-targeted therapy for basal type UC.

Biography:

Dr. Hoque is an Associate Professor of Otolaryngology-Head & Neck Surgery, Urology and Oncology at Johns Hopkins University School of Medicine. His major research interests includes: a) To understand molecular biologic basis of head and neck, lung and genitourinary cancer b) To develop and validate genetic and epigenetic approach for early cancer diagnosis, cancer risk assessment and cancer prognosis and c) To identify molecular alterations due to environmental exposures such as active smoking, passive smoking and arsenic. He has published over 95 papers in reputed journals and has been serving as an editor and/or editorial board member of several bio-medical journals.