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Targeting the YAP1/COX2/SOX2 signaling axis eliminates cancer stem cells in urothelial carcinoma

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Bladder cancer stem/progenitor cells (CSC) contribute to tumor maintenance and resistance to therapy and accumulated evidence suggest that chronic carcinogen exposure induce "stemness" in different *in vitro* and *in vivo* models. Therapeutic targeting of CSCs could improve treatment response and prolong patient survival. Here we used our recently published *in vitro* chronic arsenic (As) exposed models to characterize the property of bladder CSC due to As exposure. We hypothesized that urothelial stem cells have a survival selection advantage during carcinogen exposure such as As, and it facilitates their malignant transformation and in acquiring selective phenotypes similar to CSC.

As-exposed cells displayed more aggressive phenotype than As unexposed cells in a time dependent manner. In gene set enrichment analysis of expression array of chronic As exposed and unexposed cells; EGFR, COX2 and YAP1 were top-ranked oncogenic signature based on enrichment score in As-exposed cells. Further analysis indicated that several known basal cell markers were overexpressed in As exposed cells in comparison with As unexposed cells. Because the presence of urothelial CSCs in basal-type provides a biological explanation for their aggressive behaviors, we assessed the influence of As on generating CSC phenotypes. Our results showed that As exposure was associated with overabundance of potential CSCs characterized by sphere formation, self-renewal capacity, redifferentiation, and chemotherapy resistance. To explore global association of As exposure and CSC generation, we used the Human Stem Cell RT² Profiler™ PCR Array and found that SOX2 has been gradually overexpressed in line with acquired spheroid formation and self-renewal capacities. Moreover, SOX2 mRNA expression was significantly higher UC cell lines and As exposed cells, especially in the spheroid cells; and in urine from As exposed normal than from controls. Stable silencing of SOX2 reduces *in vitro* CSCs properties and also *in vivo* tumorigenicity. COX2 and YAP1 are also frequently overexpressed in UC cell lines, and inhibition of COX2 or YAP1 reduced SOX2 expression. Interestingly, the inhibition of COX2 and YAP1 expression inversely induced YAP1 and COX2 expression, respectively which also reflect in primary UC tumors. Combination treatment with COX2 and YAP1 inhibitors reduced SOX2 expression and suppressed spheroid formation significantly than single agent. In conclusion, chronic As exposure induces CSCs with SOX2 overexpression, an important CSC factor for UC. COX2 and YAP1 coordinately regulate SOX2 expression, and mutually compensate for the reduction of expression of SOX2 to maintain CSCs. Thus targeting the COX2/YAP/SOX2 signaling axis eliminates urothelial CSCs.

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.