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Methylation biomarkers for low grade urothelial cancer (LGUC) management

Over 90% of bladder cancer in the western world present as urothelial carcinoma (UC), from which non-muscle invasive urothelial cancers (NMIBC) is the most common histology at presentation (around 75%). NMIBC is usually treated by trans-urethral resection of bladder tumor (TURBT) where 20% of patients will be cured, 70% will recur at least once every 5 years, and the remaining will progress to muscle-invasive disease with poor prognosis. Currently there are no well validated markers that can discern the tumors at the time of diagnosis that will recur/progress from those that will not. Moreover, conventional approaches are not ideal to predict risk of recurrence/progression. Hence, it is crucial to develop molecular markers that can predict recurrence/progression at the time of diagnosis and such markers will allow a more individualized therapy based on a patient's risk. Furthermore, it would also be important to develop a test that could provide cost-effective, non-invasive monitoring for low-risk patients, while using a more active approach to identify high-risk cancers before they progress. By a candidate gene approach, we analyzed the promoter methylation (PM) of 8 genes genes (*ARF, TIMP3, RAR-β2, NID2, CCNA1, AIM1, CALCA* and *CCND2*) by quantitative methylation specific PCR (QMSP) in DNA of 17 non-recurrent and 19 recurrent noninvasive low grade papillary urothelial carcinoma (LGPUC) archival tissues. Among the genes tested, by establishing an empiric cutoff value, *CCND2, CCNA1, NID2,* and *CALCA* showed higher frequency of methylation in recurrent than in non-recurrent LGPUCC: CCND2 10/19 (53%) vs. 2/17 (12%) (p=0.014); *CCNA1* 11/19 (58%) vs. 4/17 (23.5%) (p=0.048); *NID2* 13/19 (68%) vs. 3/17 (18%) (p=0.003) and *CALCA* 10/19 (53%) vs. 4/17 (23.5%) (p=0.097), respectively. We further analyzed PM of *CCND2*, *CCNA1* and *CALCA* in urine DNA from UC patients including LGPUC and controls. The frequency of *CCND2*, *CCNA1* and *CALCA* was significantly higher (p<0.0001) in urine of UC cases [38/148 (26%), 50/73 (68%) and 94/148 (63.5%) respectively] than controls [0/56 (0%), 10/60 (17%) and 16/56 (28.5%), respectively)]. Most importantly we found any one of the 3 markers methylation positive in 25 out of 30 (83%) cytology negative LGPUC cases. We also explored the biological function of *CCNA1* in UC. Prospective confirmatory studies are needed to develop a reliable tool for prediction of recurrence using primary LGUC tissues and/or urine.

Biography

Mohammad O 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.

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