Role of FOXA1 in prostate cancer and therapeutic resistance

Signal transduction through the hormonal transcription factor Androgen Receptor (AR) is a major driver of prostate cancer initiation and progression. FOXA1, a transcription factor of the FKHD family, was recently found to be among most frequently mutated genes in both localized prostate cancer (PCa, 3.4%) and castration-resistant prostate cancer (CRPC, 12%). Further, we found that FOXA1 mRNA expression is transiently up-regulated in PCa, but ultimately down-regulated in CRPC, suggesting context dependent roles. How FOXA1 regulates hormone-naïve primary PCa and hormone-insensitive CRPC has not been carefully examined. Through genomic analysis, here we report that FOXA1 regulates two essential oncogenic processes via disparate mechanisms. FOXA1 inhibits cell motility, epithelial-to-mesenchymal transition (EMT), and tumor metastasis through modulating SLUG. On the other hand, FOXA1 regulates cell proliferation by monitoring the genomic actions of the AR; FOXA1 defines prostate-specific AR cistrome and FOXA1 loss in CRPC cells emancipates oncogenic AR activities. Moreover, FOXA1 loss in PCa leads to neuroendocrine prostate cancer, a final-stage, lethal disease with no effective treatment. This is in part mediated by the induction of interleukin 8 (IL-8) transcriptions and subsequent ERK activation. In summary, we propose a model wherein homeostasis between FOXA1 and AR levels is critical in defining prostatic AR signaling and preventing AR from oncogenic activation. FOXA1 plays important roles in maintaining the prostate lineage; therapeutic approaches that restore FOXA1 function may be useful in the treatment of late-stage CRPC patients.

Biography
Jindan Yu is a member of Department of Biochemistry and Molecular Genetics. She is currently working in Northwestern University as an Associate Professor in Medicine Department.

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