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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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