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REVIEW ARTICLE

Current perspectives on FOXA1 regulation of androgen receptor signaling and prostate cancer

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Abstract FOXA1 (also known as hepatocyte nuclear factor 3α, or HNF-3α) is a protein of the FKHD family transcription factors. FOXA1 has been termed as a pioneer transcription factor due to its unique ability of chromatin remodeling in which the chromatin can be decompacted to allow genomic access by nuclear hormone receptors, including androgen receptor (AR) and estrogen receptor (ER). In this review, we discuss our current understanding of FOXA1 regulation of prostatic and non-prostatic AR-chromatin targeting. We present an updated model wherein FOXA1:AR equilibrium in the nuclei defines prostatic AR binding profile, which is perturbed in prostate cancer with FOXA1 and/or AR de-regulation. Finally, we discuss recent efforts in exploring new horizons of AR-independent functions of FOXA1 in prostate cancer and interesting directions to pursue in future studies.

Introduction

The forkhead box A1 (FOXA1; previously termed as hepatocyte nuclear factor 3α, HNF-3α) protein belongs to a superfamily of winged helix transcription factors.[1,2] The name of "forkhead box" gene family is originally derived from a prominent phenotypic feature of developmental defects observed in Drosophila with the *fork head* gene

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mutant, which manifests in the foregut and hindgut being replaced by ectopic head structures.[3] Like other forkhead (FKHD) family proteins, FOXA1 controls gene transcription by directly binding to its consensus sequence, the FKHD motif. In addition, FOXA1 has been shown capable of opening surrounding chromatin and subsequently allowing other transcription factors, such as androgen receptor (AR), to come in close proximity to their target sites and thus exert transcriptional control of gene expression.[4–7] Although this transcription regulatory effect of FOXA1 is quite well understood, important new developments have been made recently concerning the functional roles of FOXA1 in prostate cancer. This review thus discusses current literature regarding the delicate mechanisms by which FOXA1 regulates AR signaling and the deregulation and implication of FOXA1 in prostate cancer progression.

FOXA1 in development

FOXA1 was initially discovered approximately 25 years ago as an important liver-enriched transcriptional regulator of hepatic differentiation, since it was found to occupy the promoters of liver genes α1-antitrypsin and transthyretin.[8] Subsequent mouse studies have shown that *Foxa1* expression can be observed in endoderm-, mesoderm- and ectoderm-derived tissues of adult mice.[9] It has been reported that detectable *Foxa1* mRNA could first be observed at E7 in the late primitive streak stage in the midline endoderm of mouse embryos, following that the expression could be seen in the notochord, neural plate and floor plate of the neural tube, indicating that Foxa1's roles can range from establishment of definitive endoderm to formation of neural tube patterning.[10–12]

Although *Foxa1* null mice don't exhibit discernible morphological defects, they display severe growth retardation and die between postnatal days 2 and 14 (P2 and P14), which is resulted from a combination of phenotypes including dehydration and hypoglycemia.[13,14] Therefore, these observations indicate that FOXA1 plays a pivotal role in the maintenance of glucose homeostasis and pancreatic islet function. Tissue-specific deletion of *Foxa1* in the pancreas shows that FOXA1 and FOXA2 jointly regulate the expansion of pancreatic primordial, specification of endocrine and exocrine compartments, and maturation of islet cells.[15] Similarly, there is also evidence that FOXA1 is important for lung development by regulating respiratory epithelial differentiation,[16] and that it acts in a complementary manner with FOXA2 to ensure proper branching morphogenesis of the lung.[17] Moreover, it has been demonstrated that both FOXA1 and FOXA2 in conjunction are required for initiating the onset of hepatogenesis and hepatic specification.[18] More recently, a study utilizing conditional knockout of *Foxa1* and *Foxa2* in dopamine neurons reports that both factors are required for dopamine neuron maintenance and that their loss can give rise to locomotor deficits resembling the manifestations of Parkinson's disease.[19] Taken together, mice studies corroborate the notion that FOXA1 has critical influence on organogenesis.

In particular, a number of papers have demonstrated the significance of FOXA1 during development of the prostate and mammary glands. It has been said that the mammary ductal morphogenesis, but not the alveolar lineage, is dependent on FOXA1, and that while *Foxa1*-null glands can form milk-producing alveoli, they have lost ERα expression and functional activity, which ultimately result in compromised ductal lineage specification.[20] Likewise, in the prostate, FOXA1 deficiency leads to abolished differentiation and maturation of luminal epithelial cells.[21] Initially derived from the hindgut endoderm, the mouse prostate epithelium has persistent *Foxa1* expression throughout the processes of prostate development, growth, and adult differentiation.[22] The origin of the prostate is the urogenital sinus, which is a midline structure composed of an endoderm-derived epithelial layer and a mesoderm-derived mesenchymal layer.[23] In the mouse, at approximately E17.5, prostatic morphogenesis starts to take place, prompted by responsiveness to circulating androgens and induction of AR activity.[23] During the course of development, *Foxa1* expression was characterized in all lobes of the murine prostate, and is specifically enriched in AR-expressing epithelial cells. FOXA1 plays a critical role in modulating AR-regulated transcriptional signaling in prostate epithelial cells,[6] and concordantly *Foxa1*-deficient prostate has severely impaired ductal pattern formation, due to inhibition of ductal canalization and epithelial cytodifferentiation.[21] As a consequence, the *Foxa1*-null prostate lacks structural maturity as well as secretory activities. Taken together, there is compelling evidence that FOXA1 is critically involved in growth and differentiation of prostatic cells and is required for prostate glandular morphogenesis.

FOXA1 deregulation in prostate cancer

As FOXA1 is highly involved in developmental processes and lineage specification in several organs, when expressed at aberrant levels it may disrupt normal physiological events and lead to formation of cancer. Molecular and genetic studies have shown that FOXA1 is often found to be abnormally expressed in a number of cancer types, including acute myeloid leukemia (AML), lung, esophageal, thyroid, breast and prostate cancers.[24–30] At present, the prevailing views on FOXA1 expression in prostate cancer have not reached a consensus, with contrasting evidence seen in different cohorts of cancer patients. Analyses of human prostate cancer specimens have revealed that FOXA1 is overexpressed in metastatic as well as castration-resistant prostate cancer (CRPC) patients, but its expression is lower in normal and neoplastic transitional zone tissues.[31] In addition, the level of FOXA1 may be positively correlated with conventional parameters indicative of cancer progression (including tumor stage and Gleason scores), and negatively correlated with relapse-free survival times.[30,31] In other words, high FOXA1 level is associated with poor prognosis. However, other studies have also demonstrated that low FOXA1 levels are found in metastatic and CRPC tumors and may in fact denote unfavorable prognostic outcome in advanced prostate cancer.[32,33] In order to reconcile these conflicting findings, the function of FOXA1 should be carefully dissected with respect to cellular context, taking into consideration the