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# Androgen Receptor Roles in Insulin Resistance and Obesity in Males: The Linkage of Androgen-Deprivation Therapy to Metabolic Syndrome

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**Prostate cancer (PCa) is one of the most frequently diagnosed malignancies in men. Androgen-deprivation therapy (ADT) is the first-line treatment and fundamental management for men with advanced PCa to suppress functions of androgen/androgen receptor (AR) signaling. ADT is effective at improving cancer symptoms and prolonging survival. However, epidemiological and clinical studies support the notion that testosterone deficiency in men leads to the development of metabolic syndrome that increases cardiovascular disease risk. The underlying mechanisms by which androgen/AR signaling regulates metabolic homeostasis in men are complex, and in this review, we discuss molecular mechanisms mediated by AR signaling that link ADT to metabolic syndrome. Results derived from various AR knockout mouse models reveal tissue-specific AR signaling that is involved in regulation of metabolism. These data suggest that steps be taken early to manage metabolic complications associated with PCa patients receiving ADT, which could be accomplished using tissue-selective modulation of AR signaling and by treatment with insulin-sensitizing agents.**

Prostate cancer (PCa) is the second leading cause of cancer-related mortality and the most common malignancy in men in the U.S. (1). Androgen-deprivation therapy (ADT) to suppress PCa was initially demonstrated by

Huggins and Hodges in 1941 (2) and remains as the standard treatment for PCa (3). ADT is accomplished with surgical castration (bilateral orchiectomy) or chemical castration with gonadotropin-releasing hormone (GnRH) agonists to suppress binding of androgen to the androgen receptor (AR). Although ADT improves survival at all stages of PCa, it leads to severe hypogonadism with different adverse effects, including unfavorable metabolic alterations. Treatment of the metabolic complications of ADT has been considered and has become increasingly important (4). Metabolic syndrome is a complex disorder consisting of abdominal obesity, dyslipidemia, insulin resistance, and hypertension. Obese individuals are more prone to develop insulin resistance compared with nonobese individuals. Insulin resistance promotes metabolic complications including elevated circulating triglycerides, reduced HDL, elevated fasting blood glucose levels, and high blood pressure. These metabolic abnormalities, in conjunction with abdominal obesity, represent the classical features of metabolic syndrome (5). Metabolic syndrome is an important risk factor for cardiovascular disease and associated morbidity and mortality in individuals with or without diabetes.

In this article, we will discuss the molecular aspects of mechanisms linking ADT to metabolic syndrome by focusing on evidence derived from AR-knockout (ARKO) mouse models.

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## RELATIONSHIP BETWEEN ANDROGEN DEFICIENCY AND METABOLIC SYNDROME: EVIDENCE FROM EPIDEMIOLOGICAL AND CLINICAL STUDIES

Androgen is a male sex steroid hormone that exerts important physiological functions leading to masculine characteristics, maturation of reproductive systems, and bone metabolism. The major circulating androgen, testosterone, is synthesized in testicular Leydig cells and released into blood, where it binds to steroid hormone-binding globulin (SHBG) to facilitate the transport. Within target cells, testosterone is converted to 5 $\alpha$ -dihydrotestosterone (DHT), a more potent androgen, by 5 $\alpha$ -reductase. Both testosterone and DHT bind to the AR to exert their physiological functions (6). Androgen-activated AR regulates the transcription of a variety of target genes through the interaction with different coregulators. Androgen/AR and their coregulators form a complex signaling network.

Androgen is an important determinant of body composition in men promoting growth of lean mass and suppressing deposition of fat (7). Epidemiological studies have observed a bidirectional relationship between low testosterone levels and obesity in men (8). Obesity is the single most powerful predictor of low testosterone levels in men, and one of the hallmarks of obesity in men is reduced testosterone levels. Conversely, low levels of testosterone and SHBG can predict accumulation of intra-abdominal fat, development of central obesity, and increased risk of metabolic syndrome in men (8,9).

There is growing evidence supporting a beneficial effect of testosterone therapy on body composition to reduce visceral obesity and the elements of metabolic syndrome (10,11). Results from clinical studies show that testosterone can promote insulin sensitivity in hypogonadal men with and without diabetes (12). Testosterone replacement in men with metabolic syndrome reduces body weight, waist circumference, and visceral fat mass. Plasma levels of insulin and leptin as well as some markers of inflammation were also reduced (13). Testosterone replacement therapy may also have the potential to decrease risk factors of cardiovascular diseases associated with metabolic syndrome in hypogonadal men (14).

High body-fat mass and central obesity are associated with low serum testosterone and SHBG levels (15). Reduction of testosterone levels in men with BMI  $\geq 30$  kg/m<sup>2</sup> was demonstrated in the European Male Aging study, suggesting that obesity can lead to decreased testosterone levels (16). This is further supported by studies showing that weight management by diet or surgery can increase testosterone levels proportional to the amount of weight lost (17,18). In contrast, abnormalities in the hypothalamic-pituitary-testicular axis or experimental induction of hypogonadism in healthy young men can increase fat mass rapidly (8,19).

Low testosterone and SHBG are also associated with the development of insulin resistance and metabolic syndrome in men. Cross-sectional studies have shown

an inverse relationship between testosterone levels and insulin resistance in healthy men (20). In aging men, a 25% decrease of serum testosterone leads to a twofold increase of insulin resistance (21). Acute androgen deprivation can reduce insulin sensitivity in healthy young men (22). Moreover, reduction in the total and free serum testosterone is prevalent in men with type 2 diabetes (23). These results support the notion that male hypogonadism is an independent risk factor for metabolic syndrome, and low testosterone levels can be added to the criteria for the diagnosis of metabolic syndrome in men (24).

Taken together, results derived from epidemiological and clinical studies reveal a close association between testosterone deficiency and metabolic syndrome. Given that ADT induces severe testosterone deficiency with a temporally defined onset, PCa patients receiving ADT may have even higher risks for development of metabolic syndrome as well as detrimental changes in body composition associated with the ADT treatment, for example, an increase in fat mass and a decrease in lean mass (25–27). Three months of ADT treatment significantly increases fat mass and circulating insulin levels (27). The accumulation of visceral adiposity during short-term ADT is highly correlated with increasing circulating insulin levels. Interestingly, changes in measures of insulin resistance are noted as early as 3 months after starting ADT even before the development of central obesity (28). Men undergoing long-term ADT treatment show significant insulin resistance and hyperglycemia compared with the non-ADT and control groups (29,30). Importantly, 44% of patients receiving ADT have a fasting glucose level  $>126$  mg/dL, a criterion for the diagnosis of diabetes mellitus, indicating that ADT of long duration can lead to development of diabetes (31).

In addition to the linkage of low testosterone levels with metabolic disturbances, the CAG repeat polymorphism within the AR gene also can play a role in development of metabolic syndrome. There is an inverse relationship between the length of the AR CAG repeat and its transcriptional activity on testosterone target genes (32). Some studies even suggest that serum levels of testosterone can be correlated with the CAG repeat of AR, indicating the negative-feedback loop mediated by AR to regulate testosterone levels (33). The polymorphism of AR CAG repeats is reported to influence insulin sensitivity and components of metabolic syndrome in men (34,35). These findings provide additional support for the critical role of AR in androgen/AR signaling in the regulation of metabolism.

## LESSONS FROM GLOBAL ARKO MOUSE MODEL

Although human studies have linked testosterone deficiency to the metabolic complications that occur in men receiving ADT, studying the underlying mechanisms responsible *in vivo* is complex. The mechanisms by which testosterone influences insulin sensitivity and obesity are multifactorial and are likely due to a combination of

testosterone's action on liver, muscle, and adipose tissues. The molecular basis of functional deficiency in androgen/AR signaling and the pathophysiology of developing obesity and insulin resistance remain unclear. Using the Cre-loxP-mediated recombination approach, a conditional ARKO mouse model was established to investigate roles of AR in the development of metabolic syndrome in males (36).

Global deletion of AR (GARKO) in male mice results in the characteristics of central obesity, abdominal accumulation of fat by middle age, but without change in lean mass (37). The development of late-onset visceral obesity is also observed in several parallel studies using mouse models with genetic AR deletion (38–40). Obesity in male GARKO mice was associated with elevations of circulating lipids, altered lipid metabolism in white adipose tissue, and excessive deposition of lipids in nonadipose tissues, including liver and muscle. Glucose homeostasis was affected in male GARKO mice that demonstrate fasting hyperglycemia, glucose intolerance, and insulin resistance. The ability of insulin to stimulate activation of downstream phosphatidylinositol-3 kinase was reduced by 60–63% in skeletal muscle and liver derived from male GARKO mice, supporting the development of insulin resistance and impaired insulin signaling. Leptin resistance in these obese male GARKO mice was also demonstrated by the reduced response of mice to exogenous leptin in regulation of food intake and body weight (37).

Circulating testosterone levels were remarkably low in GARKO male mice due to atrophic testes, suggesting the possibility that the insulin resistance and observed metabolic abnormalities simply reflected low levels of serum testosterone. Interestingly, serum androstenedione and estradiol were not altered in male ARKO mice and their wild-type littermates. When the nonaromatizable androgen DHT was given to male GARKO mice, DHT was

not able to reverse the metabolic abnormalities and insulin resistance (37). These findings indicate that nongenomic actions of androgen cannot directly account for the development of obesity and insulin resistance (41) and that AR is critical in mediating effects of androgens to regulate glucose and lipid metabolism.

Although compensatory mechanisms caused by congenital ablation of AR could occur and influence metabolism in the adult, the metabolic abnormalities developed in male GARKO mice in fact recapitulated the metabolic complications observed in men with testosterone deficiency and in patients with PCa receiving ADT. The ARKO mouse model therefore may serve as an *in vivo* system to investigate molecular mechanisms by which androgen/AR signaling regulate glucose and lipid homeostasis.

### CELL TYPE-SPECIFIC ARKO MOUSE MODELS

The development of insulin resistance is a complicated process involving the impaired action of insulin in various target tissues. Although underlying mechanisms of impaired insulin signaling may differ among tissues and under various circumstances, it is established that there are complex interorgan communication among various insulin target tissues (42,43). Examination of tissue-specific insulin signaling and selective insulin resistance in various tissues have advanced our understanding of the complex pathophysiology of insulin action (44).

By using transgenic mice expressing Cre recombinase in specific cell types, tissue-specific ARKO mouse models have been generated (37,45–47). Deletion of AR in this manner does not alter the serum testosterone levels in male mice (Table 1). These various ARKO mice serve as valuable animal models to dissect the pathophysiological roles of tissue-specific AR signaling involved in the development of metabolic syndrome.

**Table 1—Summary of metabolic phenotypes in male conditional ARKO mice**

Conditional ARKO mice	GARKO (AR <sup>-/y</sup> )	LARKO (L-AR <sup>-/y</sup> )	AARKO (A-AR <sup>-/y</sup> )	NARKO (N-AR <sup>-/y</sup> )
Cell specificity	General	Hepatocytes	Adipocytes	Neurons
Cre promoter	β-actin	Albumin	FABP4	Synapsin I
Insulin sensitivity	↓	↓	↔	↓
Serum insulin	↑	↑	↔	↑
Blood glucose	↑	↑	↔	↑
Glucose tolerance	↓	↓	ND	↓
Leptin sensitivity	↓	ND	↑	ND
Serum leptin	↑	↑	↑	↑
Hepatic lipids	↑	↑	↓	↑
Serum triglycerides	↑	↑	↓	↑
Free fatty acids	↑	↔	↔	↑
Visceral fat accumulation	↑	↑	↔	↑
Serum testosterone level	↓	↔	↔	↔

NARKO, neuronal-specific ARKO; ND, not determined.

### Liver-Specific ARKO Mouse Model

The liver functions as a major metabolic tissue to control glucose and lipid homeostasis. Oxidation of fatty acids by the hepatocytes supplies the substrate for glucose production. Dysregulated fatty acid oxidation and synthesis can lead to the accumulation of fat or hepatic steatosis.

Using albumin-Cre-transgenic mice, Lin et al. (45) directly addressed the role of AR in the liver by specifically deleting AR in hepatocytes (LARKO). After 8 weeks of high-fat diet (HFD) feeding, male LARKO mice developed obesity and significant hepatic steatosis (45). Hepatic steatosis is known to negatively impact insulin sensitivity and lead to insulin resistance, which is manifested by the reduced ability of insulin to suppress hepatic glucose production (48,49). HFD-fed male LARKO mice exhibited fasting hyperglycemia and insulin resistance, indicating impairments in the regulation of glucose homeostasis and insulin sensitivity. At a molecular level, decreased activation of phosphatidylinositol-3 kinase in response to insulin and increased expression of PEPCK in male LARKO liver and isolated hepatocytes were consistent with increased hepatic glucose production and development of insulin resistance.

Mechanistic studies in male LARKO mice showed that activation and upregulation of SREBP1c and acetyl CoA carboxylase produced more malonyl CoA, the substrate for de novo fatty acid synthesis. The transport of free fatty acids from the cytosol to mitochondria is required for their  $\beta$ -oxidation and is mediated by carnitine palmitoyltransferase I, located at the outer membrane of mitochondria. Malonyl CoA is an inhibitor of carnitine palmitoyltransferase I, and increased levels of malonyl CoA reduces transport of fatty acids into mitochondria, resulting in the reduction of fatty-acid oxidation. In a parallel cascade, reduction of peroxisome proliferator-activated receptor- $\alpha$  and malonyl CoA decarboxylase in livers derived from male LARKO mice further increased the production of malonyl CoA. In corresponding hepatocytes, expression of peroxisome proliferator-activated receptor- $\alpha$  was shown to be mediated by DHT-dependent activation of AR (45). These findings suggest that impeding the entry of free fatty acids into mitochondria, impairing  $\beta$ -oxidation of fatty acids, and promotion of de novo fatty acid synthesis could account for the development of hepatic steatosis in male LARKO mice.

These mechanistic studies of HFD-fed male LARKO mice demonstrate a pivotal role of hepatic AR in regulating insulin sensitivity and lipid homeostasis. Hepatic insulin resistance is shown to be sufficient to produce dyslipidemia and increase the susceptibility to atherosclerosis in mice (50,51). In human clinical studies, GnRH agonists to suppress androgen/AR signaling cause increases in total cholesterol and triglycerides (52,53). It is therefore likely that functional deficiency of AR in the liver caused by GnRH agonists leads to these lipid alterations. As large cohort studies demonstrate strong correlations between blood cholesterol levels and cardiovascular

mortality independent of other coronary risk factors (54), awareness of altered hepatic AR signaling and lipid metabolism during ADT should prompt the appropriate management of cardiovascular complications.

### Neuronal-Specific ARKO Mouse Model

Compelling data derived from animal studies are mounting that brain insulin resistance may be a critical element in the pathophysiology of obesity, type 2 diabetes, and related metabolic disorders (55–57). Defective hypothalamic insulin signaling is able to promote hepatic insulin resistance as demonstrated by the brain-specific insulin receptor knockout mouse model (55). Partial restoration of liver insulin signaling in the insulin receptor knockout mice fails to normalize insulin action on hepatic glucose production, supporting the importance of hypothalamic insulin signaling in glucose homeostasis (58).

Male neuronal-specific ARKO mice, generated by selectively targeting AR in neurons, displayed increased body weight and visceral adiposity, as well as increased levels of fasting blood glucose and insulin. Neuronal AR deficiency led to impaired insulin signaling in the hypothalamus, which in turn resulted in reduced suppression of hepatic gluconeogenic genes (46).

Hypothalamic insulin resistance is reported to act as an early event in the development of systemic insulin resistance due to prolonged exposure to excessive nutrition (59). Activation of hypothalamic nuclear factor- $\kappa$ B (NF- $\kappa$ B) signaling is critical to induction of insulin resistance following chronic overnutrition (60,61). At the neuronal level, loss of suppression by AR resulted in increased activation of hypothalamic NF- $\kappa$ B signaling within a short-term HFD-feeding period (46). Hence, functional deficiency of AR in neurons directly interferes with insulin signaling and leads to hypothalamic insulin resistance.

These findings uncover a new mechanism of insulin resistance caused by testosterone deficiency through decreased function of AR in the brain. Suppression of the hypothalamic NF- $\kappa$ B by AR provides a potential way to manage the metabolic complications that develop in patients with PCa undergoing ADT by targeting neuronal AR.

### Adipose-Specific ARKO Mouse Model

The adipose tissue is a key target of insulin action, important for glucose uptake, and a potential site for testosterone's action in regulating body mass composition.

Selectively targeting AR in adipocytes was used to generate the adipose-specific ARKO (AARKO) mouse model to study the role of AR in fat tissue. In male AARKO mice, body weight and fat pad mass were indistinguishable from that of wild-type littermates. Despite identical levels of adiposity, male AARKO mice exhibited elevated levels of serum leptin, suggesting that loss of the AR affects leptin secretion by adipose tissue. Interestingly, enhanced leptin production in AR-deficient adipose tissue did not result in leptin resistance, as male

AARKO mice showed increased sensitivity in response to exogenous leptin challenge (47). Increased estradiol levels were observed in epididymal adipose tissue, suggesting enhanced estrogen receptor (ER) transactivation contributed to upregulation of leptin gene transcription.

Adipose tissue expressed several steroidogenic enzymes that control tissue steroid concentrations and ligand bioavailability for intracellular receptors (62). It is possible that altered activities of steroid-converting enzymes due to loss of AR resulted in a larger steroid reservoir in AR-deficient adipocytes. Increased steroid precursors may have provided increased available substrate for aromatases in the adipose tissue, resulting in enhanced estradiol production. In male GARKO mice, the elevation of leptin occurred prior to the onset of obesity, suggesting a similar mechanism of increased intracellular estradiol conversion may have contributed to enhanced leptin production (37).

Sex steroid hormones are important regulators of metabolism, accumulation of fat, and distribution of adipose tissue. In humans, fat distribution is different between males and females. Sex steroid hormones predispose males to a more central accumulation of fat, whereas in females, a more subcutaneous accumulation of fat is observed (63). This difference has important metabolic consequences, as visceral obesity is considered a risk factor for cardiovascular diseases, and men have a higher incidence of cardiovascular diseases than women. Menopause in women increases central distribution of fat and incidence of cardiovascular diseases (64). The mechanism by which sex steroid hormones control the amount and distribution of fat is not clear. One mechanism may be through the transcriptional regulation of key proteins in adipose tissue (63). Future studies on the local synthesis of sex steroid hormones and the regulation of AR and ER signaling in different types of adipose tissue may increase our understanding of steroid action in the adipocyte.

#### **Muscle-Specific ARKO Mouse Model**

A critical feature of skeletal muscle in glucose homeostasis is insulin-stimulated glucose uptake and use. Testosterone is an important regulator of lean mass, and anabolic effects of testosterone on skeletal muscles are thought to be mediated predominantly through AR. AR is expressed in various cell types of skeletal muscle in humans and rodents including myocytes, satellite cells, fibroblasts, and mesenchymal stem cells (65–67), and all are potential targets of testosterone's action.

One muscle-specific ARKO (MARKO) mouse model, generated by myocyte-specific AR deletion, demonstrates altered fiber composition. Myocyte-specific deletion of AR resulted in an increase of slow-twitch fibers without affecting muscle strength. Unexpectedly, MARKO mice showed a reduction in intra-abdominal fat mass (68). In another MARKO mouse model, AR ablation in myocytes affected intrinsic contractile functions in fast- and intermediary-twitch muscles. Androgens induced hypertrophy

of muscle fibers through AR-dependent pathways in perineal muscles and AR-independent pathways in limb muscles (69). Discrepancies between the two MARKO mouse models may be related to differences in genetic backgrounds of the mouse lines, Cre recombinase transgenic mouse lines (MCK-Cre vs. HSA-Cre), and experimental protocols used. Whether insulin sensitivity or glucose homeostasis is influenced by myocyte-specific AR ablation is unclear and awaits further investigation.

Insights into AR signaling in muscle and the role of AR in regulating metabolic homeostasis may be facilitated by using transgenic animal models in which AR is selectively overexpressed in various cell types. Overexpression of AR in myocytes increased lean mass and reduced fat mass in transgenic rats. AR signaling in myocytes was sufficient to promote systemic oxidative metabolism through increasing activity of mitochondrial enzymes and oxygen consumption in skeletal muscle (70). Targeted AR overexpression in mesenchymal stem cells reduced fat mass and reciprocally increased lean mass in male mice. Transgenic AR mice showed improved glucose use in response to exogenous glucose challenge (71). These studies suggest AR signaling in muscle is involved in mitochondrial respiration and glucose disposal.

#### **ROLES OF ANDROGEN AND AR IN METABOLIC SYNDROME-ASSOCIATED CARDIOVASCULAR DISEASE**

Metabolic syndrome is a critical risk factor for cardiovascular disease. The metabolic complications associated with ADT suggest a significantly greater risk of cardiovascular disease events in patients with PCa, although the role of androgen in cardiovascular disease is controversial. Epidemiologic studies indicate that men are at a significantly higher risk of cardiovascular disease and suffer from mortality more frequently compared with women (72,73). Exogenous testosterone administration in men increases the rate of adverse cardiovascular events, including the coronary syndrome and myocardial infarction (74). The risk of developing deep venous thrombosis or pulmonary embolism in men receiving testosterone-replacement therapy has also been suggested in a recent study (75). In contrast, other clinical studies suggest a beneficial action of testosterone on vascular health and low levels of testosterone are associated with risk of cardiovascular disease (76,77). Low testosterone levels are associated with carotid and aortic atherosclerosis in men (78,79) and are a predictor of cardiovascular events in middle-aged men after adjustment for coronary risk factors (80). In men with coronary artery disease, low levels of testosterone are associated with severity of the coronary artery atherosclerosis (81). Thus, there is evidence that high levels of testosterone as well as low levels of testosterone are associated with increased cardiovascular disease risk.

Controversies are also observed in cell culture and animal studies designed to uncover actions of testosterone on the cardiovascular system. Deleterious effects of

testosterone on vasoconstriction and inflammation were shown to contribute to the progression of atherosclerosis and rupture of the myocardium following acute myocardial infarction (82–87). In contrast, much of the literature shows that testosterone can attenuate atherosclerosis, reduce the size of the myocardial infarction, and enhance vasodilation, suggesting a beneficial role of testosterone (88–93). This paradox suggests that testosterone may execute multiple roles on the cardiovascular system simultaneously in addition to its effects on risk factors, such as insulin sensitivity, dyslipidemia, obesity, and diabetes.

Although some effects of testosterone on the cardiovascular system are thought to be mediated by the ER, AR is present in all types of cells within the cardiovascular system (94). AR is expressed in endothelial cells, smooth muscle cells, macrophages, platelets, and cardiomyocytes (95,96). Testosterone itself results in a 50% increase of AR expression in the aortic arterial segment of rabbits. The vascular AR is suggested to be involved in the process of testosterone's action on the arterial vascular system (97). Osterlund et al. (98) has demonstrated AR-mediated inflammatory responses in isolated coronary artery smooth muscle cells. Furthermore, AR was shown to regulate cell proliferation in cardiomyocytes and mediate protective effects of testosterone in response to ischemic insults in rats (91,99). These studies suggest direct AR-mediated action of androgen in the cardiovascular system. It is therefore likely that AR acts in either a beneficial or harmful manner for vascular health in different cell types within the microenvironment.

Although controversial roles of androgen/AR signaling exist in the cardiovascular system, several clinical studies have reported adverse cardiovascular consequences of ADT in patients with PCa. Men who receive a GnRH agonist had a higher incidence of coronary heart disease, myocardial infarction, and sudden cardiac death (31). The use of ADT was associated with shorter time to death from cardiovascular causes and to fatal myocardial infarction after controlling for age and risk factors (100,101). In a retrospective observational study, the overall survival at 10 years was worse in men receiving ADT treatment, and cardiovascular disease was the most common cause of death in these cases (102).

The underlying mechanisms through which severe deficiency of androgen/AR signaling in ADT results in rapid development of cardiovascular disease complications remain largely unknown. Besides enhancing the development of components of metabolic syndrome, such as insulin resistance, dyslipidemia, and visceral obesity, deficiency of androgen/AR signaling may also directly impact health of the cardiovascular system. We suggest that specifically targeting AR in various cell types in the cardiovascular system may help to reveal the complex relationship between androgen and cardiovascular disease. These future investigations will shed light on better management of long-term cardiovascular health for patients with PCa receiving ADT.

## SUMMARY

A growing body of evidence in human studies demonstrates a close relationship between testosterone deficiency and the development of metabolic syndrome in men. In this review, we discussed several molecular mechanisms mediated by AR signaling that can lead to the development of metabolic syndrome. In patients with PCa receiving ADT, severe testosterone deficiency results in obesity, insulin resistance, altered lipid profiles, development of diabetes, and cardiovascular complications. However, the molecular mechanisms by which androgen/AR signaling regulates metabolic homeostasis in men are likely to involve multiple factors and cross-talk among insulin target tissues. By cell type-specific AR targeting in mice, the critical role of AR in androgen/AR signaling can be studied without alterations of testosterone levels in male mice. Results derived from various cell type-specific ARKO mouse models for the tissue-specific AR signaling are summarized in Table 1. Hepatic AR and neuronal AR signaling directly participate in cellular insulin signaling regulating systemic insulin sensitivity as well as glucose and lipid homeostasis. Awareness of altered hepatic AR signaling and lipid metabolism may prompt appropriate management of cardiovascular complications during ADT. AR signaling in the myocytes beneficially increases systemic oxidative metabolism by changing muscle fiber compositions in skeletal muscle. These findings suggest promising targets for tissue-selective treatments to manage metabolic complications found in patients with PCa during ADT.

## FUTURE PROSPECTS

In the future, rather than waiting for the diagnosis of insulin resistance and metabolic syndrome, available data suggest that patients with PCa receiving ADT should be given advice on lifestyle modification and possible early treatment for ensuing lipid disorders leading to metabolic syndrome.

The selective AR modulators (SARMs), a class of ligands that bind to the AR and display a tissue-selective activation of AR signaling, may provide a treatment choice (103). In preclinical studies, a SARM was shown to execute tissue-selective anabolic actions by restoring muscle strength and reducing body fat in ovariectomized male rats (104,105). In phase I clinical studies, first-generation SARMs induced modest gain of lean body mass in healthy volunteers (106). With improving techniques, the new generation of SARM molecules will have greater potency and better selectivity. One new SARM molecule has shown to improve lean body mass and physical function in healthy elderly men in a phase II trial study (107). The use of nonsteroidal SARMs may avoid differential activation of intracellular signaling cascades by the nongenomic action of DHT that can lead to unexpected cellular processes (106,108).

Obesity and diabetes are being recognized as risk factors for the development of cancers and prediction of aggressive cancer metastasis, including PCa. A pilot study

has shown a strong trend between metabolic syndrome and earlier development of castration-resistant PCa in patients receiving ADT (109). These findings suggest that there may be a unique therapeutic window for combining insulin-sensitizing medication with antiandrogen agents for treatment of patients with PCa affected by metabolic syndrome and advanced PCa (110,111).

It is anticipated that patients with PCa will live longer with next-generation therapies targeting androgen synthesis or directly targeting AR in combination with ADT and with better management of metabolic and cardiovascular risk factors and complications. The development of cell type-specific AR targeting or functional AR restoration is clearly warranted in the future.

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