Role of Adiponectin in prostate cancer

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ABSTRACT

Obesity is defined as a chronic and excessive growth of adipose tissue. It has been associated with a high risk for development and progression of obesity-associated malignancies, while adipokines may mediate this association. Adiponectin is an adipose tissue-derived adipokine, with significant anti-diabetic, anti-inflammatory, anti-atherosclerotic and anti-proliferative properties. Plasma adiponectin levels are decreased in obese individuals, and this feature is closely correlated with development of several metabolic, immunological and neoplastic diseases. Recent studies have shown that prostate cancer patients have lower serum adiponectin levels and decreased expression of adiponectin receptors in tumor tissues, which suggests plasma adiponectin level is a risk factor for prostate cancer. Furthermore, exogenous adiponectin has exhibited therapeutic potential in animal models. In this review, we focus on the potential role of adiponectin and the underlying mechanism of adiponectin in the development and progression of prostate cancer. Exploring the signaling pathways linking adiponectin with tumorigenesis might provide a potential target for therapy.

INTRODUCTION

Prostate cancer (PC) recently became the second most prevalent cancer afflicting men, and the fifth leading cause of cancer related death throughout the World (1, 2). Age, familial history, smoking, sedentary lifestyle and overweight are all factors in the pathogenesis of PC. Of note, obesity is well known as an increased risk for several cancers (including colon, ovary, breast, esophagus and pancreatic), also for PC (3, 4). The links between obesity and PC are complicated. Three possible mechanisms are proposed to help explain the association between obesity and the increased risk of PC: the insulin / insulin-like growth factor-1 (IGF-1) axis, sex hormones and adipokines signaling (5, 6). Adiponectin (APN), an adipocyte-secreted adipokine, operates in the maintenance of many physiological functions, having potential benefits in the prevention of certain diseases. It mainly regulates inflammation and influences glucose and lipid metabolism through its insulin sensitizing effects (7, 8). Recently, APN was proved to be one of the mediators in the development and progression of several types of obesity-associated cancers (9). In this report, we summarized recent findings on the potential role of APN and the underlying mechanism of APN in PC. In addition, the clinical values of APN for PC patients will also be highlighted.
Adiponectin and its receptors

Adiponectin, also called Acrp30, is a 28–30 kDa adipokine produced mainly by adipose tissue. Full-length APN (fAPN) consists of an N-terminal signal sequence, a short hypervariable region, a collagen-like domain and a C-terminal globular domain (10, 11). Pre-secretion, post-translational processing generates trimers, hexamers, and high molecular weight (HMW)-APN, which is generated by the proteolytic cleavage of fAPN.

Normal plasma APN levels range from 5 to 30 µg/mL, accounting for up to 0.05% of total plasma proteins in humans (11). Despite the fact that APN is produced mainly by adipose tissue, its serum concentration is reversely correlated with the body mass index (BMI) (12). One possible explanation of the reduced APN levels in obesity may be caused by the enhanced production of proinflammatory cytokines, in particular, TNF-α, IL-6. Another explanation that serves to downregulate APN expression is endoplasmic reticulum (ER) stress resulting from obesity. In addition, it is demonstrated that there is a negative feedback of APN on its own production during the development of obesity (12). APN plasma concentration was found to be sex dependent, with the levels being higher in women and lower in men (12).

Although produced by adipose tissue, APN functions via the specific receptors, AdipoR1 and AdipoR2, both of which contain seven transmembrane domains with the C-terminus inside the cells and the N-terminus outside (13). Specifically, AdipoR1, ubiquitously expressed and present in the liver, binds both gAPN and fAPN with an intermediate affinity (10, 11). Pre-secretion, post-translational processing generates trimers, hexamers, and high molecular weight (HMW)-APN. Because T-cadherin lacks both transmembrane and cytoplasmic domains, it is considered to have no effect on APN cellular signaling or function. Its main role is thought to act as an APN-binding protein, rather than a receptor.

Adiponectin and prostate cancer

Adiponectin has been consistently associated with an increased risk of progression of PC, but APN is inversely related to the degree of adiposity. It seems that plasma APN should be reduced in PC patients. Gokhale et al. (15) was the first to report that serum APN levels were significantly lower in patients with PC than in the BPH group or in healthy controls. In addition, APN levels were negatively associated with histological grade and disease stage. Next, a study of 300 Greek men by Michalakis et al. (16) revealed a significantly reduced risk of PC with higher plasma APN concentrations. In line with this, APN receptor levels are also lower in rectal PC tissues. Several studies have supported the inverse association between APN and risk of PC or high-grade PC (17–21).

In contrast, APN is highly expressed in skeletal muscle, possess a high-affinity for gAPN and a low affinity for fAPN. High APN and PC have also been associated with decreased risk of PC (22, 23). One possible mechanism behind this is the increased insulin sensitivity and decreased lipolysis resulting from increased ADIPOQ and ADIPOR expression (24, 25). Conversely, two other studies demonstrated no association in candidate SNPs and PC risk (26, 27).

Several studies have revealed the potential association between APN and prostate cancer progression. The relationship between APN and PC has also been examined by many investigators. Mistry et al. (22) firstly showed AdipoR1 and AdipoR2 expression in prostate cancer and APN being a protective response against tumor progression. However, another study performed by Rider et al. (23) revealed that APN activates the adenosine triphosphate (ATP)-stimulated, protein kinase (AMPK) is a key part of the signaling cascade downstream of AMPK, which is the mammalian homologue of the target of rapamycin (mTOR), vascular endothelial growth factor A (VEGF-A) and fatty acid synthase (FAS), all of which are involved in the regulation of cell proliferation. In PC-3 cells, activation of AMPK by APN is associated with reduction in mTOR activation, which reduces protein translation and inhibits cell growth (34). In this study, when siRNA reduced AMPK level, APN-induced growth is significantly inhibited.

Another study of modification of APN levels in PC-3 cells supported that APN activates AMPK / TSC2 to inhibit mTOR-mediated angiogenesis and PC development. The relationship between APN receptors and PC has also been examined by many investigators. Mistry et al. (22) firstly showed AdipoR1 and AdipoR2 expression in prostate cancer and APN being a protective response against tumor progression. However, another study performed by Rider et al. (23) revealed that APN activates the adenosine triphosphate (ATP)-stimulated, protein kinase (AMPK) is a key part of the signaling cascade downstream of AMPK, which is the mammalian homologue of the target of rapamycin (mTOR), vascular endothelial growth factor A (VEGF-A) and fatty acid synthase (FAS), all of which are involved in the regulation of cell proliferation. In PC-3 cells, activation of AMPK by APN is associated with reduction in mTOR activation, which reduces protein translation and inhibits cell growth (34). In this study, when siRNA reduced AMPK level, APN-induced growth is significantly inhibited.

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Potential mechanisms of adiponectin in prostate cancer

Recent advances suggested that APN plays a role in carcinogenesis through numerous mechanisms, including inhibiting proliferation and inducing apoptosis (19, 20, 34–42). Recent studies have shown that activation of the adenine monophosphate-activated protein kinase (AMPK) is a key part of the signaling cascade downstream of APN receptor (20, 34–36). The proteins downstream of AMPK include a tumor suppressor, tumor necrosis factor-α, the mammalian homologue of the target of rapamycin (mTOR), vascular endothelial growth factor A (VEGF-A) and fatty acid synthase (FAS), all of which are involved in the regulation of cell proliferation. In PC-3 cells, activation of AMPK by APN is associated with reduction in mTOR activation, which reduces protein translation and inhibits cell growth (34). In this study, when siRNA reduced AMPK level, APN-induced growth is significantly inhibited.
Table 1 - Recent Studies showing the association between APN concentrations and risk of PC.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Sample numbers</th>
<th>APN levels / OR</th>
<th>Comments / Conclusion</th>
<th>Other findings</th>
<th>TS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gotlands S (15)</td>
<td>30 PC</td>
<td>5.3 ± 1.6 µg/mL</td>
<td>APN concentrations are lower in PC than BPH or in control subjects</td>
<td>APN are negatively associated with the histologic grade and disease stage of PC</td>
<td>CC</td>
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<tr>
<td></td>
<td>41 BPH</td>
<td>14.5 ± 4.4 µg/mL</td>
<td></td>
<td></td>
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<td></td>
<td>36 Con</td>
<td>16.2 ± 4.1 µg/mL</td>
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<tr>
<td>Michalakis K (16)</td>
<td>75 PC</td>
<td>7.4 ± 5.0 µg/mL</td>
<td>Higher plasma APN concentrations are associated with a decreased risk of PC</td>
<td>AdipoR1 and AdipoR2 in cancerous were weaker expressed compared with healthy prostate tissue</td>
<td>CC</td>
</tr>
<tr>
<td></td>
<td>75 BPH</td>
<td>11.5 ± 6.4 µg/mL</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>150 Con</td>
<td>12.8 ± 8.0 µg/mL</td>
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<tr>
<td>Schenk JM. (17)</td>
<td>698 BPH</td>
<td>OR = 0.43</td>
<td>High APN concentrations were associated with reduced risk of BPH</td>
<td>Neither C-peptide nor leptin was associated with BPH risk</td>
<td>NCC</td>
</tr>
<tr>
<td></td>
<td>709 Con</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Li H (18)</td>
<td>654 PC</td>
<td>Q1: 2.7 µg/mL</td>
<td>Higher APN concentrations have a lower risk for developing high-grade or metastatic cancer</td>
<td>Leptin was unrelated to PC risk or mortality</td>
<td>NCC</td>
</tr>
<tr>
<td></td>
<td>644 Con</td>
<td>Q2: 6.3 µg/mL</td>
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<td></td>
<td></td>
<td>Q3: 13.3 µg/mL</td>
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<td></td>
<td>618 BPH</td>
<td>Q4: 31.0 µg/mL</td>
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<tr>
<td></td>
<td>775 BPH</td>
<td>Q5: 66.4 µg/mL</td>
<td></td>
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<tr>
<td>Tan W (19)</td>
<td>96 PC</td>
<td>Low level of APN</td>
<td>Decreased APN level was significantly associated with high GS</td>
<td>APN may function as a tumor suppressor through inhibiting EMT of PC cells</td>
<td>CC</td>
</tr>
<tr>
<td></td>
<td>15 BPH</td>
<td>APN was significantly decreased in PC compared with that of BPH tissues</td>
<td>Decreased APN level was significantly associated with high GS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GS = 7: 150f 26 (69%)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>GS = 7: 320f 43 (74%)</td>
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<tr>
<td>Medina EA (22)</td>
<td>220 PC</td>
<td>OR = 0.62</td>
<td>Only HMW APN decreased the risk of PC in obese man</td>
<td>HMW increased the risk of PC in normal and overweight men</td>
<td>NCC</td>
</tr>
<tr>
<td></td>
<td>239 Con</td>
<td></td>
<td></td>
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<tr>
<td>Baillargeon J (23)</td>
<td>125 PC</td>
<td>17.9 ± 0.6 µg/mL</td>
<td>APN was not significant associated with PC risk</td>
<td>BMI was not associated with incident PC</td>
<td>NCC</td>
</tr>
<tr>
<td></td>
<td>125 Con</td>
<td>19.9 ± 13.2 µg/mL</td>
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<td></td>
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<tr>
<td>Stevens VL. (24)</td>
<td>272 PC</td>
<td>OR = 1.11</td>
<td>APN was not associated with risk of aggressive PC</td>
<td>C-peptide was not associated with risk of aggressive prostate cancer</td>
<td>NCC</td>
</tr>
<tr>
<td></td>
<td>272 Con</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Nata A. (25)</td>
<td>24 PC</td>
<td>9.96 µg/mL</td>
<td>APN was significantly and positively associated with PSA levels</td>
<td>High APN increased the incidence of low or intermediate-risk PC in obese man</td>
<td>CS</td>
</tr>
<tr>
<td></td>
<td>2817 Con</td>
<td>7.84 µg/mL</td>
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</table>

APN = adiponectin; PC = prostate cancer; BPH = benign prostatic hyperplasia; Con = Control; TS = type of study; CC = case – control; NCC = nested-case-control; CS = cross-sectional; OR = odds ratio; Q5 = Highest quintile; Q3 = intermediate Quintile; OR = lowest quintile; GS = Gleason score; PSA = prostate-specific antigen.

Further, APN significantly inhibits cell proliferation induced by leptin. Different leptin / adiponectin ratios resulted in varying inhibitory effects on PC cells, indicating the balance between APN and leptin might effectively modulate PC cell growth. APN can attenuate the adverse effects of leptin and inhibit LNCaP and PC3 proliferation via modulation of p53 and bcl-2 expression (41), hence the balance of leptin and APN may be important in driving obesity-related PC progression.

Oxidative stress (OS) is a key event in the initiation, development and progression of PC. APN increased cellular anti-oxidative defense mechanisms and inhibited OS via increasing NADPH oxidase NOX2 and NOX4 expression in human 22Rv1 and DU-145 PC cell lines (42). Despite an increasing accumulation of experimental data, the mechanisms underlying the anti-proliferative and tumor-suppressing effects of APN are still not fully understood, more studies are needed. The role of APN in PC is summarized in Figure-1.

Clinical values of Adiponectin for prostate cancer patients

Based on the signaling pathway conducted by APN and its receptors, APN might represent a promising therapeutic target. Currently, the administration of APN or direct antagonist has not been reported in the literature for the treatment of human cancers. A strategy for the future treatment of PC patients with hypoadiponectinemia may include the upregulation of APN levels, APN receptors, or the development of APN receptor agonists.

Tangible benefits may come from the anti-diabetic drug Metformin. Metformin partially mimicked APN action and activated AMPK signaling in PC-3 cells, with reduction of MTOR activity thus inhibition of cell growth, suggesting that Metformin might have particular value in attenuating the adverse effects of hypo-adiponectinemia in PC (34). Metformin therapy has been correlated with reduced risk of prostate cancer in Caucasian / white men with diabetes (43) and with a survival benefit after diagnosis (44). These results underscore the importance for further studies to evaluate metformin in PC. Plasma APN levels can also be upregulated by thiazolidinediones (TZDs), such as pioglitazone, rosiglitazone, a class of PPAR-γ agonists and medicine used in the treatment of type II diabetes (TZD). Clinically, Metformin and thiazolidinediones therapy improved survival of diabetic prostate cancer patients (83).

Down-regulation of APN in PC tissues and LNCaP cells owing to highly methylation in its promoter, and 5-AZA restored its expression in vitro. Thus, methylation of APN promoter may be a key factor for evaluation of PC, and 5-AZA may be a promising stimulator of APN (19). Zorn CS et al. (46) reported that 5-AZA improves survival in the transgenic adenocarcinoma of the mouse prostate (TRAMP) model.

Recent research suggested that diet pattern as well as physical activity might increase expression of APN and delay disease progression in PC patients (47, 48). Hence, moderate physical exercise, reduction of body fat, associated with restriction of calories in diet are recommended for obesity-related prostate cancer prevention.

Another potential therapeutic molecule is the APN receptor agonist. Agonists have been developed and tested to treat multiple diseases related to hypoadiponectinemia, diabetes and other malignancies (49, 50). ADP355, a first-in-class APN receptor agonist, restricted proliferation in several APN receptor-positive cancer cell lines, and suppressed the growth of established tumors by 31% in vivo (49). ADP355, with similar effects to APN, increased apoptosis while inhibiting pancreatic cell proliferation and colony formation. In vivo, treatment of mice with AdipoRon inhibits orthotropic pancreatic tumor growth (50). APN receptor agonists may represent novel therapeutic strategies for PC in future.
Figure 1 - Signaling pathways of adiponectin in prostate cancer cells.

CONCLUSIONS

Numerous studies supporting the notion that APN acts as a protective and safe factor to prevent progression of PC, but few studies may indicate otherwise. We summarized the mechanisms underlying the anti-proliferative and tumor-suppressing effects of APN specifically in PC without reiterating other types of cancers. The signaling pathways linking APN with tumorigenesis involve several key molecules, including AdipoRs, AMPK, JNK, NOX, NF-kB, and TSC2 = tuberous sclerosis complex 2; mTOR = mammalian target of rapamycin; NF-kB = nuclear factor-KB; NOX = NADPH oxidase; OS = oxidative stress; ↓ indicates stimulation; ➣ indicates inhibition.

REFERENCES


CONFLICT OF INTEREST

None declared.


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