ORIGINAL ARTICLE

Insulin-like growth factor 1 related pathways and high-fat diet promotion of transgenic adenocarcinoma mouse prostate (TRAMP) cancer progression

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KEYWORDS
High-fat diet; Insulin like growth factor; Prostate cancer; TRAMP

Abstract

Introduction: We aimed to investigate the role of IGF-1 related pathway in high-fat diet (HFD) promotion of TRAMP mouse PCa progression.

Methods: TRAMP mice were randomly divided into two groups: HFD group and normal diet group. TRAMP mice of both groups were sacrificed and sampled on the 20th, 24th and 28th week, respectively. Serum levels of insulin, IGF-1 and IGF-2 were tested by ELISA. Prostate tissue of TRAMP mice was used for both HE staining and immunohistochemical staining of IGF-1 related pathway proteins, including IGF-1Rα, IGF-1Rβ, IGFBPs and AKT.

Results: The mortality of TRAMP mice from HFD group was significantly higher than that of normal diet group (23.81% and 7.14%, P = 0.035). The tumor incidence of HFD TRAMP mice at 20th week was significantly higher than normal diet group (78.57% and 35.71%, P = 0.022). Serum IGF-1 level of HFD TRAMP mice was significantly higher than that of normal diet TRAMP mice. Serum IGF-1 level tended to increase with HFD TRAMP mice’s age. HFD TRAMP mice had higher positive staining rate of IGF-1Rα, IGF-1Rβ, IGFBP3 and Akt than normal diet TRAMP mice.

Conclusions: IGF-1 related pathway played an important role in high-fat diet promotion of TRAMP mouse PCa development and progression.

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PALABRAS CLAVE
Dieta alta en grasa; Factor de crecimiento tipo insulina; Cáncer de próstata; TRAMP

Vías relacionadas con IGF-1 (Insulin-like growth factor-1) y promoción de dieta alta en grasas en la progresión del cáncer de próstata en ratones TRAMP (Transgenic Adenocarcinoma of the Mouse Prostate)

Resumen

Introducción: Nuestro objetivo fue investigar el papel de las vías relacionadas con IGF-1 en la promoción de dieta alta en grasas (DAG) de la progresión del cáncer de próstata en ratones TRAMP.

Métodos: Los ratones TRAMP fueron divididos aleatoriamente en 2 grupos: el grupo DAG y el grupo de dieta normal. Los ratones TRAMP de ambos grupos fueron sacrificados y se tomaron muestras en las semanas 20, 24 y 28, respectivamente. Los niveles séricos de insulina, IGF-1 e IGF-2 se probaron mediante ELISA. El tejido prostático de los ratones TRAMP se utilizó tanto para tinción H-E como para tinción inmunohistoquímica de proteínas de la vía relacionadas con IGF-1, incluyendo IGF-1Rα, IGF-1Rβ, IGFBPs y AKT.

Resultados: La mortalidad de los ratones TRAMP del grupo DAG fue significativamente más alta que la del grupo de dieta normal (23,81% y 7,14%, p=0,035). La incidencia de tumores de los ratones TRAMP de DAG a la semana 20 fue significativamente mayor que en el grupo de dieta normal (78,57% y 35,71%, p=0,022). El nivel sérico de IGF-1 de los ratones TRAMP de DAG fue significativamente mayor que el de los ratones TRAMP de dieta normal. El nivel sérico de IGF-1 tendió a aumentar con la edad de los ratones TRAMP de DAG. Los ratones TRAMP de DAG tenían una tasa de tinción positiva más elevada de IGF-1Rα, IGF-1Rβ, IGFBP3 y AKT que los ratones TRAMP de dieta normal.

Conclusiones: La vía relacionada con IGF-1 ejerció un papel importante en la promoción de la dieta de alto contenido en grasa del desarrollo y la progresión del CaP de ratón TRAMP.

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Introduction

Prostate cancer (PCa) is one of the most frequently diagnosed malignant tumors among men worldwide. Meanwhile, the incidence and mortality of PCa vary from place to place. The United States or Europe seem to have relatively higher incidence and mortality from PCa than Asia, including China, Japan, and Korea. The difference may partly be due to genetic polymorphism in the androgen receptor and androgen metabolism pathway enzymes. The incidence of PCa of Asian immigrants in the United States is also higher than that of native Asians. Another interesting phenomenon is also revealed, which is that the difference in incidence of PCa between native Americans and Asian immigrants is getting smaller, reflecting possible changes of lifestyle and environmental risk factors in Asian immigrants. In addition, a rapid increasing trend of PCa incidence was observed in Asia according to recent epidemiological research. Taking into consideration westernization of both lifestyle and dietary habits in Asia, all this evidence suggests that lifestyle or environmental factors may also contribute to PCa development and progression. High caloric intake, especially high-fat diet, is one of the main characteristics of western lifestyle. Increased fat intake has been regarded as a major cause of the increasing incidence and mortality of PCa and the reason of higher PCa incidence in western countries.

Some researchers have tried to investigate the relationship between high-fat diet (HFD) and PCa. Several epidemiology studies identified weak and positive association between total fat intake and PCa risk, particularly in advanced PCa. A facilitative effect of a HFD on PCa progression was also observed in both rats and human PCa cell transplanted rodent models. But few clarified the potential mechanism of it.

Numerous mechanisms could contribute to PCa development and progression. Several experiments have been performed to investigate the effect of a high-fat diet (HFD) on PCa development. HFD can contribute to metabolic disorders, such as obesity, diabetes, and insulin resistance, indicating that HFD is associated with insulin-related pathways. Insulin and insulin-like growth factors are reported to be responsible for increased risk of PCa. Insulin-like growth factor 1 (IGF-1) is a peptide growth factor and a potent mitogen for the growth of human PCa cell lines. IGF-1 is found to play an important role in regulating cell proliferation, differentiation, as well as apoptosis via binding to the IGF-1 receptor (IGFR1) and activating the PI3K/Akt and Ras/raf/mitogen-activated protein kinase (MAPK) pathways. IGF-1 bioactivity is regulated by serum concentrations of the various IGF binding proteins (IGFBPs), of which IGFBP-3 is the predominant one. Elevating IGFBP-3 concentrations would result in lower free IGF-1. High concentration of both insulin and IGF-1 was reported to be associated with increased PCa incidence. IGFBP-3 was also found to be negatively associated with PCa incidence. These indicate that IGF-1 related pathway may play an important role in PCa development and progression. Transgenic adenocarcinoma mouse prostate (TRAMP) animal is one of the best characterized models for PCa. TRAMP succeeds in resembling the development and progression of PCa in humans. The TRAMP model was generated using...
the minimal probasin (PB) –426/+28 regulatory sequence to restrict SV40 early gene (T and t antigens; Tag) expression in the prostatic epithelium. Prostatic intraepithelial neoplasia (PIN) and rarely PCa can be detected in TRAMP mice as early as 10–12 weeks of age. Invasive prostate adenocarcinoma can be shown at 18–20 weeks of age. By 30–36 weeks of age, almost all TRAMP mice develop PCa, and some may also develop metastasis to other organs such as lymph nodes, lungs, and bone.32

In this study, we aim to clarify whether HFD was related to the PCa development and progression of TRAMP mice. We further investigate the role of IGF-1 related pathways in the impact of HFD on PCa TRAMP mice.

Materials and methods

Animals and diets

All animal studies were approved by the Institutional Animal Care and Use Committee from the Huashan Hospital, Fudan University. Mice were kept on a 12-h light/dark cycle with ad libitum access to food and water. TRAMP mice were obtained from Jackson Laboratory (Bar Harbor, Maine, USA). Generation of transgenic mice, isolation of mouse-tiptoe DNA, and PCR-based screening assay were performed as previously reported.33 From 20 days of age, all mice were randomly separated into two groups and started to feed with normal diet and HFD. Both normal diet group (control group) and HFD group (experimental group) contained 42 TRAMP mice. As shown in Table 1, normal diet consisted of 16% calories from fats, 64% from carbohydrates, and 20% from proteins. HFD comprised 40% calories obtained from fats, 40% from carbohydrates, and 20% from proteins.

Tissue preparation

TRAMP mice from both groups were divided into three subgroups, which were planned to be euthanized and sampled on the 20th, 24th and 28th week, respectively, by asphyxiation of CO2. Each subgroup contained 14 mice. TRAMP mice were required to fast overnight before sacrifice. Blood was taken from the portal vein by 1 mL syringe. Fasting blood glucose (FBG) was measured immediately and the prostate was then quickly excised. Blood was centrifuged at 13,000 rpm for 10 min in a refrigerated centrifuge, and serum was collected to a new eppendorf tube. Both serum and prostate tissue were kept frozen at −80 °C.

Table 1  Energy and nutrient composition of diets (g%).

<table>
<thead>
<tr>
<th>Diet</th>
<th>Normal diet</th>
<th>HFD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein</td>
<td>20</td>
<td>22</td>
</tr>
<tr>
<td>Fat</td>
<td>7</td>
<td>20</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>64</td>
<td>45</td>
</tr>
<tr>
<td>Energy (Kcal/100 g)</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Protein (%)</td>
<td>16</td>
<td>40</td>
</tr>
<tr>
<td>Carbohydrate (%)</td>
<td>64</td>
<td>40</td>
</tr>
</tbody>
</table>

Serum studies

The levels of murine insulin, IGF-1, and IGF-2 were measured using mouse-specific ELISA as previously described.13,26,27 The mouse insulin assay has a sensitivity of 30 pg/mL and has no cross-reactivity with human insulin. The intraassay and interassay coefficient of variations are <10% in the range from 1 to 6 ng/mL. The mouse IGF-1 assay has a sensitivity of 1 ng/mL and no cross-reactivity with mouse IGF-2 or human IGF-1. The intraassay and interassay coefficient of variations are <10%, in the range from 1 to 10 ng/mL. The mouse IGF-2 assay has a sensitivity of 16 pg/mL and no cross-reactivity with mouse IGF-1 or human IGF-2. The intraassay and interassay coefficient of variations are <10%, in the range from 1 to 6 ng/mL.

Immunohistochemistry

Prostate tissues were fixed in 10% buffered formalin, processed in an alcohol-xylene series, and embedded in paraffin. Sections were cut at 2 μm, stained with hematoxylin and eosin (H&E). Immunohistochemistry of representative tumor sections was performed for IGF-1Rα (# sc-712, Santa Cruz Biotechnology Inc., Santa Cruz, CA), IGF-1Rβ (# sc-713, Santa Cruz Biotechnology Inc., Santa Cruz, CA), IGFBP1 (# sc-13097, Santa Cruz Biotechnology Inc., Santa Cruz, CA), IGFBP2 (# sc-6001, Santa Cruz Biotechnology Inc., Santa Cruz, CA), IGFBP3 (# sc-9028, Santa Cruz Biotechnology Inc., Santa Cruz, CA), IGFBP5 (# sc-6006, Santa Cruz Biotechnology Inc., Santa Cruz, CA), IGFBP6 (# sc-13094, Santa Cruz Biotechnology Inc., Santa Cruz, CA) and Akt (# sc-8312, Santa Cruz Biotechnology Inc., Santa Cruz, CA). Each slide was deparaffinized and rehydrated according to the standard protocol, and treated with 10 mM sodium citrate buffer in a microwave pressure cooker at 120 °C for 15 min. Sections were then immersed in 3% hydrogen peroxide and nonspecific binding was blocked in 5% normal goat serum. Polyclonal antibodies (rabbit anti-IGF-1Rα, rabbit anti-IGF-1Rβ, rabbit anti-IGFBP1, goat anti-IGFBP2, rabbit anti-IGFBP3, goat anti-IGFBP5, rabbit anti-IGFBP6, and rabbit anti-Akt) were diluted 1:100. Immunohistochemical staining was conducted following the avidin-biotin peroxidase complex method with diaminobenzidine as a chromogen. Slides were counterstained with hematoxylin, dehydrated and mounted. Brown cytoplasmic staining of stromal or tumor cells was considered positive.

Statistical analysis

The results are expressed as mean ± SD. Statistical analysis was performed using t-test, Fisher exact test or X2-test by SPSS 17.0. The difference is considered statistically significant when the P value is <0.05.

Results

Mortality rate and tumor formation rate

During our study, 13 deaths of TRAMP mice were observed, of which three were from normal diet group and 10 were
from HFD group. Mortality rate of both groups was listed in Table 2. The mortality rate of HFD group was 23.81%, which was significantly higher than that of normal diet group (7.14%, P = 0.035).

Among the three dead TRAMP mice which were fed on normal diet, one was from the 24th week subgroup, and the other two were from the 28th week subgroup. While among the 10 dead TRAMP mice which were fed on HFD, four were from the 24th week subgroup, and the other six were from the 28th week subgroup. All the TRAMP mice were sampled including both scheduled euthanized ones and the 13 dead ones. But only those scheduled TRAMP mice were included for tumor formation rate analysis.

At 20 weeks of age, 11 (78.57%) TRAMP mice from HFD group had developed histologically confirmed Pca, while only 5 (35.71%) TRAMP mice from normal diet group had Pca. Tumor formation rate at 20th week of age of HFD group was significantly higher than that of normal diet group (P = 0.022). However, tumor formation rates at both 24th and 28th week of age were similar between the two groups as shown in Table 3.

### Fasting blood glucose and serum study

FBG level as well as serum level of insulin, IGF-1 and IGF-2 were listed in Table 4. No significant difference of FBG, serum insulin, and serum IGF-2 was observed between HFD group and normal diet group at the 20th, 24th and 28th week of age. However, HFD group had significantly higher serum level of IGF-1 at both 24th and 28th weeks of age than normal diet group (P = 0.018 for 24th week, P = 0.011 for 28th week). As the age of HFD mice increased, a moderate rising trend of serum level of IGF-1 was discovered (Fig. 1).

### Immunohistochemistry of IGF-1 related proteins

As shown in Fig. 2A–H, both IGF-1Rα and IGF-1Rβ were mainly expressed in prostate epithelial cells. In normal diet group, 14 samples (43.75%) had IGF-1Rα positive staining in prostate epithelial cells, five samples (15.63%) had IGF-1Rβ positive staining in prostate interstitial cells, and five samples (15.63%) had IGF-1Rβ positive staining in prostate epithelial cells, five samples (15.63%) had IGF-1Rβ positive staining in prostate interstitial cells, and five samples (15.63%) had IGF-1Rβ positive staining in prostate interstitial cells.

Table 2 Mortality rate of TRAMP mice.

<table>
<thead>
<tr>
<th>Mortality</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HFD group</td>
<td>Normal diet group</td>
</tr>
<tr>
<td>n = 42</td>
<td>n = 42</td>
</tr>
<tr>
<td>n</td>
<td>10</td>
</tr>
<tr>
<td>%</td>
<td>23.81</td>
</tr>
</tbody>
</table>

Table 3 Tumor formation rate of TRAMP mice.

<table>
<thead>
<tr>
<th></th>
<th>HFD group</th>
<th></th>
<th>Normal diet group</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total number</td>
<td>PCa number</td>
<td>%</td>
<td>Total number</td>
</tr>
<tr>
<td>20th week</td>
<td>14</td>
<td>5</td>
<td>35.71</td>
<td>14</td>
</tr>
<tr>
<td>24th week</td>
<td>13</td>
<td>12</td>
<td>92.31</td>
<td>10</td>
</tr>
<tr>
<td>28th week</td>
<td>12</td>
<td>12</td>
<td>100</td>
<td>8</td>
</tr>
</tbody>
</table>

* P = 0.022.

Figure 1 Serum IGF-1 level in HFD TRAMP mice.

IGF-1Rα positive staining in prostate interstitial cells, and five samples (15.63%) had IGF-1Rα positive staining in both prostate epithelial cells and interstitial cells. However, in HFD group, 31 samples (79.49%) had IGF-1Rα positive staining in prostate epithelial cells, nine samples (23.08%) had IGF-1Rα positive staining in prostate interstitial cells, and eight samples (20.51%) had IGF-1Rα positive staining in both prostate epithelial cells and interstitial cells. The rate of IGF-1Rα positive staining of prostate epithelial cells was significantly higher in HFD TRAMP mice than that in normal diet TRAMP mice (P = 0.034).

As for IGF-1Rβ (Fig. 2E–H), 16 samples (50%) had IGF-1Rβ positive staining in prostate epithelial cells, six samples (18.75%) had IGF-1Rβ positive staining in prostate interstitial cells, and six samples (18.75%) had IGF-1Rβ positive staining in prostate epithelial cells and interstitial cells. The rate of IGF-1Rβ positive staining of prostate epithelial cells was significantly higher in HFD TRAMP mice than that in normal diet TRAMP mice (P = 0.034).

IGFBP3 was mainly expressed in prostate interstitial cells (Fig. 2I–L). In normal diet group, 14 samples (43.75%) had IGFBP3 positive staining in prostate epithelial cells, 17 samples (53.13%) had IGFBP3 positive staining in prostate interstitial cells, and 14 samples (43.75%) had IGFBP3 positive staining in both prostate epithelial cells and interstitial cells. However, in HFD group, 27 samples (69.23%) had IGFBP3 positive staining in prostate epithelial cells, 32...
Table 4  Fasting blood glucose, insulin, IGF-1 and IGF-2 of TRAMP mice.

<table>
<thead>
<tr>
<th>Week</th>
<th>FBG (mg/mL)</th>
<th>Insulin (pg/mL)</th>
<th>IGF-1 (ng/mL)</th>
<th>IGF-2 (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal diet group 20</td>
<td>16.03 ± 6.59</td>
<td>21.68 ± 8.36</td>
<td>207.78 ± 173.38</td>
<td>3529.06 ± 1460.74</td>
</tr>
<tr>
<td>HFD group 20</td>
<td>16.83 ± 2.87</td>
<td>21.62 ± 3.76</td>
<td>245.92 ± 172.44</td>
<td>2426.30 ± 2609.17</td>
</tr>
<tr>
<td>Normal diet group 24</td>
<td>15.89 ± 4.01</td>
<td>18.30 ± 11.65</td>
<td>307.36 ± 107.82</td>
<td>3128.70 ± 2812.29</td>
</tr>
<tr>
<td>HFD group 24</td>
<td>16.14 ± 4.55</td>
<td>22.47 ± 6.85</td>
<td>757.51 ± 617.86</td>
<td>3861.86 ± 3014.77</td>
</tr>
<tr>
<td>Normal diet group 28</td>
<td>18.12 ± 4.35</td>
<td>20.47 ± 7.19</td>
<td>357.63 ± 121.45</td>
<td>3027.65 ± 2829.47</td>
</tr>
<tr>
<td>HFD group 28</td>
<td>18.91 ± 7.10</td>
<td>19.18 ± 7.82</td>
<td>625.56 ± 330.83</td>
<td>5056.58 ± 4201.37</td>
</tr>
</tbody>
</table>

a \( P = 0.018 \).
b \( P = 0.011 \).

Figure 2  IGF-1Rα, IGF-1Rβ, IGFBP3, and Akt staining of TRAMP mice prostate cancer. (A) Negative IGF-1Rα staining of both prostate epithelial cells and interstitial cells in normal diet group. (B) Positive IGF-1Rα staining of prostate epithelial cells in normal diet group. (C) Negative IGF-1Rα staining of both prostate epithelial cells and interstitial cells in HFD group. (D) Positive IGF-1Rα staining of prostate epithelial cells in HFD group. (E) Negative IGF-1Rβ staining of both prostate epithelial cells and interstitial cells in normal diet group. (F) Positive IGF-1Rβ staining of prostate epithelial cells in normal diet group. (G) Negative IGF-1Rβ staining of both prostate epithelial cells and interstitial cells in HFD group. (H) Positive IGF-1Rβ staining of prostate epithelial cells in HFD group. (I) Negative IGFBP3 staining of both prostate epithelial cells and interstitial cells in normal diet group. (J) Positive IGFBP3 staining of both prostate epithelial cells and interstitial cells in normal diet group. (K) Negative IGFBP3 staining of both prostate epithelial cells and interstitial cells in HFD group. (L) Positive IGFBP3 staining of both prostate epithelial cells and interstitial cells in HFD group. (M) Negative Akt staining of both prostate epithelial cells and interstitial cells in normal diet group. (N) Positive Akt staining of prostate epithelial cells in normal diet group. (O) Negative Akt staining of both prostate epithelial cells and interstitial cells in HFD group. (P) Positive Akt staining of prostate epithelial cells in HFD group.
samples (82.05%) had IGFBP3 positive staining in prostate interstitial cells, and 26 samples (66.67%) had IGFBP3 positive staining in both prostate epithelial cells and interstitial cells. The rates of IGFBP3 positive staining of both prostate epithelial cells and interstitial cells were significantly higher in HFD TRAMP mice than that in normal diet TRAMP mice ($P = 0.031$ and $P = 0.009$).

AKT was mainly expressed in prostate epithelial cells (Fig. 2M–P). In normal diet group, 18 samples (56.25%) had AKT positive staining in prostate epithelial cells, four samples (12.50%) had AKT positive staining in prostate interstitial cells, and three samples (9.38%) had AKT positive staining in both prostate epithelial cells and interstitial cells. However, in HFD group, 31 samples (79.49%) had AKT positive staining in prostate epithelial cells, seven samples (17.95%) had AKT positive staining in prostate interstitial cells, and four samples (10.26%) had AKT positive staining in both prostate epithelial cells and interstitial cells. The rate of AKT positive staining of prostate epithelial cells was significantly higher in HFD TRAMP mice than that in normal diet TRAMP mice ($P = 0.035$).

Other IGFBPs also expressed in TRAMP mice prostate as listed in Table 5. However, there was no significant difference between normal diet group and HFD group.

### Discussion

Our study revealed that HFD increased both mortality rate and tumor formation rate of TRAMP mice, indicating that HFD influenced PCa development and progression. Some earlier studies by using chemically induced cell lines or xenograft model transplanted rodent models of PCa suggested that HFD could promote PCa development. A few TRAMP mice studies also showed a similar result, that HFD was related with PCa development. Park et al. found that TRAMP mice fed on HFD had progressed neoplastic lesions in the prostate compared to control group. Saw et al. reported that TRAMP mice fed on HFD had significantly increased prostate tumor weight, higher incidence of palpable tumors and carcinomas, as well as higher metastasis rate.

Both experimental and epidemiological studies have been carried out to examine the interactions between PCa and diet. Increased fat intake, as one of the important dietary components, is considered to play a vital role in promoting PCa progression. Increased fat intake and obesity is associated with hyperinsulinemia, insulin resistance, as well as IGF-1. Among these metabolic influences, IGF-1 is a peptide growth factor and a potent mitogen for the growth of human PCa cell lines. We measured serum IGF-1 level as well as expressions of other IGF-1 related proteins in TRAMP mice prostate to investigate the role of IGF-1 related pathways in HFD and TRAMP PCa development and progression. We found that HFD TRAMP mice had significantly higher serum IGF-1 level, as well as higher positive expression rate of prostate staining of IGF-1/α, IGF-1R/β, IGFBP3 and Akt, indicating that IGF-1 and IGF-1 related pathways might have a crucial impact on HFD promotion of PCa TRAMP mice development and progression.

Several studies also tried to reveal whether IGF-1 related pathways had an important impact on the relationship between HFD and PCa. Freedland et al. compared survival time of PCa xenograft mice of three different dietary treatment groups, which were carbohydrate ketogenic diet group (84% fat, 0% carbohydrate, 16% protein kcal), low-fat diet group (12% fat, 72% carbohydrate, 16% protein kcal), and Western diet group (40% fat, 44% carbohydrate, 16% protein kcal), and found that mice from Western diet group had shortest survival time, with highest serum insulin and IGF-1 levels. A similar finding was reported by Venkateswaran et al., that LNCaP xenograft athymic mice from high carbohydrate-high fat diet group had increased tumor growth and experienced a statistically significant increase in serum insulin and IGF-1 levels. Besides, tumors of mice from high carbohydrate-high fat diet group had higher levels of activated AKT and modestly higher insulin receptor levels. Kobayashi et al. fed mice with low-fat diet and found that the development of invasive murine PCa was delayed accompanied with down-regulation of the Akt-mTOR pathway. These results were consistent with our study. Up-regulated IGF-1 and Akt pathway might contribute to the promotion of PCa development and progression when exposed to HFD.

Besides, there were some other interesting studies. Thomas et al. tried to study the mouse survival and tumor volumes between Western diet group (40% fat, 44% carbohydrate, 16% protein kcal) and Western diet with intermittent fasting group (twice-weekly 24 h fasts). However, there was no difference in mouse survival or tumor volumes between groups. Intermittent fasting mice had significantly higher serum IGF-1 levels. Though increased fat intake and caloric intake might promote PCa development and progression, intermittent fasting seemed not to improve mouse survival, nor did it delay prostate tumor growth. The detailed mechanism was not clarified yet, but the proper explanation might be the metabolic adaptations to the 24 h fasting periods. What is more, Lloyd et al. found that besides the previous opinion that the amount of fat is important for PCa growth,
the type of dietary fat consumed was also crucial. LAPC-4 xenograft mice fed on fish oil as the only fat source had slower tumor growth and improved survival compared with that in mice consuming diets composed of olive oil, corn oil or animal fat.47

Conclusions

Taken together, the results of this study strongly suggest that HFD intake could promote PCa development and progression. Elevated serum IGF-1 level and activated IGF-1 related pathways had vital impact on HFD promotion of PCa development and progression. Among all the PCa risk factors, dietary components are supposed to be the ones which can be regulated easily compared with other factors, like aging, genetics, family history, and hormones. Our data provide strong evidence that the regulation of dietary components, especially restriction of fat intake, can delay the development and progression of PCa.

Conflict of interest

The authors declare that they have no conflict of interest.

References