Differential expressions of integrin-linked kinase, β-parvin and cofilin 1 in high-fat diet induced prostate cancer progression in a transgenic mouse model

MENG-BO HU¹*, JI-MENG HU¹*, LI-REN JIANG2, TIAN YANG¹, WEN-HUI ZHU¹, YUN HU¹, XIAO-BO WU¹, HAO-WEN JIANG¹ and QIANG DING¹

¹Department of Urology, Huashan Hospital, Fudan University, Shanghai 200040; ²Department of Pathology, Shanghai General Hospital, Shanghai Jiaotong University, School of Medicine, Shanghai 201620, P.R. China

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Abstract. High-fat diet induced obesity was associated with more aggressive prostate cancer. Recent research has demonstrated that integrin-linked kinase (ILK), β-parvin and downstream cofilin 1 jointly affected cancer progression. Meanwhile, these proteins were also involved in energy metabolism. Therefore, the present study was conducted to investigate the potential function of ILK, β-parvin and cofilin 1 in the high-fat diet-induced progression of prostate cancer. Transgenic mice with prostate cancer were employed, fed with different diets and sacrificed at 20 and 28 weeks. Tumor differentiation, extracapsular extension and metastasis were compared between the groups. Expression levels of ILK, β-parvin and cofilin 1 in prostate were evaluated by immunohistochemical analysis and determined by an immunoreactivity score. Public databases were applied for analysis and validation. It was detected that high-fat diet feeding promoted cancer progression in transgenic mice with prostate cancer, with increased expressions of β-parvin (P=0.038) and cofilin 1 (P=0.018). Higher expressions of ILK, β-parvin and cofilin 1 were also associated with poorer cancer differentiation. Additionally, higher mRNA levels of CFL1 were correlated with a worse disease-free survival in patients of certain subgroups from The Cancer Genome Atlas database. Further studies were warranted in discussing the potential roles of ILK, β-parvin and cofilin 1 in high-fat diet feeding induced progression of prostate cancer.

Introduction

Prostate cancer (PCa) recently ranked as the second most diagnosed malignancy and the fifth leading cause of cancer death in men globally (1). Its development and progression were closely associated with another global epidemic, obesity, as extensive evidence showed up demonstrating various epidemiological and biological associations (2). Obesity was proved to be associated with more aggressive PCa, e.g., higher pathological grade (3), higher recurrence rate after definitive therapy (4), and higher cancer-specific mortality (5). However, the exact molecular mechanisms contributing to obesity induced PCa progression remained largely unclear.

The progression and metastasis of cancer required cell mobilization and epithelial mesenchymal transition (EMT), involving the filopodium-like protrusions (FLPs) of cancer cells that interacted productively with surrounding microenvironment (6). The researchers identified that the activation of integrin-linked kinase (ILK), β-parvin, cofilin pathway could promote cancer progression, via enhancing the formation of FLPs and maintaining its existence, which raised a brand new perspective in cancer researches (6). Meanwhile, the signaling of ILK, β-parvin or cofilin were also involved in obesity and energy metabolism as recently proposed (7-9). Liu et al (7) discovered that oleic acid, with high levels in sera of obese patients, would activate ILK signaling pathway and therefore promote proliferation of renal cell carcinoma. It was also demonstrated that ILK might promote diet-induced insulin resistance in obese mice, by impairing insulin signaling and insulin perfusion through capillaries via ILK-PINCH-parvin complex (IPP) (8). Besides, Cofilin 1 (CFL1) gene expression was proved to be markedly elevated in patients with metabolic syndrome in Turkish population (9). Despite the complicated crosstalk and molecular network, these findings guided us to explore whether ILK/β-parvin/cofilin pathway played a role in obesity induced cancer progression.

To better elucidate the effect of obesity on development and progression of PCa, we applied high-fat diet (HFD) to induce obesity in transgenic adenocarcinoma of mouse prostate (TRAMP) animal model, which was considered the best model to resemble the natural process of PCa progression in obese subjects (10). We aimed to verify the hypothesis that

Correspondence to: Dr Hao-Wen Jiang, Department of Urology, Huashan Hospital, Fudan University, 12 Middle Wulumuqi Road, Shanghai 200040, P.R. China
E-mail: oncouro_jhw@126.com

*Contributed equally

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ILK/β-parvin/cofilin pathway would affect the cancer progression in obese patients. With public database, we endeavored to further validate the differential expressions of ILK, β-parvin and cofilin in PCAs, investigate their roles in cancer survival, and explore the possible molecular network.

Materials and methods

Animals and diets. The present study was carried out in strict accordance with the National Institutes of Health guide for the care and use of Laboratory animals (NIH Publications no. 8023, revised 1978). The protocol was approved by the Institutional Animal Care and Use Committee from Department of Laboratory Animal Science, Fudan University (20160816A197). The TRAMP mice were obtained from Jackson Laboratory (Bar Harbor, Maine, USA), bred and maintained under specific pathogen free conditions (SPF, Grade III) at Department of Laboratory Animal Science, Fudan University (Shanghai, China, certificate no. SCXK-HU-2014-0004). Each mouse was kept separately in a cage, bedding of cork dust, with a 12-hour light-dark cycle. All male TRAMP mice were selected by genotyping, and randomly admitted to two groups where the mice were fed with micronutrients-matched control diet (CD) or HFD ad libitum at 5 weeks of age as previously described (11). CD (16% calories from fat) and HFD (40% calories from fat) was supplied by Puluteng Bio-technology, Shanghai, China.

TRAMP mice were sacrificed at 20 or 28 weeks of the age, resulting in a total of four groups in the present study (CD-fed 20-week TRAMP, n=12; HFD-fed 20-week TRAMP, n=12; CD-fed 28-week TRAMP, n=12; HFD-fed 28-week TRAMP, n=12). The maximum diameter of tumor allowed was 1.5 cm, and none of tumors in the present study reached this diameter.

Systemic evaluation and tissue preparation. All TRAMP mice received body weight and blood glucose examinations before sacrifice. Then, the mouse underwent general anesthesia with intraperitoneal injection of pentobarbital (50 mg/kg), scanned by GE eXplore Locus micro-CT scanner (GE Healthcare Biosciences, Chicago, IL, USA) for systemic evaluation, and euthanized by asphyxiation of CO₂ (flow rate at 1.5 l/min). The prostate tumor, genitourinary tract, epididymal fat, enlarged lymph nodes, liver and lung were removed from the mouse, weighed, and fixed for further analysis.

Pathological and immunohistochemical analysis. Prostate and other prepared tissues were fixed in 10% buffered formalin, processed in an alcohol-xylene series, and embedded in paraffin. A series of sections were prepared with hematoxylin and eosin staining, for evaluation of tumor differentiation, extracapsular extension and confirmation of distant metastasis. The IHC was performed in mouse prostate, as presented in Table I. In 28-week group, the body weight of mice fed with HFD was higher than that fed with CD (34.2 g vs. 28.2 g, P<0.001). Meanwhile, the genitourinary weight was also higher in HFD-fed mice in 28-week group (1.54 g vs. 1.21 g, P<0.05). The epididymal fat weight was higher in HFD-fed mice in both 20-week (1.05 g vs. 0.53 g, P<0.01) and 28-week group (1.32 g vs. 0.58 g, P<0.01).

We further determined the development and progression of PCAs, by evaluating the tumor differentiation, extracapsular extension and metastasis (Table I). PCA formation was detected from all TRAMP mice in the present study. Compared with...
There was a trend towards poorer PCa differentiation in HFD-fed mice, whereas no statistical significance was detected. Moreover, HFD-fed mice suffered higher rates of extracapsular extension (20-week, 16.7% vs. 8.3%; 28-week, 66.7% vs. 50.0%), as well as higher rates of distant metastasis, e.g., retroperitoneal lymph nodes or lung metastasis (28-week, 41.7% vs. 25.0%). In quantitative analysis, the average positive margins of extracapsular extension and average sites of metastasis were both significantly higher in 28-week HFD-fed mice.

**Table I. Comparisons of systemic characteristics and tumor progression between control diet-fed and high-fat diet-fed TRAMP mice.**

| Variables                          | 20-week          | 28-week          | 20-week          | 28-week          |
|------------------------------------|------------------|------------------|------------------|------------------|
|                                   | Control diet     | High-fat diet    | Control diet     | High-fat diet    |
|                                   | (N=12)           | (N=12)           | (N=12)           | (N=12)           |
| Body weight (g)                   | 20.8±0.52        | 22.3±1.1         | 28.2±0.61        | 34.2±1.44f       |
| Blood glucose (mmol/l)            | 15.1±0.95        | 15.2±1.41        | 14.8±1.07        | 18.8±1.85        |
| Genitourinary weight (g)          | 0.86±0.06        | 1.02±0.08        | 1.21±0.07        | 1.54±0.13d       |
| Epididymal fat weight (g)         | 0.53±0.09        | 1.05±0.14c       | 0.58±0.1         | 1.32±0.22c       |
| Tumor diameter (mm)               | 6.17±0.19        | 6.08±0.17        | 7.67±0.16        | 8.17±0.25        |
| Tumor differentiation (%)         |                  |                  |                  |                  |
| Well                               | 50.0             | 41.7             | 8.3              | 8.3              |
| Moderate                           | 25.0             | 33.3             | 33.3             | 16.7             |
| Poor                               | 25.0             | 25.0             | 58.3             | 75.0             |
| Extracapsular extension (%)       | 8.3              | 16.7             | 50.0             | 66.7             |
| Extracapsular extension (positive margins per mouse prostate) | 0.08±0.08 | 0.33±0.22 | 0.75±0.25 | 1.83±0.46c |
| Metastasis (%)                    | 0                | 0                | 25.0             | 41.7             |
| Metastasis (sites per mouse)      | 0                | 0                | 0.33±0.19        | 2.75±1.09d       |

*Data presented as mean ± standard error of the mean.  
*Extracapsular extension was quantitatively evaluated based on the average number of margins that was invaded in mouse prostate (upper, lower, anterior, posterior, left, right).  
*Metastasis was quantitatively evaluated based on the average number of sites that was metastasized in distant organs.  
P<0.05, P<0.01 and P<0.001 high-fat diet vs. control diet fed TRAMP mice from the same week sub-group. TRAMP, transgenic adenocarcinoma of mouse prostate.

**Figure 1.** Representative IHC staining demonstrating ILK expression of different IRS category in TRAMP prostate and ILK levels compared among different prostate tissue and between different diet feeding. (A-D) Representatives images showing (A) negative (IRS category=0), (B) weak (IRS category=1), (C) moderate (IRS category=2) and (D) strong (IRS category=3) expressions of ILK in prostate specimens (magnification, x400). (E and F) Boxplots graphs showing the IRS category of ILK expression across benign prostate tissue, well-differentiated, moderately-differentiated and poorly-differentiated prostate cancer in 20-week and 28-week TRAMP mice, respectively. The horizontal line indicates the median and the central box indicates the inter-quartile range, with whiskers indicating the lowest and highest results. *P<0.05, significant differences are indicated as compared with benign subgroup. (G) Boxplots graphs showing the IRS category of ILK expression in prostate cancer between CD-fed and HFD-fed TRAMP mice of 20 and 28 weeks of age. The horizontal line and central box show the median and inter-quartile range, with whiskers indicating the lowest and highest result. ILK, integrin-linked kinase; TRAMP, transgenic adenocarcinoma of mouse prostate; IHC, immunohistochemistry; CD, control diet; HFD, high-fat diet; IRS, immunoreactivity score.

CD-fed mice, there was a trend towards poorer PCa differentiation in HFD-fed mice, whereas no statistical significance was detected. Moreover, HFD-fed mice suffered higher rates of extracapsular extension (20-week, 16.7% vs. 8.3%; 28-week, 66.7% vs. 50.0%), as well as higher rates of distant metastasis, e.g., retroperitoneal lymph nodes or lung metastasis (28-week, 41.7% vs. 25.0%). In quantitative analysis, the average positive margins of extracapsular extension and average sites of metastasis were both significantly higher in 28-week HFD-fed mice.

**Protein expression of ILK, β-parvin and coflin 1 in HFD-induced PCa progression.** The representative IHC images of ILK, β-parvin and coflin 1 in prostate specimens
(including benign prostate tissue and PCAs), with IRS category ranging from 0-3 were presented as reference, respectively (Figs. 1-3). The staining for ILK, β-parvis and cofilin 1 was mainly located at cytoplasm.

Compared to benign prostate tissue, the ILK immunoreactivity was stronger in poorly differentiated PCa in both 20-week and 28-week mice (Fig. 1E and F). Meanwhile, the expression of ILK presented with a slight increase in 28-week HFD-fed mice ( IRS category=2.50±0.67 vs. 2.00±0.74, P=0.242) (Fig. 1G) as compared with CD-fed mice.

Immunoactivity of β-parvis also increased steadily as PCa progressed, and was higher in poorly differentiated PCa than that in benign prostate tissue (Fig. 2E and F). In 28-week mice, the β-parvis expressions were also higher in HFD-fed group ( IRS category=2.25±0.62 vs. 1.50±0.80, P=0.038) (Fig. 2G).
As for cofilin 1 expression, we identified a higher IRS category in poorly-differentiated PCa in 20-week mice (Fig. 3), while no significant difference was detected in 28-week mice (Fig. 3F). Besides, the cofilin 1 expressions were higher in 28-week HFD-fed group (IRS category=2.50±0.67 vs. 1.50±0.80, P=0.018) (Fig. 3G).

ILK, PARVB and CFL1 jointly participated in PCa progression and correlated with worse disease-free survival within a public database. The genetic alterations in ILK, PARVB and CFL1 were evaluated in TCGA database from 499 PCa samples. In total, ~17% of PCa patients exhibited alterations (mainly in mRNA upregulation and amplification) in either ILK, PARVB or CFL1 levels (Fig. 4A), with both mRNA and protein expression Z-score threshold ±2. Both ILK-PARVB and PARVB-CFL1 gene pairs showed tendencies towards co-occurrence (Fig. 4B). We further discovered that upregulation of gene ILK and PARVB, as well as the upregulation and amplification of gene CFL1 were all correlated with an increase in the corresponding mRNA (Fig. 4C). Besides, slight to moderate positive correlations were detected in three gene pairs (ILK-PARVB, PARVB-CFL1, Pearson 0.286, P<0.001; ILK-CFL1, Pearson 0.197, P<0.001; PARVB-CFL1, Pearson 0.433, P<0.00) (Fig. 4D).

In the analysis of DFS, a total of 499 PCa patients from TCGA provisional database were enrolled. Among them, 92 (18.4%) patients suffered disease recurrence and progression. DFS was compared between subgroups expressing higher vs. lower levels of mRNA (75th and 25th percentile as cutoff) (Fig. 5). In the whole cohort, a tendency towards worse DFS was observed in the patients with higher CFL1 mRNA expression (Log-Rank P=0.083) (Fig. 5A). In subgroup analysis, higher mRNA expression in CFL1 was correlated with worse DFS (Log-Rank P=0.048) (Fig. 5B) in patients with stage III and IV PCa. Meanwhile, in patients with Gleason score≥7, trends towards worse DFS were also detected in patients with higher mRNA expression of PARVB (Log-Rank P=0.095) (Fig. 5C) and CFL1 (Log-Rank P=0.064) (Fig. 5C).

Discussion

Increasing evidence indicated a positive association between obesity and PCa incidence and aggressiveness (15). Generally,
the positive association was due to three major mechanisms, including decreased testosterone, adipokine alterations and insulin resistance (2,16). Recently, several studies reported the involvement of ILK, β-parvin and cofilin in patients with obesity or metabolic syndromes (7-9). Meanwhile, a pioneering research conducted by Shibue et al firstly identified that the activation of ILK/β-parvin/cofilin pathway was critical in the formation of FLPs and the progression of carcinomas (6). Therefore, the present study aimed to validate the expression of ILK, β-parvin and cofilin in PCa in TRAMP model, and to further explore the role of obesity induced protein expression alterations in the progression of PCa.

Dietary high fat was proved to induce obesity by increasing fat deposit in body, and in turn, the excessive fat would further affect cancer progression (17). Several studies were conducted in murine xenograft (18,19) and genetically engineered animal models (20), and discovered that HFD-fed would cause obesity and promote PCa development and progression. Among them, the application of genetically engineered mouse (GEM) caught great attention from researchers. Till now, four kinds of GEM model (TRAMP, LADY, Hi-Myc, Pten-null) were widely used (21). Among them, the TRAMP model was the first and also one of the most widely used model. The TRAMP model could successfully recapitulate all the parameters of PCa progression in human, including formation and progression from prostatic hyperplasia, intraepithelial neoplasia, adenocarcinoma to metastatic PCa (22). Besides, the great frequency and breadth of metastases was another merit of TRAMP in the research of cancer aggressiveness. The TRAMP model was specifically appreciated in the research of tumor microenvironment-cancer progression relationship, as neoplastic prostates were marked by stromal remodeling (reactive stroma) (22). Consistent with previous studies, the present study demonstrated that HFD feeding increased body weight and adipose tissue deposit in TRAMP mice, and HFD-fed mice possessed PCa with poorer differentiation, higher rates of extracapsular extension and metastasis, especially in 28-week group.

In the present study, ILK (encoded by gene ILK) was proved to be overexpressed in PCa, especially in poorly-differentiated PCa, which was consistent with previous outcomes in breast cancer, melanoma, colon cancer and PCa (23). Several in vivo studies showed the role of ILK in different aspects of cancer progression, including cell growth, EMT, migration and invasion (24). We also detected a slight increase of ILK expression in HFD-fed mice, though without statistical significance, and the outcomes warranted further investigation.
β-parvin (encoded by PARVB) linked with ILK and constituted IPP complex, which was known to facilitate FLPs formation, promote cell motility and extracellular matrix adhesion (6,25). Of note, the present study for the first time described the expression of β-parvin in PCa, and identified its overexpression in poorly-differentiated PCa. Moreover, we identified that HFD feeding could increase the expression of β-parvin in PCa. From TCGA database, we further discovered a trend towards worse DFS in PCa patients (Gleason score ≥7) with higher mRNA expression of PARVB. Previous studies reported conflicting outcomes, as PARVB was downregulated in breast cancer (26) and urothelial cell carcinoma (27), while overexpressed and correlated with tumor progression in colorectal cancer (12) and tongue squamous cell carcinoma (28), which implied an organ-specific expression or function of β-parvin.

Cofilin 1 (encoded by CFL1), an actin binding protein that played a key role in actin filament dynamics, functioned in cancer cell migration, invasion and mitosis (29). The present study found that cofilin 1 was overexpressed in moderately and poorly-differentiated PCa of TRAMP mice, which was in consistency with previous study (30). From TCGA database, higher mRNA expression of CFL1 was considered a risk factor for worse DFS in patients with Stage III or IV PCa. In HFD-fed group, we detected an increase in cofilin 1 expression.

In TCGA prostate adenocarcinoma database, ILK, PARVB and CFL1 all presented mainly with mRNA upregulation. A tendency towards co-occurrence was also identified in gene pairs of ILK-PARVB and PARVB-CFL1. These observations implied close relationships among these genes and the possible mechanisms contributed to carcinogenesis in their neighborhood network.

Several limitations existed in the present study. First, the key objects (ILK, β-parvin and cofilin 1) was only examined and evaluated by IHC, which required further western blotting and reverse transcription polymerase chain reaction study to confirm. Second, the alterations in the level of these proteins might result from both the diet and the progression of PCa. The discrimination of these two factors was difficult. Third, the TCGA database did not contain obesity, BMI, or diet habit as a clinical parameter, so we failed to apply these factors in the stratified analysis. Besides, the K-M survival analysis from TCGA database could not take elemental parameters (age, race) into account during analysis, therefore the associations between the subject proteins and patient survival were warranted by more cohort studies.

In conclusion, the present study demonstrated that HFD feeding contributed to higher expressions of β-parvin and cofilin 1 in PCa tissue and promoted cancer progression in TRAMP mice. Besides, higher expressions of ILK, β-parvin and cofilin 1 were associated with poorer cancer differentiation. In TCGA database, higher mRNA levels of CFL1 were identified to be correlated with worse disease-free survival in certain subgroups. Further studies were warranted in discussing the potential roles of ILK, β-parvin and cofilin 1 in HFD feeding induced progression of PCa.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

MBH, JMH, TY, WHZ, YH and XBW performed the animal studies and histological staining. LRJ performed the pathological analysis. MBH performed the general statistical analysis and drafted the manuscript. HW3 and QD conceived the study and participated in its design and coordination. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was performed in strict accordance with the National Institutes of Health guide for the care and use of Laboratory animals (NIH publication no. 8023, revised 1978). The protocol was approved by the Institutional Animal Care and Use Committee from Department of Laboratory Animal Science, Fudan University (approval no. 20160816A197).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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