TRIM36, a novel androgen-responsive gene, enhances anti-androgen efficacy against prostate cancer by inhibiting MAPK/ERK signaling pathways

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Introduction

Background: Androgen receptor (AR) signaling is essential for prostate cancer development. However, the disease progresses to testosterone independence as resistance to these drugs develops. A method to prolong the drug response time and improve the drug efficacy is still unavailable. In this study, we investigated the functional analysis and androgen regulation of TRIM36 and its underlying mechanisms enhancing anti-androgen efficacy against prostate cancer (PCA).

Methods: TRIM36 expression has been detected by mRNA microarray analysis, quantitative reverse transcription (qRT-PCR), Western blotting and Liquid chromatography-Mass Spectrum (LC-MS/MS) in matched prostate cancer and adjacent normal tissues, and prostate cell lines RWPE-1, C4-2, LNCaP, DU145, PC3. A total of 95 cases of prostate cancer after radical prostatectomy were analysed in a tissue microarray (TMA) for TRIM36 and androgen receptor (AR) protein expression. Prostate cancer cells stably expressing shRNA knockdown TRIM36 were used for CoX assay, clone formation assay and xenograft with or without ADT drugs. Androgen regulation was examined by ChIP, dual-luciferase reporter assay, qRT-PCR and Western blot analysis.

Results: In this study, we found that 63.4% (64/95) of PCa in TMA expressed the TRIM36 protein. Interestingly, patients with negative TRIM36 expression had a shorter biochemical recurrence-free survival. TRIM36 expression was significantly associated with the Gleason score (P<0.005), delayed prostate cancer cell cycle progression and inhibited cell proliferation in vitro and in vivo, and these effects were mediated via inhibition of the MAPK/ERK phosphorylation pathway. Remarkably, we found that rescuing the expression of TRIM36 during anti-androgen therapy could improve the drug efficacy.

Conclusions: Collectively, TRIM36 is a novel androgen-responsive gene, and it dramatically enhanced the efficacy of anti-androgen drugs against prostate cancer.

Methods

- **Tissue microarray (TMA) of 95 Pca and definition of TRIM36 expression**
  - A total of 95 cases of prostate cancer (PCa) in TMA were used for the analysis of TRIM36 expression.

- **Function of TRIM36 in PCa cell lines**
  - A total of 4 PCa cell lines (LNCaP, DU145, C4-2, and PC3) were used for the analysis of TRIM36 expression.

- **Expression of TRIM36 in prostate cancer cell lines**
  - A total of 4 PCa cell lines were used for the analysis of TRIM36 expression.

- **Androgen-responsive expression of TRIM36 in prostate cancer cell**
  - A total of 4 PCa cell lines were used for the analysis of TRIM36 expression.

- **Anti-androgen therapy reduces TRIM36 expression**
  - A total of 4 PCa cell lines were used for the analysis of TRIM36 expression.

- **Rescued TRIM36 increased the anti-androgen sensitivity**
  - A total of 4 PCa cell lines were used for the analysis of TRIM36 expression.

Clinical Outcome

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Table 1. Relationship of TRIM36 expression and clinicopathologic characteristics of patients

Conclusion

- **TRIM36 inhibits the MAPK/ERK phosphorylation pathway**
  - A total of 4 PCa cell lines were used for the analysis of TRIM36 expression.

Conclusions: Collectively, TRIM36 is a novel androgen-responsive gene, and it dramatically enhanced the efficacy of anti-androgen drugs against prostate cancer.