Molecular mechanism of spirit-quieting traditional Chinese medicine in the treatment of prostate cancer metastasis patients with depression

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Abstract

Prostate cancer is a common male urinary system cancer globally with a poor prognosis. Our research aims to explore the role of spirit-quieting Traditional Chinese Medicine in the treatment of prostate cancer metastasis patients with depression and its underlying mechanism. Currently, based on the theory of enzyme-activated bone degradation, we consider that MAOA mediates a vicious cycle among tumor cells, osteoblasts, osteoclasts and stromal cells facilitating PCa metastasis to bone and visceral organs, which was effectively reduced by TCM MAOA inhibition disengaging the Shh-IL6-RANKL signaling network in the tumor microenvironment. Additionally, the protein expression level of MAOA was found by using clinical specimens from the HPA database.

Keywords Prostate cancer metastasis; depression; MAOA; Traditional Chinese Medicine; Chai-Hu-Jia-Long-Gu-Mu-Li-Tang

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Prostate cancer (PC) was the second most common malignant tumor in men worldwide. The 5-year survival rate of prostate cancer in the United States was approaching 98%, while in china it was below 70%[1]. Although most patients are diagnosed early and may be cured with surgery and/or radiation therapy, approximately one third of men treated will fail therapy and develop advanced prostate cancer[2]. For decades, the management of patients with advanced prostate cancer has been hormonal therapy, known as androgen deprivation therapy (ADT), which is intended to lower testosterone levels[3]. Despite initial response, essentially all patients will develop metastatic castration-resistant prostate cancer (mCRPC). Standard first-line treatment for mCRPC is docetaxel plus prednisone[4]; however, patients will usually experience disease progression during or after docetaxel

treatment due to inherent or acquired resistance. Metastatic castration-resistant prostate cancer is in critical need of new and innovative treatment strategies. From 2010, efforts to expand the treatment landscape for mCRPC resulted in FDA approval of ten more agents which improved survival, including androgen receptor (AR)-targeted therapies (apalutamide, enzalutamide, abiraterone, darolutamide), a chemotherapy (cabazitaxel), a radioisotope (radium-223), a cancer vaccine (sipuleucel-T) and DNA-damaging agents (olaparib, rucaparib, niraparib)[2]. Despite the approval of several new agents for advanced disease, each of these has prolonged survival by only a few months. Consequently, new therapies are sorely needed.

The proposal of the theory of enzyme-activated bone degradation makes the researchers of prostate cancer bone metastases see new hope. Enzyme-activated bone degradation theory: Monoamine oxidase A (MAOA) is an important mediator in prostate cancer metastasis to bone and viscera. It can activate the paracrine signaling pathway Shh-IL6-RANKL in tumor-stromal cell interaction and stimulate osteoblasts to secrete IL -6 and RANKL, promote osteoclastogenesis, which facilitates the growth and colonization of prostate cancer cells in the bone microenvironment. Prostate cancer cells change the expression levels of osteoblast proteins (such as RANKL, OPG) through signaling molecules such as parathyroid hormone-related proteins, and promote osteoclastogenesis and its activity. The ensuing bone destruction will release molecules such as TGF-β and BMPs from the mineralized bone matrix, and these molecules will further promote tumor growth, thus forming a vicious circle. The bone microenvironment enables tumor cells to establish persistent vicious circle conditions, but not a single cell but a multicellular network plays a role in the development of prostate cancer bone metastases. Therefore, targeted blockade of MAOA can effectively delay bone metastasis of prostate cancer[5].

Traditional Chinese medicine (TCM) is an important means of treating diseases in China. It contains rich practical experience and medical technology of ancient medical scientists, and TCM has made great progress in the treatment of prostate cancer in modern medicine[6]. Prostate cancer belongs to the category of “uroschesis,” “stranguria,” and “hematuria” in TCM, and its treatment should detoxicate and abscise mass, activate blood to remove blood stasis, and strengthen body resistance to consolidate constitution[7]. One of the characteristics of TCM theory is that TCM contains multiple formulae in a single prescription, which can effectively provide personalized medicine and reduce side effects. However, this prescription model also increases the difficulty of independently analyzing the clinical efficacy of a single formula. Previous studies have shown that different Chinese herbal compounds play different roles in the care of patients with prostate cancer. For example, quercetin inhibits prostate cancer by attenuating cell survival and inhibiting anti-apoptotic pathways[8]. Wogonoside could suppress Wnt/β-catenin pathway and reversing the EMT process in PC3 cells[9]. Ginsenoside Rg3 exhibits anticancer effects on prostate cancer cells through ROS-mediated arrest of the cell cycle[10]. However, some prostate cancer treatments can increase the severity of a patient's depression, for example, by increasing anhedonia and erectile dysfunction. Many patients with prostate cancer

experience severe levels of depression, which can negatively affect their treatment and disease course[11]. TCM for depression might be associated with a lower risk of overall mortality of prostate cancer with depression[12].

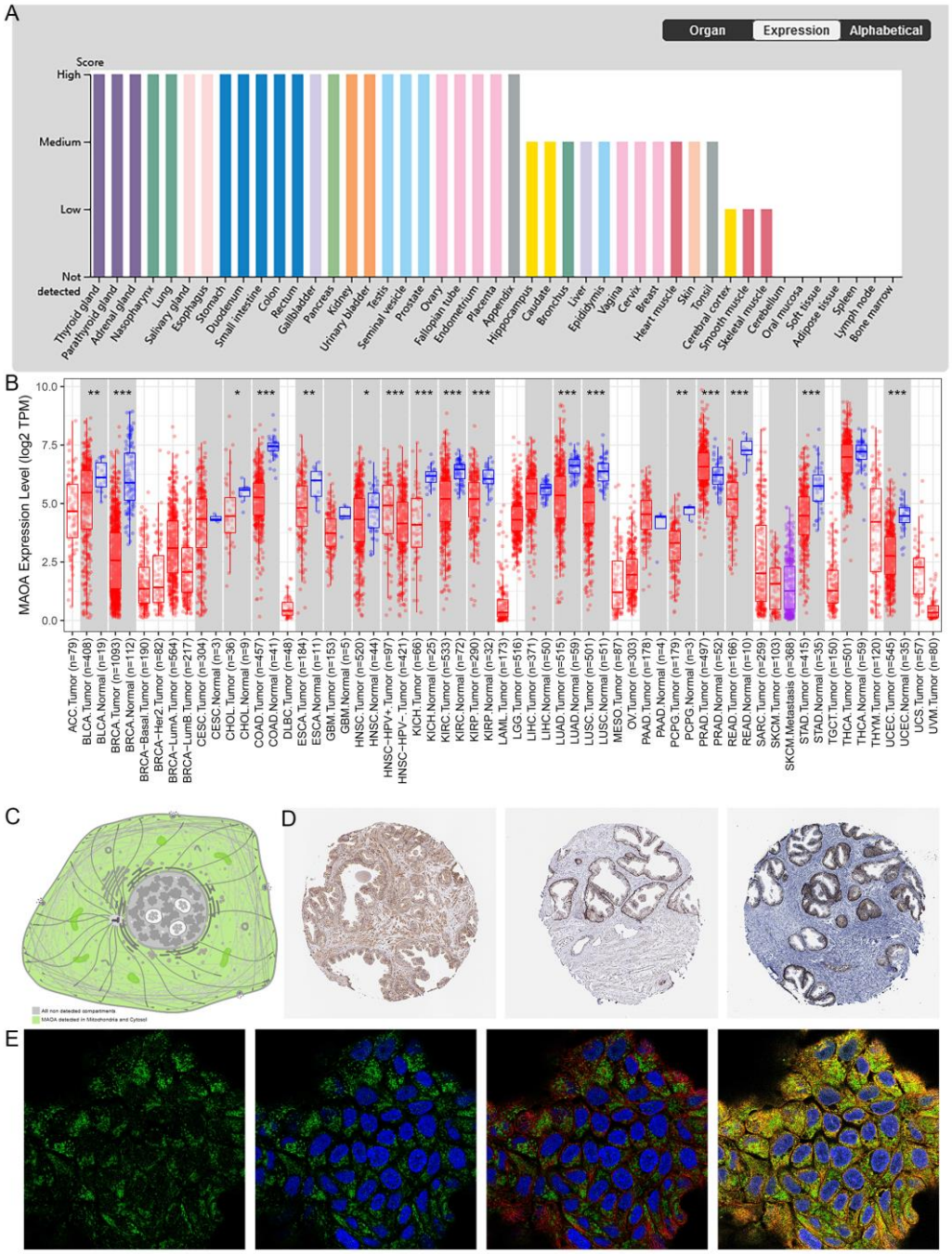

Figure The protein expression of MAOA in normal and cancer tissues.

A. The protein expression of MAOA in human normal tissues.

B. The mRNA expression levels of MAOA in different cancer types were explored by TIMER.

C. Immunohistochemistry (IHC) showed MAOA protein was mainly distributed in mitochondria and cytosol.

D. Immunohistochemistry images of MAOA in prostate cancer tissues detected in the HPA database.

E. Immunofluorescent analysis in RT4 cell lines and with all tested antibodies.

Chai-Hu-Jia-Long-Gu-Mu-Li-Tang can reduce the symptoms of hypogonadism caused by castration therapy, including sexual dysfunction, hot flashes, night sweats, and insomnia[13]. It also reduces the expression of cancer cell proteases, such as tumor-specific matrix metalloproteinases-2 and -9 and impedes the proliferation of prostate cancer[14]. Currently, based on the theory of enzyme-activated bone degradation, we consider that MAOA mediates a vicious cycle among tumor cells, osteoblasts, osteoclasts and stromal cells facilitating PCa metastasis to bone and visceral organs, which was effectively reduced by TCM MAOA inhibition disengaging the Shh-IL6-RANKL signaling network in the tumor microenvironment.

Additionally, the protein expression level of MAOA was found by using clinical specimens from the HPA database. The MAOA protein expression data was shown for each of the 45 normal tissues (Figure A), and it revealed that most of the normal tissues presented high staining. As for cerebellum, oral mucosa, soft tissue, adipose tissue, spleen, lymph node, and bone marrow, MAOA was undetectable. To further evaluate the differential expression of MAOA, we compared the its expression levels in the TCGA dataset using TIMER2.0. As shown in Figure B, MAOA expression was significantly lower in various cancer types, including bladder urothelial carcinoma (BLCA), breast invasive carcinoma (BRCA), cholangiocarcinoma (CHOL), colon adenocarcinoma (COAD), esophageal carcinoma (ESCA), head and neck squamous cell carcinoma (HNSC), kidney chromophobe (KICH), kidney renal clear cell carcinoma (KIRC), kidney renal papillary cell carcinoma (KIRP), lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), pheochromocytoma and paraganglioma (PCPG), rectum adenocarcinoma (READ), stomach adenocarcinoma (STAD), and uterine corpus endometrial carcinoma (UCEC). However, the expression of MAOA in prostate adenocarcinoma (PRAD) was significantly elevated. Besides, the data also showed that MAOA expression was aberrantly higher in HPV-positive HNSC than HPV-negative HNSC. Immunohistochemistry (IHC) showed MAOA protein was mainly distributed in mitochondria and cytosol (Figure C). Meanwhile, MAOA was also high expressed in prostate cancer (Figure D). Summary of the subcellular location, based on the immunofluorescent analysis in all studied cell lines and with all tested antibodies (Figure E). Association of key molecules of oncogenesis and metastasis with MAOA suggests that spirit-quieting Traditional Chinese Medicine might be effective in the treatment of prostate cancer metastasis patients with depression.

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