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The Association between Prostate Cancer and CXCL9 Gene Expression

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Abstract

Chemokine CXCL9 is a member of the CXC family and plays an important role in the chemotaxis of immune cells. In this study, changes in the CXCL9 expression were investigated in prostate cancer and adjacent normal tissue. The prostate cancer tissues and the corresponding adjacent tissues used in this study were collected from 30 patients. The real-time quantitative PCR (qRT-PCR) was performed for evaluated changes in the CXCL9 expression in prostate cancer and adjacent normal tissue. The mRNA levels of CXCL9 in prostate cancer samples was greater than normal samples (P=0.04). The results suggested that the mRNA expression levels of CXCL9 were positively associated with prostate cancer.

INTRODUCTION

Prostate cancer is the most common cancer among men (after skin cancer) [1], so that about 1 in 9 men will be diagnosed with prostate cancer during their lifetime. Prostate cancer is more likely to be developed in older men, particularly African-Americans [2]. About 6 in 10 men who are 65 or older are diagnosed with prostate cancer, and it is rare in men under 40 [3]. The average age of cancer diagnosis is about 66. Also, some common risk factors for prostate cancer include race, age, genetics, diet, and high testosterone levels [4]. The genetics of inherited prostate cancer are poorly understood. Family history of prostate cancer is a strong predictor of disease with inherited germline mutations being estimated to account for approximately 9% of all cancers and 45% of cases in younger men [5]. Linkage mapping studies have identified chromosomal regions 1q24-25, 1q42.2-43, 1p36, Xq11, Xq27-28, 20q13, and 11p that correlate with the inherited disease [6]. Recent advances in immunology, tumor biology, and genomics have paved the way for the development of gene-based therapy [7]. With the task of sequencing and identifying all human genes well underway, the first tentative steps toward clinical trials using gene-based treatment of urologic cancers, including those of the bladder, renal cell, and prostate, have begun [8]. Currently, immunotherapy has been reported to be an effective treatment for cancer patients. Several strategies, including cancer vaccines and immune checkpoint inhibitors, have been investigated in clinical studies for cancer patients [9].

However, T cell immunotherapy of prostate cancer is still at an early stage of clinical development. It has been reported that several molecules are potent T cell checkpoint inhibitors that reverse immunologic tolerance in many types of cancer, including prostate cancer [10]. Therefore, the molecules that serve crucial roles in T cell activity during prostate cancer may be useful for treating this disease. CXC motif chemokine ligand9 (CXCL9) is a chemokine that regulates the host's response to inflammation by recruiting leukocytes to the inflammatory environment [11]. Chemokines serve important roles in the immune responses of the body. As CXCL9 can interact with various ligands, it serves a certain biological role in the inflammatory response [12]. In addition, inflammation is closely associated with the occurrence and development of tumors. In this study, changes in the CXCL9 expression were investigated in prostate cancer and adjacent normal tissue.

METHODS AND MATERIALS

The prostate cancer tissues and the corresponding adjacent tissues used in this study were collected from 30 patients experienced prostate cancer surgery. No patients underwent radiotherapy or chemotherapy before surgery. All samples were stored at -80 °C until RNA extraction. Total RNA was extracted using YTzol pure RNA (Yekta tajhiz azma, Iran) following

the manufacturer's description. cDNA Synthesis Kit (Yekta tajhiz azma, Iran) was used to perform RTPCR to synthesize cDNA. Then cDNA was used as a template to perform qPCR. GAPDH was used as an internal reference gene. The following primer sequences were used: CXCL9 F, 5'AGG GTC GGC TGT TCC TGC ATC3' and R, 5'TTC ACA TCT GCT GAA TCT GGG TTT A3'; GAPDH F, 5'GCA CCG TCA AGG CTG AGA AC3' and R, 5'TGG TGA AGA CGC CAG TGG A3'. All data were analyzed using SPSS version 19.0 statistical software (IBM Corp., Armonk, NY, USA).

RESULTS

The mRNA expression levels of CXCL9 were measured in clinical samples. The mRNA levels of CXCL9 in prostate cancer samples was greater than normal samples (P=0.04). The results suggested that the mRNA expression levels of CXCL9 were positively associated with prostate cancer.

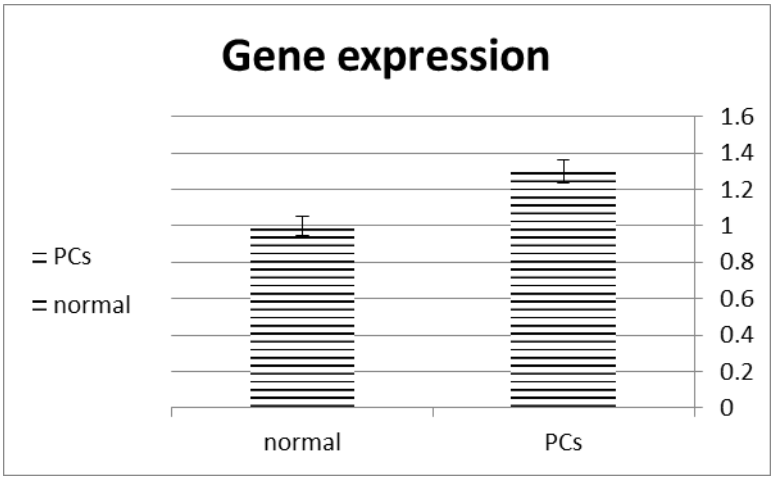

Fig. 1. The results suggested that the mRNA expression levels of CXCL9 were positively associated with prostate cancer

DISCUSSION

The development of malignant tumors depends on the tumor microenvironment, where chemokines and their receptors are important participants [13]. Chemokine CXCL9 is a member of the CXC family and has an important role in the chemotaxis of immune cells. It is secreted by various cell types, including immune cells (e.g., T lymphocytes, NK cells, dendritic cells, macrophages, eosinophils, and non-immune cells (hepatic stellate cells, preadipocytes, thyrocytes, endothelial cell, tumor cells, and fibroblasts, etc.) [14]. CXCL9 has a versatile and controversial role in tumors, and accumulating evidence suggests that CXCL9 is closely associated with the prognosis of tumor patients [15]. Prostate cancer, as a highly malignant tumor with complex pathogenesis, is one of the most common cancers among men. Abnormal expression levels of chemokines have been identified in prostate cancer [16]. Many chemokines may have inhibitory effects on the tumor, and certain chemokines may promote tumor progression [17]. Several chemokines, including CXCL4 and CXCL10, were used in translational medicine [18]. In this study, changes in the CXCL9 expression were investigated in prostate cancer and adjacent normal tissue.

The results showed a significant increase in the expression of this gene in tumor tissues. Chemokines serve an important role in the tumor microenvironment, and it was hypothesized that CXCL9 serves an indirect role in affecting white blood cells. Hu et al. reported that prostate cancer cells could secrete CXCL9 more than the normal cells, and CD4+ T cells recruited by endogenous CXCL9, consequently, promoted prostate cancer metastasis via modulation of FGF11/miRNA-541/AR/MMP9 signaling [19]. Liu et al. showed that recombinant mouse and human CXCL9 and CXCL10 facilitated the proliferation of murine and human glioma spheres, suggesting that they may promote tumorigenesis. Besides, studies also demonstrate that CXCL9 is highly upregulated in glioblastoma and primary pediatric CNS germ cell tumor (germinoma type) [20]. Accumulating evidence indicates that manipulating the tumor microenvironment that involves CXCL9 can enhance the therapeutic efficacy of strategies via tumor-specific T cells. Nevertheless, a more detailed characterization and mechanism of CXCL9 role in tumor biology are desperately required, as it may improve cancer treatment and possibly lead to clinical applications in cancer prognosis, diagnosis, and therapy.

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