PERSPECTIVE

Structure and function of FUS gene in prostate cancer

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ABSTRACT
BACKGROUND: FUS reduces the proliferator factors such as cyclin D1 and Cdk6, and increases Cdk and p27. Therefore, FUS prevents the growth of prostate cancer cells.
METHODS: This review tried to summarize data about FUS gene expression in correlation with the degree of prostate cancer. To find the relevant studies, the search in PubMed, Science Direct, and Scopus were performed.
RESULTS: Increasing the expression of FUS decreases and increases the rate of apoptosis of prostate cancer cells, respectively. In fact, FUS reduces the proliferator factors such as: cyclin D1 and Cdk6, and increases Cdk (an anti-proliferation factor) and p27 (a proliferative inhibitory factor). Therefore, FUS prevents the growth of prostate cancer cells. An immuno-histochemical analysis showed that FUS gene expression had an inverse correlation with the degree of prostate cancer, which suggests that patients with higher levels of FUS are more likely to survive and less likely to have bone pain.
CONCLUSION: The key to FUS is the signaling of the androgen receptor and the progression of the cell cycle in prostate cancer. Based on these findings, we might be able to consider exogenous expression of FUS as a treatment for prostate cancer *(Fig. 1, Ref. 32).*
KEY WORDS: prostate cancer, FUS, androgen receptor, cyclin D1.

Introduction

The prostate gland is a small gland located below the bladder and covers the upper portion of the urethra. In developed countries, prostate cancer is the second most common cancer (after skin cancer) and the second leading cancer (after lung cancer) in men. Prostate malignancies were shown in 1 out of 6 people.

Epidemiological studies (epidemiology) showed that hereditary factors contribute to this disease in 10 % of the cases (1, 2). The highest occurrence of prostate cancer was found in African population and the lowest numbers were found in the Asian population. Several studies were conducted on family history of prostate cancer. The main reason for this study is to investigate the involved genes. Prostate cancer is a disease, in which malignant cells pycnocline from prostate tissues erratically and increasingly proliferate and lead to an increase in prostate gland size (3).

It is estimated that more than 300,000 new cases are discovered every year, of which 41,000 definitely lead to death (3). Due to the high incidence of this disease in each community, special

attention to timely diagnosis and also effective treatment seems necessary.Prostate cancer is almost invariably dependent on the androgen receptor (AR) pathway, which,when activated, stimulates cell proliferation. Androgen receptor (AR) is required for the survival and growth of prostate cancer cells.

Prostate cancer is almost invariably related to the Androgen Receptor (AR) pathway, androgen receptor is a member of the receptor family of transcription factors. As soon as it is bonded to the androgen, the transcript of the androgen receptor regulates the target gene expression (4).

This receptor is activated when cell proliferation is stimulated. Several factors are involved in the progression of the cell cycle, which is regulated in response to androgens, for example, cyclin D1 increase (7–5). The endogenous amino zone (NTD) of the androgen receptor is essential for the activity of both the ligand and the unrelated receptor ligand (8). However, none of these cases of prostate cancer are treated with LHRH. Although the hormone blocks the production of androgens or anti-androgens, binds to AR and keeps it in an inactive state, this treatment is initially successful, later the treatment is failing and the tumor progresses. Most of the evidence illustrates that the receptor still grows in these conditions (9).

Androgen receptor (AR) is associated with survival and growth of prostate cancer cells. At first, it seemed that progressing prostate cancer could be treated with eradication of androgens.

Unfortunately, this treatment eventually fails, and the disease leads to death, which is called a castration resistant prostate cancer (CRPC). However, ongoing follow ups in the development of drugs can be useful for improving the understanding of the

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protein-protein interactions, which are involved in AR. In this regard, considering the genes involved in prostate cancer and interactions with the androgen receptor can lead to new and effective therapies in the future.

One of the new genes which are mentioned in this regard, is FUS RNA binding protein. This gene, characterized by FUS, is a kind of protein encoding gene. Also known as TLS, ALS6, ETM4, FUS1, POMP75 and HNRNPP2 (11). The gene encodes a multifunctional protein consisting of non-homogeneous nuclear ribonucleolase complex (hnRNP).

The hnRNP complex is involved in interacting with the pre-mRNA and sending out of the mRNA product to the cytoplasm. This protein belongs to the FET family of RNA-binding proteins that play a role in cellular processes including the gene expression, genome protection, and the mRNA / microRNA process [10].

Methods for review

An extensive search was performed in PubMed, Science Direct, Scopus and Google scholar to identify clinical and animal studies on the Structure and Function of FUS gene in prostate cancer published from inception up January 15, 2018. Search terms were ("prostate cancer" AND "FUS" AND "androgen receptor" AND "cyclin D1"). The search was performed in titles and abstracts that were restricted to articles published in English and sometimes French languages. All titles, abstracts, and full texts of potentially relevant studies were assessed for eligibility.

In this study, we mention the structure and function of the FUS, then review the related article, while explaining the various studies that have been done in the past few years, study the association of this gene with prostate cancer and the mechanism involved in this field. At the end, we give a final conclusion.

Structure and function of the gene

This gene (FUS) has 16 introns and 15 exons with16p11.2 chromosomal position, which is presented in Figure 1 (10).

Mutation in the FUS gene causes Amyotrophic Lateral Sclerosis (ALS) in 2009 (11, 12). In ALS disease, motor neurons have problems and lead to obstacle in muscle and movement control, at the end patient is unable to move (13). Approximately, about 40 mutations have been reported, most of which were present in the second richest G and C-terminal NLS-containing region. The P525L mutation in the FUS is associated with the primary attack in ALS, in contrast, the subsequent attack of ALS is due to the R521C mutation in the FUS gene. Although the mutation in the FUS is responsible for only a small percentage of ALS (4.3 %), the FUS protein is a common cytoplasmic component in an ALS

that is unrelated to SOD1 (most ALS cases are due to mutations in SOD1). The common FUS mutations that cause ALS include R521C (11, 12, 14), R521H (11, 12), H517Q (15), R521S (16), R514S (11), and R521L (15). . All of the FUS mutations occur in Axon 15 (16).

Also, the mutation S462F has recently been reported and recently known one polymorphism called Q210H, all associated with ALS. It has been suggested that ALS is associated with single nucleotide polymorphisms (SNPs) in various genes such as FUS (17).

The FUS encodes a multi-functional protein that requires the pre-mRNA interconnections (18), has a stable chromosome (19), expands the cell (20), and transcribes (22, 21).

The gene is member of a protein cell group called FET / TET. This family of proteins includes Fused in Sarcoma (FUS) / Translocated in LipoSarcoma (TLS), EWig, Sarcoma Protein (EWS), TATA binding protein-Associated Factor, and TAF15. FET proteins showed various functions including transcriptional combinations, binding, cell propagation, and DNA modification.

FET proteins have similar transcriptional active domains (TADs) at the end of the second amino acid (NTD) and have a main form of detected RNA (RNA recognition motif or RRM) and repeat the RGG tripeptide at the end of their carboxyl (23, 24). It has been shown, that FUS have interaction with DNA banding-domains (DBDs) of retinoid X receptors, estrogen, thyroid, and glucocorticoid receptors (25).

FUS bonding to other DBDs of hormone receptors does not interfere with DNA bonding activity, although the role of the FUS in its transcriptional activity has not been clear (25).It has also been shown that FUS has a strong active transfer site that is functionally active in the prostate cancer cells (4).

Gene and cancer correlation – mechanism and review of research

As stated, the AR target is involved in the growth of prostate cancer cells therefore is valuable in recognition of new therapies. On the other hand, the FUS reduces a target protein of AR in response to androgen. Increasing the expression of FUS significantly delayed growth of androgen-caused prostate cancer cells both in in-vivo and in-vitro.

Regulation of expression of several factors, which are involved in the cell cycle (such as cyclin D1), FUS effect on them, prevents the entry into the G1 phase and the activation of apoptosis. Thus, the FUS illustrate tumor suppression characteristics.

Brooke et al (26) performed a proteomic imaging of LNCaP of the prostate cancer cell following stimulation with androgen and results showed a decrease in FUS expression at the level of RNA and protein.

Perrotti et al (27) showed that FUS was regulated at the protein level by c-jun, and Velasco et al (28) reported that c-jun was regulated by androgen. In support of these findings, Brooke et al (26) observed an increase in c-jun protein after eight hours of androgen injection. Whereas FUS decreased with increasing c-jun, scientists assumed that androgen might reduce FUS by increasing c-jun. However, c-jun suppression did not have an effect on

Fig. 1. FUS chromosome position.

the decrease in androgen receptors associated with FUS. Scientists concluded that reducing FUS in response to androgens was done at the transcriptional level (26). As FUS levels decreased by increasing androgen receptors, scientists assumed, FUS might be a suppressor of prostate cancer. In LNCaP cells, it was observed that FUS expression significantly prevented cell growth and this is because the FUS expression causes inhibition of the G1 phase and apoptosis increase (26).

It has been shown that AR played an important role in regulating regulatory factors in development of the cell cycle, especially in development of G1 / S, since androgen depletion can inhibit G1 (29). According to these findings, Brooke et al (26) reported that in LNCaP cells followed the elimination of androgens, prevented from entering the G1 phase, while the addition of androgen led to an increase in number of progressive cells to S and G2 / M phases. In any case, the increased expression of FUS blocked the effect of androgen and prevented the G1 phase and also increased the number of the G1 subtypes.

Increasing activity of caspases and division of PARP confirmed that this G1 subtypes contained apoptotic cells, consequently, FUS increased apoptosis in prostate cancer cells (26).

The analysis of the cell cycle regulators showed that manipulation of FUS levels affected the expression of several important factors, especially cyclin D1, CDK 6 and P 27 in the G1 / S stage. It has been shown that cyclin D1 and P27 were targets for androgen, which caused an increase in cyclin D1 and a decrease in P 27 and also the prolongation of G1 stage (29–31). It has also been observed that the expression of exogenous FUS resulted in a decrease in expression of cyclin D1 and increase in the expression of P 27, which suggests that FUS inhibits G1 and thus inhibits androgenetic proliferation, which is partly through mediation of cyclin D1 and P 27 factors.

FUS directly uses the CCND 1 regulatory area encoding the cyclin D1 by stranded noncoding RNA (ncRNA) that is transcribed from different locations in the / 5 upstream region.

This effect results in interference with the complex transcriptional complexion, and hence the expression of cyclin D1 decreases (27). The cyclin D1 regulation has been observed in response to increasing or decreasing FUS at the level of RNA.

Brooke et al (26) showed that FUS levels were regulated by androgens, and Canduson et al (32) showed that reduction of their cyclin D1 was an androgen receptor suppressor. Therefore, there is a complex interaction between FUS, androgen receptor and cyclin D1, which should be further investigated in the future. However, it has been shown that the manipulation of FUS levels affected multiple levels of regulatory protein in the cell cycle, and it has been shown that FUS might be a vital link between androgen signaling and cell cycle progression.

Information from both the laboratory and the human body has shown that FUS has anti-tumor features (26).

FUS expression in the prostate tumor samples is correlated with the degree of prostate cancer, and patient information analysis showed that patient with higher FUS levels had the chance of more survival and lower bone pain (a major cause of illness in Prostate cancer patients) (26).

Therefore, the lack of FUS expression might be important in the progression of the disease. Although increased levels of FUS have reduced tumor growth, with a deletion of FUS inducing expression, tumor growth has increased again, while the FUS repression has reduced tumor volume by one-half a week (26).

Conclusion

Androgen signaling reduces FUS and subsequently increases the growth of prostate cancer cells as the result of important regulatory factors in the progression of the cell cycle.

In the same vein, FUS expression declines in the advanced stage of prostate cancer, therefore, loss of FUS may increase androgen signaling and subsequently increase the growth of prostate cancer cells. However, increased expression of FUS in the human body reduces tumor growth and prevents the G1 stage and increases apoptosis in prostate cancer cells.

Perhaps FUS induces this effect through the reductive effect on cyclin D1 and an increasing effect on P27. Therefore, FUS manipulation can be considered as a treatment for prostate cancer.

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