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Basic fibroblast growth factor and keratinocyte growth factor over-expression in benign prostatic hyperplasia☆

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Abstract

The prostate growth is under the indirect control of androgens through the medium of many growth factors. The fibroblast growth factors (FGFs) seem to play an important part in stimulating the development of this organ. In this work, the expression of two FGFs: bFGF (or FGF2) and KGF (or FGF7), was studied in RT-PCR and semi-quantified in densitometry. Both genes expression was increased in BPH in comparison with normal prostates. A two to three times and a 1.5 to four times over-expressions were observed for bFGF and KGF, respectively. An over-expression of these growth factors could lead to a cell multiplication resulting in a pathological development of the prostate size. Moreover, bFGF and KGF act in parallel in the prostate, one stimulating the prostatic stroma and the other one stimulating the epithelium. These two growth factors could participate in the increase of the two tissues constituting the prostate. © 2001 Éditions scientifiques et médicales Elsevier SAS

Keywords: Prostate; BPH; Basic fibroblast growth factors; Keratinocyte growth factor; Reverse transcription and polymerase chain reaction

1. Introduction

The prostate is a secondary endocrine organ. Its growth is regulated by several growth factors under the control of androgens in an active form (5-α-dihydrotestosterone) [1]. Fibroblast growth factors (FGFs) and transforming growth factors β (TGFβ) seem to play an important part in prostate growth since FGFs, which have mitogen and angiogenic activities, activate prostate growth whereas TGFβ inhibits it [2].

In the prostate, the principal FGFs are FGF7 or KGF (keratinocyte growth factor) which is the major FGF expressed, and then FGF2 or basic FGF (bFGF) and then FGF1 or acidic FGF (aFGF) [3].

Normal prostate growth appears especially in an embryonic stage and then the prostate grows up more moderately from puberty to about 20. Then the prostate size is stable until the age of about 50, beyond benign prostatic hyperplasia develops [4]. This hyperplasia is due to a dysregulation of cell multiplication which induces an abnormal increase of prostate size.

Growth factors and particularly FGFs seem to be involved in this cell multiplication activation. Indeed, bFGF concentration increases for 2.5 to three times in BPH in comparison with normal prostate [5]. Moreover, KGF concentration also seems to increase in hyperplastic tissues with regard to normal prostate tissues [6]. However, aFGF concentration does not seem to be modified in BPH.

This work tried to state precisely bFGF and KGF concentrations increase in BPH. The expression of bFGF and KGF genes was studied by reverse transcription and polymerase chain reaction (RT-PCR) in hyperplastic prostatic tissues and in normal tissues.

2. Material and methods

This study was performed with prostatic fragments collected from 20 men aged 48–79 undergoing

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transuretral resection of prostate for BPH, and seven men with no prostate disease.

An anatomo-pathological analysis of the hyperplastic tissues was carried out to confirm the BPH diagnosis and to reject prostate cancer tissues.

bFGF and KGF genes expression was evaluated by RT-PCR in the presence of an internal standard which expression is stable in the prostate, glyceraldehyde phosphate dehydrogenase (GAPDH) and permitted a semi-quantitative approach of these genes expression.

Total RNAs were isolated by Trisol extraction and transcribed in complementary DNA in the presence of reverse transcriptase and amplified in PCR. The amplified products were then visualised on Nu-sieve gel with ethydium bromide and analysed in densitometry. A statistical evaluation of the results was performed using the non parametric Mann–Whitney *U*-test.

3. Results

For each patient, two pieces of prostatic tissue were studied in duplicate and variations between mRNA expression in different regions were slight, showing some homogeneity in the prostate.

An over-expression of the bFGF gene was observed in BPH in comparison with normal prostates. Densitometric study showed an expression increase of two to three times superior in BPH (Fig. 1).

In the same way, KGF gene was over-expressed in BPH and densitometric analysis revealed a 1.5 to four times increase in the expression of this gene (Fig. 2).

4. Discussion

bFGF and KGF have two different targets in the normal prostatic tissue. Indeed, bFGF is a potent mitogen for stromal cells and KGF stimulate epithelial growth [3]. These two fibroblast growth factors seem to play a complementary role in the prostate, each of them activating its own cell type.

In this study, we showed an over-expression of two to three times of bFGF and of 1.5 to four times of KGF. This work confirms studies by Begun et al. [5] who observed a 2.5 to three times over-expression in BPH with regard to normal prostates and Ropiquet et al. [6] who found KGF over-expressed in BPH in comparison with normal tissues.

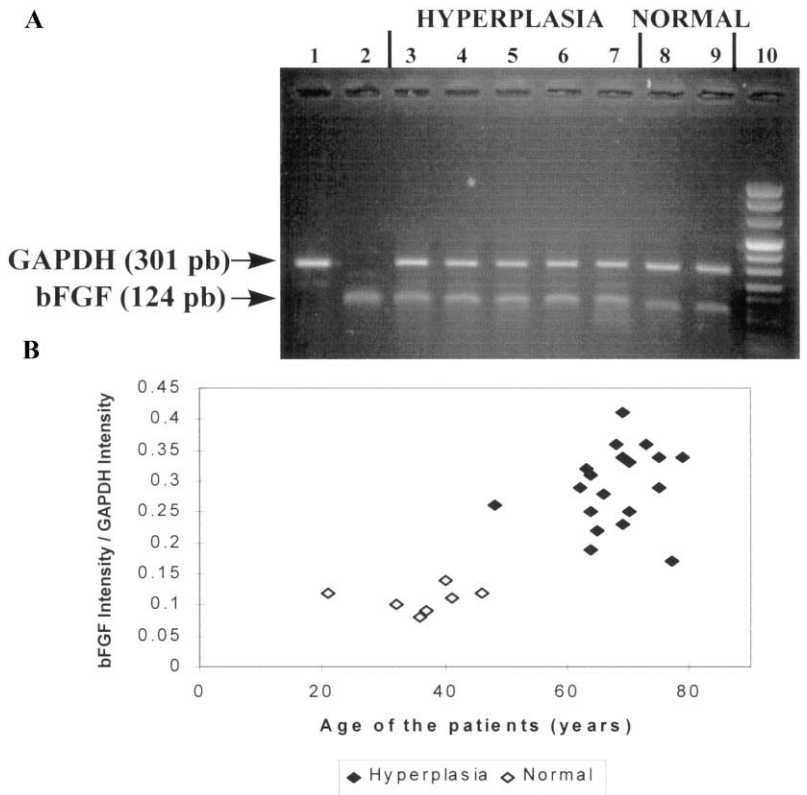

Fig. 1. bFGF mRNA expression in BPH tissues and normal tissues. **A**: Amplification products of bFGF and GAPDH. lane 1: amplification product of bFGF mRNA. lane 2: amplification product of GAPDH mRNA. lanes 3 to 7: co-amplification products of bFGF and GAPDH mRNAs in BPH. lanes 8 to 9: co-amplification products of bFGF and GAPDH mRNAs in normal tissues. lane 10: molecular weight. **B**: bFGF expression expressed versus GAPDH in normal and BPH patients. The difference between values in normal prostates and BPH is significant (P0.01).

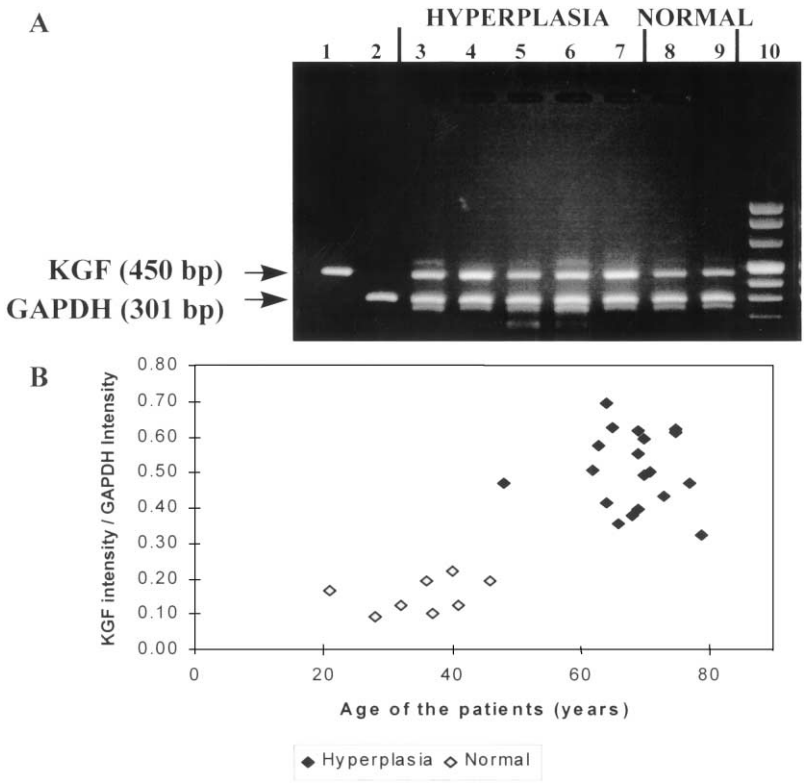

Fig. 2. KGF mRNA expression in BPH tissues and normal tissues. **A**: Amplification products of KGF and GAPDH. lane 1: amplification product of KGF mRNA. lane 2: amplification product of GAPDH mRNA. lanes 3 to 7: co-amplification products of KGF and GAPDH mRNAs in BPH. lanes 8 to 9: co-amplification products of KGF and GAPDH mRNAs in normal tissues. lane 10: molecular weight. **B**: KGF expression expressed versus GAPDH in normal and BPH patients. The difference between values in normal prostates and BPH is significant (P0.01).

In BPH, the increase of the concentration of these two growth factors could be responsible for a not-regulated cell multiplication in the stroma on the one hand, concerning bFGF and in the epithelium on the other hand, concerning KGF. This parallel cell growth activation would induce a pathological increase of the prostate size.

The results observed show FGFs participation in the development of BPH which origin could situate in an imbalance of the expression of the different positive and negative growth factors present in the prostate. However, the reasons causing this imbalance are still unclear since, for example, no genetic mutation (like it happens in prostate cancer) was observed in BPH. This still has to be studied.

Our future studies turn on other FGFs which could be implicated in the development of BPH and on their receptors.

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