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Effect of HARP on the Growth of Human Prostate Cancer Cells

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S u m m a r y. Understanding how the regulation of growth factor pathways alters during prostate cancer progression, may enable researchers to develop targeted therapeutic strategies for advanced disease. In this study, we investigated the interplay between peptide growth factors that have been described to play a key role in prostate tumor progression and we focused on the role of a novel growth factor, known as HARP (Heparin Affin Regulatory Peptide), using human prostate cancer cell lines.

INTRODUCTION

Diagnosed prostate cancer is the most common cancer in men and the second highest cause of cancer death in men in Western society (1). The prostate gland is composed of epithelial and stromal cells, which interact during normal prostatic morphogenesis and homeostasis (2). This process requires complex interactions between peptide growth factors and growth modulators that may be regulated either by androgens or by other factors. In cancer, some growth factor pathways become autocrine, enabling the epithelial cells to grow independently of stromal cells. In addition, prostate cancer progression involves the shifting of cells from androgen-dependent growth to an androgen-independent state (3).

Recent findings have highlighted the importance of Fibroblast Growth Factors (FGFs) in urological cancers. The FGFs represent one of the largest families of polypeptide growth and differentiation factors for cells of mesodermal and neuroectodermal origins (4). Probably the best-studied FGF in prostate cancer is bFGF. Clinically, bFGF is implicated in benign and malignant growth of the prostate and there is substantial evidence that its enhanced expression contributes to a more aggressive phenotype in prostate cancer (5,6).

Heparin Affin Regulatory Peptide (HARP) is an 18 kDa protein that belongs to a novel family of heparin-binding molecules (7). Different studies have shown that this polypeptide is present in many tissues, such as the nerves, heart, uterus, cartilages and bone extracts (8,9). HARP induces the proliferation of endothelial, epithelial and fibroblastic cells and is involved in cancer progression as an angiogenic and a tumor growth factor (10,11).

In the present study, we investigated whether HARP is expressed in two prostate cancer epithelial cell lines. We also studied its effect on the proliferation of these cells, as well as the possible interplay between bFGF and HARP.

METHODS

Human prostate cancer epithelial cells, LNCaP and PC-3 (ATCC) were grown in RPMI 1640 medium, supplemented with 10% fetal bovine serum (FBS) and antibiotics. The effect of bFGF and HARP on cell proliferation was determined by direct cell counting or by the MTT assay, as previously described (12). HARP present in the culture medium of cells was detected by Western analysis of samples enriched in heparin binding proteins, using heparin-Sepharose beads as previously described (13). The protein levels corresponding to the immunoreactive bands were quantified using the Image PC analysis software (Scion Corporation, Frederick, MD). The significance of variability between the results from vari-

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ous groups and the corresponding controls was determined by unpaired t-test or ANOVA.

RESULTS

Both cell lines tested produced and secreted HARP in their culture medium. When bFGF was added in the culture medium of LNCaP cells at a concentration of 10 ng/ml, the secretion of HARP was significantly induced 24 and 48h after the addition of bFGF. In contrast, when bFGF was added in the culture medium of PC-3 cells at the same concentration, the secretion of HARP was significantly inhibited 24 and 48h after the addition of bFGF. bFGF caused a significant concentration-dependent increase in the number of both LNCaP and PC-3 cells, 2 and 5 days after the addition of the growth factor in the cell culture medium. The effect was maximum at the concentration of 1 ng/ml. The effect of HARP on the proliferation of the cells was different between the two cell lines: It increased the number of LnCaP cells in a statistically significant and concentration-dependent manner, while it had no effect on the proliferation of PC3 cells.

CONCLUSIONS

HARP is expressed in prostate cancer epithelial cell lines.

bFGF differentially affects HARP protein levels in LNCaP and PC-3 cells although it induced the proliferation of both cell lines.

HARP differentially affects the proliferation of LNCaP and PC-3 cells.

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