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Expression patterns of AKT/protein kinase B, insulin-like growth factor-1, insulin-like growth factor-2 and insulin-like growth factor binding protein-3 in human prostate cancer

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Primary prostate cancer, prostatic adenocarcinoma (CaP), is one of the most frequent cancers among men and is the second-leading cause of cancer death in men in the Western world. Although early detection through serum testing for prostate specific antigen (PSA) and improved procedures for surgical intervention and radiation therapy have significantly reduced the number of fatalities, prognosis of CaP is still difficult. While many tumors are indolent, some grow aggressively, form metastases and eventually kill the patient. The emergence of effective new prognostic markers and approaches for therapy will depend on the elucidation of the molecular and cellular mechanisms involved in initiation and progression of prostate cancer. Therefore, it is necessary to establish a definitive molecular pathway of prostate cancer initiation and progression, accompanied by a precise understanding of the functional roles of candidate genes and regulatory pathways.

Insulin-like growth factors (IGF1 and IGF2) are important growth factors in the development of prostate cancer and its progression. The biological activity of IGFs is mediated via the type I IGF-receptor (IGF-IR) signaling pathway, which involves activation of the protein kinase AKT/PKB, and is regulated by inhibitory IGF-binding

proteins (IGFBP). Changes which raise the balance of IGF/IGF-IR activity versus IGFBP function can potentially contribute to carcinogenesis. Activation of the AKT pathway can suppress the apoptotic response, undermine cell cycle control and selectively enhance the production of key growth and survival factors related to the progression of CaP.

This study was designed to examine the expression of AKT, IGF1, IGF2 and IGFBP3 proteins by immunohistochemistry in human prostate cancer specimens and their correlation with clinicopathological parameters: Gleason score, pathological tumor stage (pT) and preoperative PSA serum level. Sixty three prostate cancer specimens were obtained from 63 patients (63.3 ± 4.8 years) who underwent radical prostatectomy for prostate cancer. Serial adjacent sections from each tissue block were subjected to immunohistochemical staining using a standard procedure (avidin – biotin - alkaline phosphatase). The primary antibodies used were: anti- AKT1/2, SC-1619, a goat polyclonal antibody; anti-IGF1, Sm1.2, anti-IGF2, S1F2, and anti-IGFBP3, MAB305, mouse monoclonal antibodies. The specificity of the antibody reactions was demonstrated by negative and positive controls, competitive immunohistochemistry and western blot analysis, as appropriate. The immunoreaction was scored separately in benign prostate tissue, low and high grade PIN lesions and prostate cancer tissue according to the following criteria: no visible reactivity was scored as negative (0), the positive reactions were scored into 3 grades according to the intensity of staining: (1), weak; (2), moderate; (3), strong and into 2 grades according to the fraction of positive cells: (1), <50% positive cells; (2), ≥50% positive cells. A score for the immunoreactivity was secondarily calculated, i.e. score = staining intensity × fraction of positive cells. All data were submitted to statistical analysis in a SAS system.

The results showed that AKT, IGF1 and IGF2 proteins were overexpressed in prostate cancer tissues compared to benign prostate tissues with respect to the intensity, fraction of positive cells and score of the immunoreactivity. Statistical analysis revealed increases in the expression of AKT, IGF1 and IGF2 from benign tissue over PIN lesions to tumor and with tumor progression. IGFBP3 expression was unchanged among all tissue types, regardless of intensity, fraction of positive cells and score of the immunoreactivity. The expression of AKT in prostate cancer, regarding the intensity, and the expression of IGF1 and IGF2, regarding the intensity, fraction of positive cells and score of the immunoreactivity were positively correlated to high

preoperative PSA serum levels (≥10ng/ml). Moreover, high expression of IGF2 in prostate cancer, with respect to fraction of positive cells and score of the immunoreactivity, was associated with high Gleason score (≥7). IGFBP3 expression was not correlated, regardless of intensity, fraction of positive cells or score of the immunoreactivity, with either preoperative PSA serum level or Gleason score or pT. In addition, no statistical correlation was found between the expression of AKT, IGF1, IGF2 and pT.

The present study revealed that the IGF/IGFBP balance is altered in prostate cancer. This alteration is characterized as significant overexpression of IGF1 and IGF2 whereas IGFBP3 expression was unchanged in tumor compared to benign prostate tissue. AKT/PKB, a central element of the IGF/IGF-IR/AKT signaling pathway is also overexpressed in prostate cancer. These data provide evidence that the IGF signaling pathway plays an important role in the initiation and progression of human prostate cancer. In addition, AKT and IGF1, IGF2 expression were positively correlated to at least one of the clinicopathological parameters. Further investigations on this pathway may illustrate the implications in prognosis and treatment of prostate cancer.