Detection of circulating tumor cells in patients with prostate cancer

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Abstract: The utility of nested reverse transcriptase-polymerase chain reaction (RT-PCR) was examined by using as primers the prostate-specific antigen (PSA) and prostate-specific membrane antigen (PSM) markers for prostate cancer staging. This method allows detection of a small number of cells expressing the human PSA or PSM gene, even when these cells are extensively diluted in a population of non PSA or PSM expressing cells. This method was performed on 25 patients with prostate cancer. Six patients had the RT-PCR for PSA or PSM negative. Four patients were positive on the PSA and negative on the PSM; these patients were without progression. Fifteen patients were tested positive on both markers. In twelve of them the progression of cancer took place and six of these 12 (50%) died within two years. The aim of this study was to test if PSA and PSM are good prognostic markers for monitoring the metastasing process in prostate cancer.

Key words: prostate cancer, RT-PCR, micrometastases, circulating tumor cells.

Abbreviations: CaP, prostate cancer; PSA, prostate-specific antigen; PSM, prostate-specific membrane antigen.

Introduction

In Europe and in the United States, prostate cancer (CaP) is the most commonly diagnosed malignancy in elder men and the second leading cause of cancer-related deaths in the male population (Diefenbach et al., 2002). There has been a shift in the philosophy of treating CaP in recent years (Hussain, 2003). Despite the high frequency, little is known about the molecular mechanisms involved in prostate tumorigenesis. Radical prostatectomy is the most effective treatment for patients with organ-confined CaP. Currently, the serum prostate-specific antigen (PSA) level is used for monitoring the course of disease after radical prostatectomy (Leak et al., 2002). However, many cases show that this level is not reliable. Therefore, there is an urgent need to develop new approaches able to detect the metastasing process of this disease. A perspective way can be the detection of micrometastases in the peripheral blood of patients with CaP. The circulating tumor cells in patients with CaP are originally epithelial prostatic cells that are characterized by very specific expression of genes for PSA and prostate-specific membrane antigen (PSM).

PSA is monomeric, 33 kDa large glycoprotein member of glandular kallikreins family. PSA is secreted primarily by epithelial cells that line the prostatic acini and ducts. Further members of the kallikrein gene family are the gene encoding glandular kallikrein 2, KLK2, which is also expressed in prostate, and the tissue kallikrein gene KLK I, which is expressed in pancreas and kidney. The PSA encoding gene KLK3 is localized on chromosome 19q13 (David et al., 2002; Stephan et al., 2002; Ito, 2004). It was sequenced; the complete gene is 6153 bp long and consists of 4 introns and 5 exons. It is expressed in most tissue types but at remarkable levels in prostate, and is tightly regulated by androgens through the androgen receptor (Cleutjens et al., 1996; Hernandez et al., 2004).

PSM is a type II transmembrane protein with folate hydrolase and N-acetylated-alpha-linked-acidic dipeptidase activity. PSM is a 750 amino acid residue long protein that has an apparent molecular weight of 100 kDa (due to post-translational modification) It is expressed by normal and neoplastic prostate cells. The PSM gene consists of 19 exons spanning approximately 60 kb of genomic DNA. By radiation hybrid analysis, the gene encoding PSM was mapped to 11p11-p12. On 11q14 there is a homologous but not identical gene to PSM (Tasch et al., 2001; Xiao et al., 2001).

The presence of PSA and PSM in the circulation could be one of the steps in the cascade of metastasing

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