Growth inhibition properties of the putative prostate cancer biomarkers PSP94 and CRISP-3

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One of the major problems in prostate cancer (PCa) diagnosis and treatment relates to the difficulty in discriminating between slow-growing, indolent cancers and more aggressive tumors with a lethal outcome.1 Therefore, much research has been devoted to the identification of reliable biomarkers that predict disease progression and treatment outcome. Two interacting prostate proteins, namely, the prostatic secretory protein of 94 amino acids (PSP94), encoded by the MSMB gene, and the cysteine-rich secretory protein CRISP-3, also known as SGP28, have been advanced as PCa biomarkers.2–5 In parallel, much attention has gone to the functional characterization of these proteins. Pathak et al.6 now report in the Asian Journal of Andrology that both PSP94 and CRISP-3 function as growth inhibitors of subsets of PCa cell lines, despite their inversely correlated expression levels during PCa progression (Figure 1a). Intriguingly, the CRISP-3-mediated growth inhibition was not affected by the presence of PSP94, suggesting a PSP94-independent role for CRISP-3 in prostate tumorigenesis.

PSP94 (10.7 kDa), also known as β-microseminoprotein or inhibin, is a small cysteine-rich protein, whereas CRISP-3 (28 kDa) is a glycoprotein with an amino- terminal sperm coating glycoprotein domain and a carboxy-terminal cysteine-rich domain. Both PSP94 and CRISP-3 are synthesized by the epithelial cells in the prostate gland and are secreted into the seminal plasma.2,7 In the seminal fluid of healthy males PSP94 is much more abundant than CRISP-3. However, both proteins can also be detected in serum where the level of PSP94 correlates with that in seminal plasma.8 However, this correlation does not hold for CRISP-3, because the latter is also derived from other sources, including neutrophilic granulocytes. Several gene expression-profiling and immunohistochemical studies have revealed that the expression of the MSMB gene gradually decreases during development PCa, i.e., from primary PCa to the late, highly invasive, androgen-independent state (reviewed in Ref. 2). In contrast, CRISP-3 is among the most upregulated genes in PCa5,7 (Figure 1a). Importantly, the altered levels of CRISP-3 and PSP94 in PCa are associated with a poor outcome in patients that underwent radical prostatectomy, suggesting that these proteins have potential as predictive biomarkers for PCa.9

The MSMB gene is (epi)genetically silenced in PCa.10–13 Recently, genome-wide association studies identified a C/T single nucleotide polymorphism rs10993994 in the promoter region of the MSMB gene that correlated with a significantly increased risk of developing PCa.10,11 The “TT” genotype, comprising two risk alleles, was associated with a lower expression of the MSMB gene and a severely decreased binding of the transcription factor CREB (cyclic AMP response element-binding protein), which was explained by changes of the CREB-binding site.12 In addition, the expression of MSMB is downregulated in PCa by methylation of...
and inhibits tumor growth. It also reduces (epi)genetically misregulated in PCa. It modulates circulating follicle-stimulating hormone levels, regulates sperm function and inhibits tumor growth. It also reduces the proliferation of rat cancer cell lines, human androgen-independent prostate cell lines and xenografted tumors by inducing apoptosis. The ectopic expression of CRISP-3 caused a growth inhibition of PC-3 cells by CRISP-3 was not affected by the stable expression of PSP94, which is further evidence that this effect of CRISP-3 is not mediated by PSP94. A limitation of the study of Pathak et al. is that the growth inhibition assays were based on the assumption that the transfection efficiency and the antibiotic selection are identical for the empty and PSP94-/CRISP-3-expressing cell line. The absence of an effect on PC-3 cells is at variance with another report and the general established function of PSP94 as a tumor suppressor. However, as suggested by the authors, such differences can be due to the distinct modes of PSP94 delivery, i.e., by the transfection of the PSP94-expressing construct or the addition of PSP94 protein to the culture medium. The use of stable inducible cell lines would further evidence that this effect of CRISP-3 could be overcome by using stable cell lines, preferably with an inducible system. The potential value of microseminoprotein-3 and beta-microseminoprotein as prostate cancer biomarker and therapeutic target. The novel serum marker, total prostate secretory protein 3 and beta-microseminoprotein levels in seminal plasma of young, healthy males. 

14 Garde SV, Basrur VS, Li L, Finkelman MA, Krishan A et al. Prostate secretory protein (PSP94) suppresses the growth of androgen-independent prostate cancer cell line (PC3) and xenografts inducing apoptosis. Prostate 1999; 38: 118–25.