Prostate cancer is the most frequently diagnosed malignancy in men and the second leading cause of cancer deaths among men in Western countries (1). There is an urgent need for appropriate diagnostic and prognostic markers, in addition to the established serum protease prostate-specific antigen (PSA), allowing an early diagnosis and the prediction of the clinical behavior of individual tumors. Although the involvement of certain genes and of chromosomal aberrations in prostate carcinogenesis has been suggested (2, 3), the molecular mechanisms underlying the initiation and progression of prostate cancer are only poorly understood.

Calcium-Binding Proteins S100A8 and S100A9 as Novel Diagnostic Markers in Human Prostate Cancer

Alexander Hermani, Jochen Hess, Barbara De Servi, Senad Medunjanin, Rainer Grobholz, Lutz Trojan, Peter Angel, and Doris Mayer

Abstract

Purpose: S100 proteins comprise a family of calcium-modulated proteins that have recently been associated with epithelial tumors. We examined the expression of two members of this family, S100A8 and S100A9, together with the S100 receptor RAGE (receptor for advanced glycation end products) in human prostate adenocarcinomas and in prostatic intraepithelial neoplasia.

Experimental Design: Tissue specimens of 75 patients with organ-confined prostate cancer of different grades were analyzed by immunohistochemistry for expression of S100A8, S100A9, and RAGE. In addition, in situ hybridization of S100A8 and S100A9 was done for 20 cases. An ELISA was applied to determine serum concentrations of S100A9 in cancer patients compared with healthy controls or to patients with benign prostatic hyperplasia (BPH).

Results: S100A8, S100A9, and RAGE were up-regulated in prostatic intraepithelial neoplasia and preferentially in high-grade adenocarcinomas, whereas benign tissue was negative or showed weak expression of the proteins. There was a high degree of overlap of S100A8 and S100A9 expression patterns and of S100A8 or S100A9 and RAGE, respectively. Frequently, a gradient within the tumor tissue with an increased expression toward the invaded stroma of the prostate was observed. S100A9 serum levels were significantly elevated in cancer patients compared with BPH patients or healthy individuals.

Conclusion: Our data suggest that enhanced expression of S100A8, S100A9, and RAGE is an early event in prostate tumorigenesis and may contribute to development and progression or extension of prostate carcinomas. Furthermore, S100A9 in serum may serve as useful marker to discriminate between prostate cancer and BPH.

Prostate cancer is the most frequently diagnosed malignancy in men and the second leading cause of cancer deaths among men in Western countries (1). There is an urgent need for appropriate diagnostic and prognostic markers, in addition to the established serum protease prostate-specific antigen (PSA), allowing an early diagnosis and the prediction of the clinical behavior of individual tumors. Although the involvement of certain genes and of chromosomal aberrations in prostate carcinogenesis has been suggested (2, 3), the molecular mechanisms underlying the initiation and progression of prostate cancer are only poorly understood.
in serum (20). Furthermore, overexpression of S100 mRNAs, including S100A8 and S100A9, was reported for gastric cancers (21). In contrast, S100A8 and S100A9 are frequently down-regulated in poorly differentiated esophageal squamous cell carcinomas (22, 23). Recently, expression of S100A2 and S100A4, two other proteins of the S100 family, was shown to be altered in human primary prostate cancer of different grades (24). For S100A2, a progressive loss with increasing tumor grade was observed, whereas S100A4 showed increased expression in tumors with higher grades.

For several members of the S100 protein family, a function as ligands for the receptor for advanced glycation end products (RAGE) has been discussed (25, 26). RAGE is a cell surface molecule that has been described as a multiligand receptor of the immunoglobulin superfamily. The interacting ligands of RAGE include advanced glycation end products, amyloid, afibrogen, β-amyloids, and S100 proteins (25, 27–29). The direct interaction of S100 proteins with RAGE has been shown for S100A12 (END-RAGE), S100B, S100A1, and S100P (25, 26, 30), and it is suggested that also other S100 family members are able to modulate RAGE signaling. Engagement of RAGE by a ligand triggers activation of central cellular pathways, including mitogen-activated protein kinases, Cdc42/Rac, and nuclear factor κB signaling pathways, thereby influencing features like cell survival, cell motility, and inflammatory response (25, 31). Blockade of RAGE signaling function was reported to lead to decreased growth and metastasis of tumors in mice (31). Expression of RAGE in prostate cancer was described with an increased expression in metastatic compared with nonmetastatic cases (32).

In the present study, we investigated the expression of S100A8 and S100A9 and of their putative receptor RAGE in human prostatic tissue in addition. We tested the value of S100A9 as a serum marker for prostate cancer.

**Materials and Methods**

**Tissue samples and patient sera.** Prostate tissue was obtained with consent from patients who underwent radical prostatectomy after diagnosis of cancer. Tumors were diagnosed and classified according to the Gleason system (33). H&E–stained paraffin sections serial to those submitted to *in situ* studies were used for verification of the diagnosis in the respective tissue specimens investigated. A total of 75 specimens from 24 low-grade (Gleason score 5–6), 19 Gleason score 7, and 32 high-grade (Gleason score 8–10) organ-confined prostate cancers, scaled according to Humphrey (34), were investigated. In these specimens, we observed 18 prostatic intraepithelial neoplasias (PIN). In 48 specimens, extended areas of benign prostatic tissue, including normal glands and single hyperplastic glands, were present.

Serum samples were obtained before surgery with consent from patients with subsequently diagnosed prostate cancer (*n* = 56) and from patients with benign prostatic hyperplasia (BPH, *n* = 56) as well as from 18 healthy men. Serum PSA of patients with BPH or cancer was determined before surgery. At time of surgery, patients’ age ranged between 55 and 82 years, and healthy men’s age ranged between 33 and 50 years.

**Immunohistochemistry.** For immunohistochemical staining of proteins, dewaxed formalin-fixed paraffin sections (4 μm) were rehydrated and submitted to epitope retrieval by microwaving either in 0.1 mol/L Tris (pH 9.5)/5% urea buffer for the detection of S100A8 and S100A9 proteins or in 0.01 mol/L citrate buffer (pH 6.0), respectively, for the detection of RAGE. After blocking with 5% bovine serum albumin in PBS, S100A8 and S100A9 were detected by specific rabbit polyclonal antibodies (Santa Cruz, Heidelberg, Germany, and kindly provided by J. Roth, Institute of Experimental Dermatology, University of Münster, Münster, Germany) and by the S100A9-specific mouse monoclonal antibodies S36.48 (a generous gift of Dr. P. Pfeifer, BMA Biomedicals, Augst, Switzerland) and 60B7 (kindly provided by R. Nozawa, Laboratory of Host Defenses, University of Shizuoka, Shizuoka, Japan). A rabbit polyclonal antibody (Santa Cruz) was used for detection of RAGE. A peroxidase 3,3′-diaminobenzidine system (DAKO, Hamburg, Germany) was used for the staining procedure. Finally, sections were counterstained with hematoxylin and mounted in glycerol/gelatin.

For each antigen detected, staining intensity and area of positive epithelial tissue were evaluated semiquantitatively. Staining intensities were defined as moderate (1) or strong (2), whereas absent to faint staining was considered as negative (0). For each section, areas with similar staining intensity were evaluated together. The total areas with moderate and strong staining, respectively, were estimated as percentage of the total area of a given epithelial growth pattern observed in a section. The cutoff for considerable positivity was set to 30%. When both moderate and strong staining was detected in the same section, the area representing the higher percentage of positivity, irrespective of the staining intensity, was used for statistical evaluation. Exact permutation test was used for comparison of benign prostatic tissue with tumor tissue and Fisher’s exact test for comparison of low and high-grade tumors.

**In situ hybridization.** *In situ* hybridization of S100A8 and S100A9 mRNAs was done on formaldehyde-fixed paraffin sections using standard procedures. Sequences selected for the generation of riboprobes specific for S100A8 and S100A9 transcripts, as verified by BlastN2 search, were amplified by reverse transcription-PCR using gene specific primers for S100A8 (forward primer: 5′-ATTGCCCACGCCTCTACAGG-3′; reverse primer: 5′-TGGGCTTCCTCATGCCCTTT-3′) and S100A9 (forward primer: 5′-CAGCTTGAACCCGAACATAGA-3′; reverse primer: 5′-CCACAGCCAAAGACAGTITGA-3′). PCR products representing nucleotides 128 to 329 (S100A8, Genbank accession no. NM_002964) and nucleotides 64 to 537 (S100A9, Genbank accession no. NM_002965) were cloned into pGEM-T vector (Promega, Mannheim, Germany) and confirmed by sequencing. Digoxigenin-labeled antisense and sense riboprobes were generated by *in vitro* transcription according to the digoxigenin application manual of Roche (Mannheim, Germany). Hybridization was done at 55°C overnight. Hybridized probes were detected using an alkaline phosphatase–conjugated antidigoxigenin antibody (Roche) and an alkaline phosphatase reaction using nitroblue tetrazolium/5-bromo-4-chloro-3-indolyl phosphate as substrates.

**ELISA.** A sandwich immunoenzyme assay for detection of S100A9 (BMA Biomedicals) was used to determine S100A9 concentrations in serum. The immunoassay was carried out following the manufacturer’s instructions. For statistical comparison of groups of individual values, the Mann-Whitney test was applied and data were used for evaluation of a receiver operator characteristic analysis.

**Results**

Immunohistochemical staining of human prostate tissue sections from 75 cases of prostate cancer revealed extensive expression of S100A8 and S100A9 proteins in adenocarcinomas of 58 (77%) and 51 (68%) cases, respectively. Protein expression was evaluated semiquantitatively in tumor and surrounding benign tissue. Both proteins showed a significant up-regulation (*P* < 0.0001, S100A8 and *P* < 0.0001, S100A9) in adenocarcinomas compared with benign prostatic tissue (Table 1). Comparison of low-grade and high-grade cancers revealed a preferential positivity of high-grade cancers (*P* = 0.053, S100A8 and *P* = 0.027, S100A9). Cancers diagnosed as Gleason 7 showed an intermediate ratio of positive to total number of cases compared with low-grade and high-grade tumors.
cancers for S100A8. For S100A9, the relative amount of positive Gleason 7 cases was lower than in low-grade cancers. There was no obvious difference between cancer grades concerning staining intensity.

A marked overlap between S100A8 and S100A9 staining patterns was apparent in corresponding tissue areas of serial sections (Fig. 1A and B). S100A8 and S100A9 protein expression was detected in single benign prostate glands usually adjacent to tumor tissue and commonly restricted to the basal cell layer (Fig. 1C). Benign hyperplastic glands showed no, or only weak, expression of the S100 proteins (Fig. 1D). In addition, positive staining was found in 8 of 18 PINs, indicating an up-regulation of S100A8 and S100A9 expression also in precancerous lesions (Fig. 1E).

Table 1. Evaluation of S100A8, S100A9, and RAGE positivity in human prostate cancer

<table>
<thead>
<tr>
<th>Grading</th>
<th>n</th>
<th>S100A8</th>
<th>P*</th>
<th>S100A9</th>
<th>P</th>
<th>RAGE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign prostatic tissue†</td>
<td>48</td>
<td>7/48</td>
<td>&lt;0.0001</td>
<td>5/48</td>
<td>&lt;0.0001</td>
<td>2/48</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Low grade (Gleason score 5-6)</td>
<td>24</td>
<td>15/24</td>
<td>0.053</td>
<td>14/24</td>
<td>0.027</td>
<td>13/19</td>
<td>0.16</td>
</tr>
<tr>
<td>Gleason score 7</td>
<td>19</td>
<td>13/19</td>
<td></td>
<td>9/19</td>
<td></td>
<td>13/19</td>
<td></td>
</tr>
<tr>
<td>High grade (Gleason score 8-10)</td>
<td>32</td>
<td>28/32</td>
<td>0.053</td>
<td>28/32</td>
<td>0.016</td>
<td>23/32</td>
<td>0.013</td>
</tr>
<tr>
<td>PIN</td>
<td>18</td>
<td>8/18</td>
<td>0.053</td>
<td>8/18</td>
<td></td>
<td>6/18</td>
<td>0.013</td>
</tr>
</tbody>
</table>

NOTE: Positively stained tissue was evaluated. Low-grade cancers were compared with high-grade cancers and PIN with benign prostatic tissue using Fisher’s exact test. *P < 0.05 was considered statistically significant.
†Benign prostatic tissue was compared with respective tumor tissue of the same cases using an exact permutation test. P values shown for benign prostatic tissue document significantly lower expression of S100A8, S100A9, and RAGE in benign prostatic tissue than in adenocarcinomas of all grades.

Fig. 1. Immunohistochemical staining of S100A8 (A) and S100A9 (B-Ł) protein in human prostate tissue. A and B, serial sections of an adenocarcinoma stained with S100A8 and S100A9 antibodies showing an overlapping expression pattern; C, benign gland showing S100A9-positive basal cells; D, weak to absent staining of S100A9 in hyperplastic glands; E, positive staining of PIN; F, expression gradient with increased positivity of tumor cells toward the stroma; G, S100A9 expression in a perineural tumor; nf, nerve fiber; H, high-grade adenocarcinoma with cribriform pattern; I, partially or completely stained glands beside negative glands; J, heterogeneous expression pattern of S100A9 in a low-grade tumor; K, tumor cells with nuclear staining; L, positive tissue histiocytes demonstrating specificity of antibody reaction. Magnifications: ×45 (A and B), ×120 (C, I, K, and L), and ×60 (D-H and J).
In 27 of 75 cases (36%), a staining gradient for the two S100 proteins was observed with an increased staining intensity in tumor cells adjacent to the stromal compartment or the capsule of the prostate (Fig. 1F). This gradient pattern was observed in carcinomas independently from the tumor grade. In addition, S100A8 and S100A9 expression was frequently observed in tumor tissue surrounding nerve fibers (Fig. 1G). In high-grade tumors, as shown for a cribriform tumor gland (Fig. 1H), and also in other growth patterns, a marked heterogeneity in immunoreactivity was generally observed. Tumor glands showing no staining were found adjacent to partly positive and strongly positive glands (Fig. 1I). Typically, groups of tumor glands or individual glands as well as single cells within the glands showed positive reaction (Fig. 1J). In 29 of 75 cases (39%), nuclear staining in addition to, or instead of, cytoplasmic staining was observed at least in subpopulations of cells (Fig. 1K), although without visible correlation with the tumor grade. The different antibodies used for detection of S100 proteins yielded similar staining patterns. S100A8 and S100A9 were detected in tissue histiocytes with all antibodies tested (Fig. 1L) independent of the histopathologic properties of different specimens, indicating a specific reaction under the experimental conditions applied. Additional staining was found in blood vessels, whereas stromal cells usually showed no specific staining reaction, although positively stained areas were observed in the stromal compartment. Expression of S100A8 and S100A9 by stromal cells, however, was not detected by RNA in situ hybridization of S100A8 and S100A9 mRNAs on prostate tissue sections using specific probes.

In situ hybridization revealed a marked overlap in S100A8 and S100A9 mRNA expression patterns in agreement with results obtained by immunohistochemistry. Positive reaction was observed in basal cells of benign glands (Fig. 2A and D) and in adenocarcinomas of different grades (Fig. 2B, E, G, and H). The staining showed varying intensity in different positive tumor areas, including PIN, the latter showing positive staining both in basal cells and in intraepithelial neoplastic cells (Fig. 2I).

Expression of the S100 receptor RAGE in prostate cancer was previously reported by Kuniyasu et al. (32). We were interested whether expression of RAGE coincides with the expression of S100A8 and S100A9. Immunohistochemical analysis of RAGE on the same set of prostate cancer tissues used for detection of the S100 proteins revealed a marked overlap of RAGE with S100A8 or S100A9 staining patterns (Fig. 3A-D and Supplemental Figs. S1 and S2). Also, for RAGE, a strong expression in tumor tissue invading the stroma or adjacent to connective tissue of the prostate capsule was observed (Fig. 3E). In addition, similar to S100A8 and S100A9, strong positivity was found in perineural tumor tissue (Fig. 3F). RAGE expression was detected in adenocarcinomas of different grades with a weak trend to increased positivity of high-grade cancers ($P = 0.16$; Table 1).

We next addressed the question of a putative diagnostic value of the S100 proteins as serum markers. For this purpose, an ELISA that was specific for S100A9 was selected. Comparing S100A9 serum levels of 37 cases of prostate cancer with 18 healthy controls, we discovered increased concentrations of S100A9 in serum of cancer patients ($P = 0.0037$; Fig. 4A). This observation, together with the finding of poor expression of S100A9 in benign hyperplastic tissue, prompted us to compare a larger number of prostate cancer cases ($n = 56$) with individuals diagnosed for BPH ($n = 56$).
We found significantly increased S100A9 serum levels in prostate cancer patients in comparison with BPH patients ($P < 0.0001$; Fig. 4B), the latter exhibiting values that were similar to values obtained for healthy individuals. These data indicate that elevated S100A9 serum concentrations are connected with cancer patients but not with patients suffering from a benign prostatic disease. S100A9 levels of low-grade and high-grade cancer patients were both elevated without significant differences.

**Fig. 3.** Detection of RAGE by immunohistochemistry. A to C, serial sections of prostate cancer tissue stained for RAGE (A), S100A8 (B), and S100A9 (C) showing an overlapping expression pattern; D, expression pattern of RAGE in a section serial to Fig. 1A and B, which show similar patterns of S100A8 and S100A9 staining; E, increased RAGE staining intensity in tumor tissue adjacent to stroma; F, RAGE-positive perineural tumor. Magnifications: $\times 45$ (A-E); $\times 60$ (F).

**Fig. 4.** S100A9 serum concentrations in prostate cancer patients (CaP) compared with healthy controls and BPH. A, box plot showing elevated S100A9 serum levels in patients with prostate cancer compared with healthy men ($P = 0.0037$); B, S100A9 levels are significantly increased in cancer patients compared with BPH patients ($P = 1.6 \times 10^{-7}$); C and D, receiver operator characteristic analysis of S100A9 and PSA comparing BPH and prostate cancer for all patients analyzed (C) and for patients with PSA < 10 ng/mL (D).
between the two groups. A comparison of S100A9 concentrations and the corresponding PSA serum levels in a receiver operator characteristic analysis revealed that S100A9 values provided a diagnostic reliability that was similar to the one based on PSA values in the cases analyzed (Fig. 4C). However, PSA and S100A9 were independent parameters. The evaluation of S100A9 serum levels of patients with PSA values <10 ng/mL still allowed a highly significant discrimination of BPH and cancer by S100A9 (P < 0.0001), exceeding that achieved with PSA (P = 0.02; Fig. 4D; Table 2).

The present data show that S100A8 and S100A9 mRNA and proteins are up-regulated in PIN and in prostatic adenocarcinomas of different histopathologic grades. The expression patterns of both proteins are similar to that observed for the S100 receptor RAGE. S100A9 was additionally detected with patterns of differential gene expression during wound-healing processes and are considered to be expressed in a cell type–or tissue-specific manner. However, deregulated expression of several members of the S100 family, including S100A8 and S100A9, under various pathologic conditions has been reported (7, 35). Besides the well-documented expression in inflammatory skin diseases (15), S100A8 and S100A9 and other members of the S100 family recently have been associated with rheumatoid arthritis (36), psoriasis (37), cutaneous wound repair (16), and various experimental and human neoplasms (4, 17–19). It is noteworthy that the patterns of differential gene expression in cancer, particularly in prostate and liver cancer, strongly correlate with the pattern of differential gene expression during wound-healing processes (38). These observations suggest additional functions of the S100 protein family in injury and disease pathogenesis. Our findings on the expression of S100A8 and S100A9 in prostatic adenocarcinomas support this hypothesis. Using immunohistochemistry and RNA in situ hybridization on human prostate tissue samples of patients with diagnosed prostate cancer, we could show that S100A8 and S100A9 are up-regulated in prostatic adenocarcinomas and in PIN, suggesting an early involvement of the proteins in prostate cancer. It is intriguing that the tumor cells, as precursors of which the luminal cells are considered (39), greatly restore the ability of S100A8 and S100A9 expression, whereas in benign glands expression was found only in the basal cell layer, which is responsible for the epithelial/stromal contact. Recently, different compounds that also participate in the formation of extracellular matrix of connective tissue or basement lamina were found to associate with S100 proteins. For neutrophils, involvement of S100A8 and S100A9 in the modulation of transendothelial migration by interaction with glycosaminoglycans and carboxylated glycans has been shown (40, 41). In addition, S100A8 and S100A9 have been described to increase adhesion of monocytes to fibronectin (42). Worth mentioning in this context is the observed close spatial correlation of S100A8- and S100A9-positive basal cells and the stroma on the one hand and positive cancer cells and stroma on the other hand (see also Supplemental Fig. S2). Our finding of increased S100A8, S100A9, and RAGE expression toward the invaded connective tissue further suggests a functional relation with the extension of epithelial tissue. With respect to migration events, an involvement of RAGE engaged by S100B, S100A1, and amphoterin has been associated with neurite outgrowth (26, 28). Furthermore, RAGE has been shown to play an important role for tumor growth and metastases formation in mice (31). Engagement of RAGE is known to trigger different signaling cascades, usually leading to activation of the transcription factor nuclear factor κB (25, 26, 43). Interestingly, overexpression of p65, the active subunit of nuclear factor κB, was found to occur as an early event in the development of prostate cancer (44). Furthermore, active nuclear factor κB was frequently detected in prostatic adenocarcinomas with peripheral location and has been linked functionally to mechanisms that promote perineural invasion (45), which is the major mechanism of prostate cancer spread outside the prostate (46). Together with our findings of enhanced expression of RAGE and S100A8/S100A9 in prostate cancer and of frequent positivity of perineural tumor tissue (see also Supplemental Figs. S1 and S2), it is intriguing to speculate that S100/RAGE signaling events may be involved in the development of survival or growth advantages via nuclear factor κB. Therefore, the S100/RAGE signaling pathway may represent a suitable target for prevention or treatment strategies for prostate cancer. In addition, our data provide evidence for a diagnostic value of the S100 proteins. We found a significant increase of S100A9 serum concentrations in prostate cancer patients compared with healthy individuals or to BPH patients. In comparison to PSA, currently the best diagnostic serum marker for prostate cancer, S100A9 distinguished with a higher sensitivity between BPH and cancer patient groups with low PSA levels. Thus, S100A9 may represent a helpful candidate for the dissection of prostate cancer and BPH cases, where PSA measurement fails to provide reliable diagnostic information. Most recently, S100A9 was discovered by another group in voided urine after prostatic massage from patients with prostate cancer using two-dimensional gel electrophoresis (47). Together with the present study, this finding further supports the putative diagnostic value of S100A9 measurement in body fluids as a marker for prostate cancer.

### Table 2. Statistical evaluation of S100A9 and PSA serum levels for dissection of BPH patients from cancer patients

<table>
<thead>
<tr>
<th>Patient group</th>
<th>n</th>
<th>CaP</th>
<th>BPH</th>
<th>S100A9</th>
<th>PSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA &gt; 0 ng/mL</td>
<td>56</td>
<td>56</td>
<td>1.6 × 10⁻⁷</td>
<td>1.5 × 10⁻⁶</td>
<td></td>
</tr>
<tr>
<td>PSA_{&lt;10 ng/mL}</td>
<td>34</td>
<td>56</td>
<td>5.1 × 10⁻⁶</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>PSA_{&lt;10 ng/mL}</td>
<td>34</td>
<td>49</td>
<td>1.3 × 10⁻⁵</td>
<td>0.0006</td>
<td></td>
</tr>
</tbody>
</table>

Note: P values were calculated using Mann-Whitney test, for comparison of S100A9 and PSA in cancer patients with BPH patients grouped regarding PSA levels.

Abbreviation: CaP, prostate cancer.
In summary, our data show that S100A8 and S100A9 are up-regulated in adenocarcinomas of the prostate and in PIN. The expression of both proteins markedly overlaps with the expression of the S100 receptor RAGE, which has been associated with invasive potential of different tumors. The use of S100A9 as a serum marker for the early detection of prostate cancer additionally may help to facilitate diagnosis of prostate cancer patients with BP1H.

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