Reduced Infiltration of Class A Scavenger Receptor Positive Antigen-Presenting Cells Is Associated with Prostate Cancer Progression

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ABSTRACT

The class A macrophage scavenger receptor (SR-A) is expressed in antigen presenting cells and is involved in host immune responses. Germ-line mutation of this gene has been associated with increased risk of human prostate cancer. However, there is little known about its expression in normal or neoplastic human prostate tissues. Double immunofluorescent labeling with monoclonal antibodies to SR-A and specific macrophage and dendritic cell markers was used to identify cells expressing SR-A in human prostate tissues. SR-A immunohistochemical staining was performed on paraffin sections of normal prostate, prostatic intraepithelial neoplasia (PIN) lesions, and prostate cancers from radical prostatectomy specimens. SR-A was expressed in a subset of macrophages and dendritic cells that infiltrated prostatic tissues. The majority of SR-A-positive cells coexpressed CD68, and a relatively low percentage expressed S100 protein. The number of SR-A-positive cells was significantly increased in PIN as compared with normal prostatic tissue (P = 0.0176). In contrast, the number of SR-A-positive cells decreased with tumor progression. A lower SR-A-positive cell density was associated with higher clinical stage (P = −0.26; P = 0.0234). Inverse associations were also found between SR-A density and positive lymph nodes (P = −0.23; P = 0.0437), tumor size (P = −0.31; P = 0.0100) and preoperative PSA levels (P = −0.32; P = 0.0057). SR-A density is a significant predictor of disease-free survival after surgery univariately (P = 0.0003), as well as multivariately, adjusted for known clinical and pathological markers including preoperative prostate-specific antigen, clinical stage, Gleason score, surgical margin, extraprostatic extension, and seminal vesicle invasion, as well as lymph node metastasis (P = 0.0021). The preferential accumulation of SR-A-positive cells in PIN suggests a role for SR-A in the APC response to early malignancy. A reduction in the number of SR-A-positive cells demarcates tumor progression as indicated by clinical and pathological correlations. Our results additionally indicate that systematic measurement of SR-A density is a strong prognostic marker for clinical outcome after surgery.

INTRODUCTION

Chronic or recurrent infection caused by bacteria or viruses has been suggested as an etiologic factor of human prostate cancer (1). This notion has been supported by epidemiological findings indicating that patients with prostatitis or sexually transmitted disease are at higher risk for prostate cancer (2–4) and some pathological observations that indicate frequent coexistence of prostatic infection/inflammation with premalignant lesions and localized prostate cancers (5, 6). A causal relationship between inflammation/innate immunity and cancer has become more widely accepted, yet the molecular and cellular mechanisms that underpin this relationship remain largely unresolved (7). The possible link between inflammatory changes and prostate cancer risk received some support from recent genetic studies, which identified germ-line mutations of the class A macrophage scavenger receptor (SR-A) gene that is involved in host defense immunity as associated with increased risk of prostate cancer (8, 9). It was postulated that defective expression of SR-A, which is associated with macrophage function, could lead to uncontrolled inflammatory damages resulting in malignancy.

The SR-A gene (also known as macrophage scavenger receptor I, MSR1) is located on short arm of chromosome 8p22, a site linked to some hereditary prostate cancers (10). It encodes multiple SR-A isoforms generated by alternative splicing (11). The type 1 and 2 SR-A isoforms are multidomain, trimeric cell membrane glycoproteins that can recognize multiple ligands including modified lipoproteins, polyglycanic acid, polyninosinic acid, polysaccharide, and other polyanionic molecules (12, 13). Because of the broad spectrum of ligands, SR-A is multifunctional (13). SR-A is able to mediate the uptake of modified low-density lipoproteins involved in lipid metabolism and arteriosclerosis (14, 15). As one of the pattern recognition molecules on the surface of macrophages, SR-A is capable of recognizing bacteria and, thus, is involved in host innate immunity (16, 17). SR-A has also been shown to function in uptake and clearance of various cellular components and apoptotic cells, suggesting a role in tissue homeostasis (18). Although SR-A is predominantly localized to macrophages, its expression in vascular endothelial cells, smooth muscle cells, fibroblasts, and cultured dendritic cells has been reported (19–21). However, little is known about SR-A expression or its localization pattern in normal human prostatic tissues. Furthermore, to our knowledge, there has been no study directly addressing its functional role in prostate cancer.

In this study we document SR-A protein expression in both normal and neoplastic human prostates using immunohistochemical techniques. We show that SR-A expression is associated with antigen-presenting cells including both macrophages and dendritic cells. We also demonstrate that SR-A-positive cells infiltrate prostatic intraepithelial neoplasia (PIN) lesions at significantly higher densities compared with normal tissues. Importantly, significant inverse associations between the SR-A-positive cells and the clinical/pathological features of prostate cancer and patient clinical outcome are also demonstrated.

MATERIALS AND METHODS

Patients and Tissue Processing. Paraffin sections from 5 normal prostates obtained from organ donors, 9 prostatectomy specimens in which there were PIN lesions but no detectable local cancers, and 90 prostate cancer specimens obtained at radical prostatectomy were used in this study. The specimens were obtained from the Specialized Program of Research Excellence Tissue Bank, The Methodist Hospital, Baylor College of Medicine. Patients who had undergone radical prostatectomy were age 45–77 years (mean, 63). No patient received any treatment for cancer before surgery that was done by a single surgeon between 1983 and 1996. The Institutional Review Board-approved consent forms were used to obtain assent from the patients. Preoperatively, the patients had a cancer staged according to the Union Internationale Contra Cancrum clinical staging system (1992) as T1a-c (n = 21), T2a-c (n = 44), and T3a (n = 13). After the surgery, the prostate specimens were sliced into 5-mm-thick tissue blocks as described previously (22). The tissue blocks were then fixed in 10% formalin and embedded in paraffin. H&E-stained sections from each tissue block were evaluated by a single pathologist (T. M. W.) for tumor histological differential status as dem-
onstrated by Gleason score and pathological stage (Tumor-Node-Metastasis system). The index cancers were identified and used for immunohistochemistry. Recurrence was defined as a postoperative prostate-specific antigen (PSA) level \(>0.4 \text{ ng/ml} \) (Hybritech, Inc., San Diego, CA) on two successive measurements.

**Immunohistochemistry.** The prostate sections were deparaffinized and rehydrated. They were then heated in citrate buffer (0.01 M; pH 2.0) within an 800 W microwave oven for 12 min for antigen retrieval. Endogenous peroxidase in sections was inactivated in 2% \(\text{H}_2\text{O}_2\) for 10 min. The sections were then blocked in 3% normal horse serum in 0.2 M PBS (pH 7.4) and followed by incubation in monoclonal antibody to human SR-A (TransGenic, Inc., Kumamoto, Japan). This antibody recognizes the recombinant human SR-A corresponding to amino acid residues 131–451 of SR-A and was able to react with both the type 1 and type 2 isoforms (23). This antibody was diluted 1:25 in PBS with 0.5% normal horse serum. The sections were incubated in the primary antibody for 2 h at room temperature. They were then processed after standard avidin-biotin complex immunostaining procedures with an ABC kit (Vector Laboratories, Burlingame, CA). Immunoreaction products were visualized in a 3,3'-diaminobenzidine/\(\text{H}_2\text{O}_2\) solution. The specificity of the immunoreactions was confirmed by the negative results from adjacent sections that were incubated either in PBS or in normal mouse serum replacing the specific antibodies. Immunofluorescent double labeling was performed as for single staining for SR-A up to the first primary antibody incubation. Sections were then incubated with biotinylated goat antimouse IgG (1:100) for 40 min, followed by incubation in FITC-conjugated streptavidin (Zymed) for 30 min.

After washing twice in PBS the sections were reblocked in 1.5% horse serum for 20 min and incubated with the monoclonal antibody either to S100 or to CD68 (Dako, Glostrup, Denmark) for 60 min. The S100 and CD68 antibodies were detected with Cy-3 conjugated donkey antimouse IgG (Jackson ImmunoResearch Lab.). Sections were visualized using a fluorescence microscope. Specificity of double labeling was verified by replacing S100 or CD68 antibody with normal mouse serum.

**Histological Analysis.** SR-A-positive cells were quantified by systematically screening the entire cancer. All of the counting was done without knowledge of the clinical information. For each specimen 15–30 ocular measuring fields, each composed of 100 grids and having a real area of 0.0625 mm\(^2\) were randomly chosen under a microscope at a power of \(\times 400\) within a cancer. Sections were positioned such that each measuring field was completely occupied by only cancer tissue. All of the SR-A-positive cells in each measuring field were counted and stratified as those localized to cancer stroma versus those in contact with cancer cells or penetrating into a cancer lumen. The number of SR-A-positive cells per mm\(^2\) of total cancer tissue area was defined as SR-A\(_{\text{total}}\). The number of stromal SR-A-positive cells per mm\(^2\) of cancer stroma area was recorded as SR-A\(_{\text{stroma}}\). Similarly, SR-A\(_{\text{cancer}}\) was determined from the number of SR-A-positive cells per mm\(^2\) in the cancer cell compartment. From each of the normal and PIN specimens, 5–20 measuring fields over glandular epithelia and their surrounding stroma were evaluated, and SR-A-positive cells were counted and expressed as SR-A\(_{\text{total}}\).

**Statistical Analysis.** The correlation of SR-A-positive cells with pathological and clinical variables was evaluated using the Spearman’s correlation

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![Fig. 1](cancerres.aacrjournals.org) Avidin-biotin complex immunostaining demonstrating scavenger receptor class A expression in human prostate using a monoclonal antibody. Positively labeled cells are shown in normal prostate (A); a prostatic intraepithelial neoplasia lesion (B); prostate cancer (C); and areas of inflammation within a benign prostate (D and E). Original magnification, A–D: \(\times 200\); E: \(\times 400\).
coefficient testing. One-way ANOVA was used to compare means of CD68 and S100 percentages between three types of tissue. Comparisons in SR-A total among normal, PIN, and prostate cancer specimens were made using Mann-Whitney test. Univariate analysis of SR-A levels as continuous markers and multivariate analyses were performed using the Cox proportional hazard regression model. The hazard ratio and its 95% confidence interval were recorded for each marker. Survival curves of relapse-free survival were obtained using a Kaplan-Meier analysis and tested by log-rank test. $P < 0.05$ were considered statistically significant in all of the analyses. All of the analyses were performed with statistical software SPSS 11.0 (SPSS Inc., Chicago, IL).

RESULTS

SR-A Is Localized to a Subset of Macrophages and Dendritic Cells in Normal Prostatic Tissues and in Prostate Cancer. SR-A expression was detected in all of the prostate samples analyzed including normal prostate, PIN, and prostate cancer specimens. SR-A was localized to the cell membrane and cytoplasm of mononuclear cells in all of the specimens (Fig. 1). In normal and neoplastic prostate tissues, SR-A-positive cells mainly infiltrated prostatic stroma, and to a lesser extent, the epithelia. SR-A-positive cells exhibited morphological features similar to those of macrophages, although they appeared to have a smaller average size than macrophages. Infrequently, some SR-A-positive cells with vascular endothelial cell features were also observed. To determine the fraction of SR-A-positive macrophages we used antibodies specifically for SR-A and for CD68, a glycoprotein primarily expressed in macrophages (24) in double-labeling analysis of 5 normal, 6 PIN, and 12 cancer specimens (Fig. 2). Although highly variable, the SR-A-positive/CD68-positive cell fraction was 30.3, 28.3, and 36.3 median percent in normal, PIN, and tumor tissues, respectively. These differences were not statistically significant. Within the SR-A-positive cell group, the majority of cells were immunoreactive for antibody to CD68 (Table 1). The mean

<table>
<thead>
<tr>
<th>Specimens</th>
<th>CD68</th>
<th>S100</th>
<th>CD68</th>
<th>S100</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (range)</td>
<td>Mean (range)</td>
<td>Mean (range)</td>
<td>Mean (range)</td>
</tr>
<tr>
<td>Normal</td>
<td>93.0 (86.2–96.1)</td>
<td>14.6 (3.8–24.6)</td>
<td>90.5 (86.0–96.8)</td>
<td>16.4 (6.5–25.8)</td>
</tr>
<tr>
<td>PIN</td>
<td>6</td>
<td>32.3</td>
<td>14.2</td>
<td>0.7–32.3</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* SR-A, scavenger receptor class A; PIN, prostatic intraepithelial neoplasia; n, number of specimens.
values of the CD68-positive/SR-A-positive cell fraction were 93, 90.5, and 93.3% in normal, PIN, and tumor specimens, respectively. The differences between tissue groups were not statistically significant ($P = 0.2430$). To determine whether the CD 68-negative/SR-A-positive cells contained a dendritic cell subpopulation, some sections were double-labeled with SR-A antibody and S100 antibody (Fig. 3), which recognizes Langerhans cells, a subset of dendritic cells present in multiple organs including human prostate (25). The results indicated that the mean fraction of S100-positive/SR-A-positive cells was 14.6, 16.4, and 14.2% in normal, PIN, and prostate cancer specimens, respectively. These differences were not statistically significant ($P = 0.8401$). Overall, these results suggest that in benign and neoplastic human prostate tissues SR-A-positive cells predominantly represent macrophages together with a small subset of specialized dendritic cells.

In Benign Prostatic Tissues SR-A Positive Cells Accumulate in Areas of Inflammation and in PIN Lesions. In normal prostatic tissues from organ donor specimens the number of SR-A-positive cells was low, with the majority of cells present in the stroma, and a relatively small fraction present in the glandular epithelium and lumens (Fig. 1A). However, in the benign prostatic tissues from cystoprostatectomy specimens significantly higher numbers of SR-A-positive cells accumulated in the areas undergoing inflammatory changes (Fig. 1D) Some of the SR-A-positive cells penetrated into the lumens and displayed features of foamy cells (Fig. 1E). SR-A-positive cells infiltrated PIN lesions at significantly higher densities compared with normal prostatic tissues from organ donors ($P = 0.0167$) or prostate cancers ($P = 0.0012$; Fig. 4). In prostate cancer specimens, tumor-associated SR-A-positive cells were distributed in distinguishable compartments i.e., the tumor-associated stroma or cancer cell region in which they are in direct contact with cancer cells or were penetrating into cancer cell lumens. In malignant tissues the majority of SR-A-positive cells were distributed within the tumor-associated stroma.

Correlation of SR-A-Positive Cells with Clinical Parameters and Tumor Pathology. Among the 90 cancer specimens examined, 78 had complete pathological and clinical follow-up information and, therefore, were used for correlation analyses. This cohort consisted of patients with 52 (67%) having positive extracapsular extension, 22 (28%) having positive seminal vesicle invasion, 15 (19%) having positive lymph nodes, and 18 (23%) having positive margins. Clinical stages were distributed as 21 (27%) T1, 44 (56%) T2, and 13 (17%) T3a. Seven patients (9%) had Gleason score <6, 19 patients (24%) had Gleason score 6, 36 patients (46%) had Gleason score 7, and 16 patients (20.5%) had >7. Preoperative PSA levels (ng/ml) ranged from 0.7 to 100 with a mean level of 15.0 and median of 10.5. Tumor volumes (ml) ranged from 0.9 to 20.18 with mean volume of 4.3 and median of 2.8. The numerical densities of SR-A-positive cells in...
for every 10 units reduction in SR-A total risk of experiencing a recurrence during follow-up. The value of SR-A total, SR-A stroma, or SR-A cancer was significantly inversely associated with disease-free survival (hazard ratio (HR) = 0.983; HR \textsuperscript{-1} = 1.017; P = 0.0003; Table 3). The inverse hazard ratio of 1.017 means that patients with a high SR-A\textsubscript{total} level had 3.6 times more chances of experiencing a recurrence during the follow-up time than a patient with a high SR-A\textsubscript{total} level. This difference in risk can be also observed on the Kaplan-Meier plot (Fig. 5). When SR-A\textsubscript{stroma} was stratified using the median (≤ 154.92 mm\textsuperscript{2}) as cutoff, similar results were observed: patients with low expression had 2.8 times more chances of experiencing a recurrence during the follow-up time (P = 0.0021). These results strongly support the hypothesis that high densities of SR-A-positive cells within the total cancer area and cancer stroma were associated with a lower rate of recurrence after surgery. In this series of patients, other known predictors of recurrence were recorded as SR-A\textsubscript{stroma}, SR-A\textsubscript{cancer}, or SR-A\textsubscript{total}, respectively. In general, patients with cancers of relatively high clinical stage, a higher Gleason score, seminal vesicle invasion, or lymph node involvement tended to have relatively lower SR-A\textsubscript{total} and/or SR-A\textsubscript{stroma}, and some of these associations were found to be statistically significant (Table 2). The Spearman correlation analyses showed that both SR-A\textsubscript{total} and SR-A\textsubscript{stroma} were inversely correlated with clinical stage (ρ = -0.31; P = 0.0100), lymph node involvement (ρ = -0.32; P = 0.0057), and preoperative PSA levels (ρ = -0.32; P = 0.0057). However, correlations between Gleason score and SR-A\textsubscript{total}, SR-A\textsubscript{stroma}, or SR-A\textsubscript{cancer} were not statistically significant (all P > 0.05).

**SR-A\textsubscript{total} Is a Predictor of Disease-Free Survival.** The recurrence-free follow-up time for the 78 cases ranged 0.8–131.7 months and averaged 47.75 months. Forty of the 78 patients (51%) had biological recurrences (PSA ≥ 0.4 ng/ml, on two successive measurements) during follow up. The value of SR-A\textsubscript{total}, SR-A\textsubscript{stroma}, or SR-A\textsubscript{cancer} as a continuous predictive marker for recurrence was analyzed separately in this set of patients using the Cox proportional hazard regression model. Univariate, only the SR-A\textsubscript{total} but not SR-A\textsubscript{cancer} or SR-A\textsubscript{stroma} was significantly inversely associated with disease-free survival (hazard ratio (HR) = 0.983; HR \textsuperscript{-1} = 1.017; P = 0.0003; Table 3). The inverse hazard ratio of 1.017 means that for every 10 units reduction in SR-A\textsubscript{total} risk of experiencing a recurrence (estimated by HR) during the follow-up time increases by 17%. The SR-A\textsubscript{total} data of this cohort were additionally stratified with the median value of 72.8 mm\textsuperscript{2} as a cutoff point, with 39 cases (50%) falling into the low category (SR-A\textsubscript{total} ≤ 72.8), and 39 cases (50%) falling into the high (SR-A\textsubscript{total} > 72.8) category. A highly significant association of the low SR-A\textsubscript{total} category with poor disease-free survival was established by the univariate analysis (HR = 0.238; HR \textsuperscript{-1} = 3.58; P = 0.0002; Table 3). Thus, a patient with a SR-A\textsubscript{total} level ≤ 72.8 mm\textsuperscript{2} had 3.6 times more chances of experiencing a recurrence during the follow-up time than a patient with a high SR-A\textsubscript{total} level. This difference in risk can be also observed on the Kaplan-Meier plot (Fig. 5). When SR-A\textsubscript{stroma} was stratified using the median (≤ 154.92 or > 154.92 mm\textsuperscript{2}) as cutoff, similar results were observed: patients with low expression had 2.8 times more chances of experiencing a recurrence during the follow-up time (P = 0.0021). These results strongly support the hypothesis that high densities of SR-A-positive cells within the total cancer area and cancer stroma were associated with a lower rate of recurrence after surgery. In this series of patients, other known predictors of recurrence were recorded as SR-A\textsubscript{stroma}, SR-A\textsubscript{cancer}, or SR-A\textsubscript{total}, respectively. In general, patients with cancers of relatively high clinical stage, a higher Gleason score, seminal vesicle invasion, or lymph node involvement tended to have relatively lower SR-A\textsubscript{total} and/or SR-A\textsubscript{stroma}, and some of these associations were found to be statistically significant (Table 2). The Spearman correlation analyses showed that both SR-A\textsubscript{total} and SR-A\textsubscript{stroma} were inversely correlated with clinical stage (ρ = -0.31; P = 0.0100), lymph node involvement (ρ = -0.32; P = 0.0057), and preoperative PSA levels (ρ = -0.32; P = 0.0057). However, correlations between Gleason score and SR-A\textsubscript{total}, SR-A\textsubscript{stroma}, or SR-A\textsubscript{cancer} were not statistically significant (all P > 0.05).

**Table 2: Correlation of SR-A\textsuperscript{A}-expressing cells with clinical and pathological parameters of prostate cancer**

<table>
<thead>
<tr>
<th>SR-A\textsuperscript{A} + cells vs.</th>
<th>Total area</th>
<th>Stroma area</th>
<th>Cancer cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical stage</td>
<td>n</td>
<td>ρb</td>
<td>p</td>
</tr>
<tr>
<td>Gleason score (cont.’)</td>
<td>78</td>
<td>-0.257</td>
<td>0.0234</td>
</tr>
<tr>
<td>Positive surgical margins</td>
<td>78</td>
<td>-0.198</td>
<td>0.0817</td>
</tr>
<tr>
<td>ECE</td>
<td>78</td>
<td>-0.025</td>
<td>0.8280</td>
</tr>
<tr>
<td>SVI</td>
<td>78</td>
<td>-0.178</td>
<td>0.1186</td>
</tr>
<tr>
<td>Positive LN</td>
<td>78</td>
<td>-0.117</td>
<td>0.3075</td>
</tr>
<tr>
<td>Preoperative PSA (ng/ml)</td>
<td>72</td>
<td>-0.229</td>
<td>0.0437</td>
</tr>
<tr>
<td>Tumor volume</td>
<td>70</td>
<td>-0.306</td>
<td>0.0100</td>
</tr>
</tbody>
</table>

a: SR-A, scavenger receptor class A; ECE, extracapsular extension; SVI, seminal vesicle invasion; LN, lymph node; PSA, prostate-specific antigen.

b: Spearman correlation coefficient.

c: Radical prostatectomy specimens.

**Table 3: Univariate and multivariate Cox Proportional hazards model for time to recurrence**

<table>
<thead>
<tr>
<th>Prognostic factors</th>
<th>Model</th>
<th>Hazard ratio \textsuperscript{-1}</th>
<th>95% confidence interval</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>SR-A\textsubscript{stroma} ≤ 154.92</td>
<td>Univariate</td>
<td>1.17</td>
<td>1.01–1.26</td>
<td>0.0003</td>
</tr>
<tr>
<td>SR-A\textsubscript{stroma} ≤ 154.92</td>
<td>Multivariate \textsuperscript{a}</td>
<td>1.23</td>
<td>1.01–1.04</td>
<td>0.0029</td>
</tr>
<tr>
<td>SR-A\textsubscript{stroma} &gt; 154.92</td>
<td>Univariate</td>
<td>3.58</td>
<td>1.81–7.09</td>
<td>0.0002</td>
</tr>
<tr>
<td>SR-A\textsubscript{stroma} &gt; 154.92</td>
<td>Multivariate \textsuperscript{a}</td>
<td>4.93</td>
<td>1.95–12.42</td>
<td>0.0007</td>
</tr>
<tr>
<td>SR-A\textsubscript{stroma} &gt; 154.92</td>
<td>Multivariate \textsuperscript{a}</td>
<td>2.84</td>
<td>1.46–5.54</td>
<td>0.0024</td>
</tr>
<tr>
<td>SR-A\textsubscript{stroma} &gt; 154.92</td>
<td>Multivariate \textsuperscript{a}</td>
<td>2.35</td>
<td>1.01–5.50</td>
<td>0.0485</td>
</tr>
</tbody>
</table>

a: \textsuperscript{-1} is an inverse relationship between SR-A and risk of recurrence.

b: SR-A, scavenger receptor class A.

c: Hazard ratio and 95% confidence interval are for 10 unit changes in SR-A\textsubscript{total}.

d: Multivariate models also included clinical stage, Gleason score, seminal vesicle invasion, surgical margin, lymph node involvement, preoperative prostate-specific antigen level, extracapsular extension, and tumor size.

e: Marker grouped as high versus low.

**Fig. 5. A,** recurrence-free survival probability after radical prostatectomy for patients with high or low expression levels of scavenger receptor class A (SR-A) in total cancer area (SR-A\textsubscript{total}) stratified according to the median value of SR-A\textsubscript{total} (≤ 72.8 or > 72.8). **B,** recurrence-free survival probability after radical prostatectomy for patients with high or low expression levels of SR-A in cancer-associated stroma (SR-A\textsubscript{stroma}) stratified according to the median value of SR-A\textsubscript{stroma} (≤ 154.92 or > 154.92).
ence-free survival including extracapsular extension, seminal vesicle invasion, lymph node metastasis, surgical margin status, preoperative PSA level, tumor volume, and Gleason score were all significant predictors in univariate analyses, as expected. Multivariate analysis that included SR-A_total and all of the above parameters showed that SR-A_total is a very strong independent predictor of disease progression when used either as a continuous or a grouped variable. For any two patients with identical clinical/pathological characteristics, a patient with low levels (72.8/mm²) of SR-A_total had a 4.9 times greater chance of experiencing a recurrence during the follow-up time than a patient with high levels (P = 0.0007), whereas for every 10-unit decrease in SR-A_total this risk increased by 23% (P = 0.0029). A similar conclusion could be drawn from multivariate analysis of SR-Astroma, showing a 2.3 times higher risk of recurrence for patients with low SR-Astroma (≤154.92 mm²; P = 0.049; Table 3). These results indicate that high densities of SR-A-positive cells within the total cancer area and stroma as indicated by SR-A_total and SR-Astroma are independent predictors of a lower recurrence rate after surgery.

DISCUSSION

In this study we showed that SR-A is expressed in a subset of macrophages and dendritic cells in human prostate tissues. Both cell types can be categorized as APCs, share the same origin from myeloid cells in bone marrow, and have overlapping antigen-processing functions (26). This expression pattern suggests a close association between the function of SR-A and activities of APCs. In benign prostatic tissues, SR-A-positive cell infiltrates were minimal and present in active inflammatory lesions, supporting the well-documented role of SR-A in immune cell-mediated host defense. SR-A-positive cells infiltrated PIN lesions at significantly higher densities compared with normal or malignant prostatic tissues. This result is intriguing, yet its biological significance is not immediately apparent. Although there is a report that proposed a link between the chronic inflammation-associated, proliferative atrophy in human prostate with PIN lesions (6), to our knowledge inflammatory activities have not been specifically correlated with PIN lesions. Interestingly, relatively high levels of apoptosis occur in PIN as well as in prostate cancer (27). Yet increased apoptosis is accompanied by increased mitosis such that a net gain in cell number is achieved in both neoplastic lesions (28). APCs including both macrophages and dendritic cells are capable of uptake of apoptotic cells (29, 30), and a role for several members of the scavenger receptor family in this process has been identified (18, 19), uptake of apoptotic cells (29, 30), and a role for several members of the scavenger receptor family in this process has been identified (18, 19). The present study demonstrating increased numbers of SR-A-positive cells at both mRNA and protein levels (34). Interestingly, there is accumulating evidence that interleukin 6 expression in cancer cells is progressively increased with increasing malignant potential and positively associated with metastasis (45, 46). Thus, it seems reasonable to assume that transforming growth factor β1 and/or interleukin 6 may suppress SR-A expression in the antigen-presenting cells in human prostate cancer.

The finding that there is a down-regulation of SR-A expression during cancer progression has important implications in developing cancer immunotherapeutics. Because SR-A may be involved in tumor antigen processing (21), an impaired or insufficient SR-A expression in APCs could directly jeopardize the processing of tumor antigen and thereby compromise host immune surveillance of malignant cells, and ultimately, lead to an attenuated host antitumor immune response. It is conceivable that normal SR-A expression and function in APCs is necessary to achieve optimal responses in specific immunotherapy protocols for prostate cancer. The finding showing the progression-associated SR-A down-regulation also has clinical relevance, because the measurement of the SR-A_total was found to be independently predictive for recurrence-free survival in the patients after surgery. These results warrant additional studies on a larger, randomly selected population in both retrospective and prospective studies to establish its value as a clinical biomarker for prognosis of human prostate cancer.

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