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Ki67, gelsolin and PTEN expression in sarcomatoid renal tumors

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Abstract Sarcomatoid renal tumors differ morphologically and prognostically from other renal tumors. Using tissue microarray technology, we show that sarcomatoid renal tumors have a distinct protein expression profile for biomarkers Ki67, gelsolin and PTEN, when compared with clear-cell and papillary renal tumors. Our results confirm the previous reports that Ki67 is highly expressed in sarcomatoid tumors. We also show that gelsolin expression differs between the studied tumor types, suggesting different roles for gelsolin in the carcinogenesis of different renal tumor types.

Keywords Ki67 · Gelsolin · PTEN · Renal cell carcinoma · Tissue microarray analysis

Introduction

Renal malignancies comprise a heterogeneous group of tumors with wide genetic, morphological and prognostic variation. Renal tumor subtypes have characteristic protein expression profiles [22]. Renal clear-cell carcinoma has been extensively studied for many traditional and emerging biomarkers, but less is known about the protein expression in other types of renal cell carcinoma (RCC). Clear-cell and papillary RCC are thought to originate from the proximal nephron [11,21], whereas sarcomatoid renal carcinoma results from the dedifferentiation of an existing renal epithelial malignancy [1,10].

Using our newly established kidney tumor tissue microarray, the aim of this study is to analyze the expression levels of Ki67, gelsolin and PTEN in different subtypes (clear-cell, papillary, and sarcomatoid) of RCC [4]. Ki67 protein is a marker of active cell proliferation. Ki67 expression is usually increased in all malignant renal tumors, and expression of Ki67 is directly correlated with the grade of the tumor [13,18]. Gelsolin, a member of the actin-binding protein family, is involved in normal human cells in the regulation of actin cytoskeleton dynamics and signaling pathways, as well as apoptosis [6]. In normal human adult kidney, gelsolin is highly expressed in distal tubules and collecting ducts [9]. During carcinogenesis, both up- and down-regulation of gelsolin have been reported [7, 14, 16, 17,19]. The mechanisms by which gelsolin exerts its functions in cancer development are still uncertain. PTEN tumor suppressor protein regulates signal transduction pathways in normal cells, whereas in tumor cells it suppresses migration and invasion [8,20].

Materials and methods

A total of 309 formalin-fixed paraffin-embedded primary kidney cancer specimens were obtained from the Department of Pathology at the University of California, Los Angeles Medical School. The original H & E stained slides were staged according to TNM classification, graded according to Fuhrman, and histologically subtyped according to the recommendations of the UICC [2, 15,21]. There were 255 tumors with clear-cell morphology, 40 tumors with papillary morphology and 14 tumors with sarcomatoid morphology. All tumor grades were represented in the array. The majority of clear-cell tumors were of grades 2–3, and the majority of papillary tumors were of grade 1. The tumors were arrayed and immunohistochemical stainings for Ki67, gelsolin and PTEN

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antibodies were performed as described [12]. Each tumor was represented in the array by three cancer tissue spots. One additional normal kidney tissue spot was also arrayed from each specimen, whenever available. A semi-quantitative assessment of antibody staining was performed blinded to clinicopathological variables. The percentage of the tumor cells with specific staining was recorded as 0%, 5%, 10% etc. for Ki67, gelsolin and PTEN (nuclear staining for Ki67, cytoplasmic staining for the others). The median biomarker expression value, constructed from the expression values of the three cancer tissue spots for each tumor, was used in the analyses. For sarcomatoid tumors, only the tissue spots with sarcomatoid morphology were included in the analyses. The Wilcoxon two-sample test was performed to analyze biomarker expression between tumor types.

Results

Ki67, gelsolin and PTEN staining levels were assessed in the different RCC subtypes within the tissue microarray. As expected, Ki67 expression was higher in sarcomatoid than in clear-cell or papillary tumors (Fig. 1, $P < 0.05$ and < 0.005, respectively). Interestingly, gelsolin expression was higher in papillary than in clear-cell or sarcomatoid tumors (Fig. 1, $P < 0.0001$ and < 0.05, respectively). PTEN expression did not statistically differ between sarcomatoid and clear-cell or papillary tumors. However, PTEN expression was lower in clear-cell than papillary tumors (Fig. 1, $P < 0.005$).

Discussion

The current study describes the protein expression of Ki67, gelsolin and PTEN in different subtypes of RCC, comparing sarcomatoid with clear-cell and papillary tumors. As the prognosis of sarcomatoid tumors is worse than that of other renal tumors [11], one might expect that the malignant phenotype would be reflected in the tumor biomarker expression as well. Ki67, a marker of active cell proliferation, is indeed highly expressed in sarcomatoid tumors (Fig. 1), which is in concordance with the aggressive nature of this tumor type [1,10], and confirms the previous reports of increased Ki67 expression in sarcomatoid tumors [3, 5,13]. On the other hand, gelsolin expression is low in clear-cell and sarcomatoid tumors, but high in papillary tumors (Fig.1). This is intriguing in the light of the reports of a tumor suppressing role for gelsolin in cancers of the bladder, prostate and breast [7, 16,19], as our results showing differences in gelsolin expression suggest that gelsolin may have multiple roles within the studied renal tumor types. Tumor suppressor protein PTEN was highly expressed in both papillary and sarcomatoid tumors in our study, whereas PTEN expression was significantly lower in clear-cell than papillary tumors (Fig. 1). However, in all of the studied tumor types, PTEN was generally expressed in 80–90% of tumor cells, which might suggest that PTEN expression is not severely affected in any of the tumor types in our study sample, and the difference between clear-cell and papillary tumors might be a bystander phenomenon.

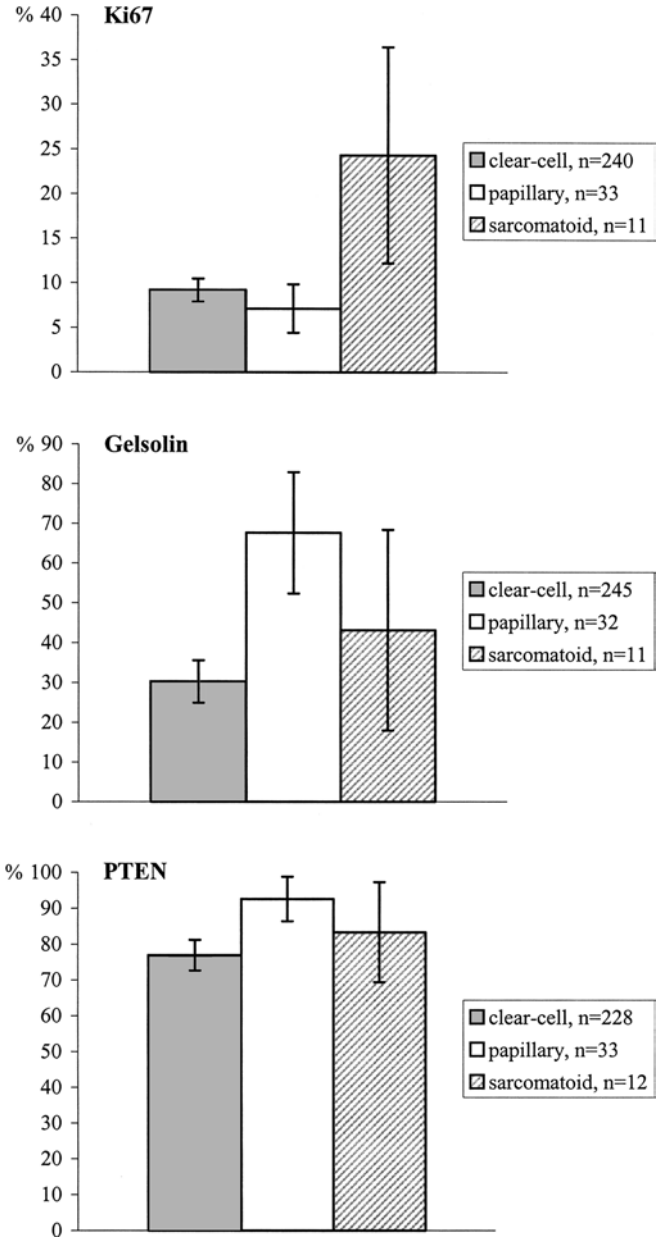

Fig. 1 Biomarker expression in clear-cell, papillary and sarcomatoid renal tumors. The percentage of positively staining tumor cells is indicated on *y-axis*. Values are shown as mean ± SD

Furthermore, we also observed that all but two normal kidney tissue samples in our array express PTEN in every cell. Further studies controlling for clinicopathological variables, such as grade and stage, are needed to fully characterize the above findings.

As a conclusion, we show that sarcomatoid renal tumors have a distinct protein expression profile, when compared with clear-cell and papillary tumors. Ki67 expression in the sarcomatoid tumors is significantly higher than in clear-cell or papillary tumors, whereas gelsolin expression is lower in sarcomatoid than papillary tumors. PTEN is highly expressed in all of the studied tumor types. Our findings support the evidence

of Ki67 as a biomarker for renal tumors, whereas the roles of gelsolin and PTEN in the carcinogenesis of different renal tumor types remain to be elucidated by future studies.

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