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Original contribution

Fibroblast activation protein predicts prognosis in clear cell renal cell carcinoma☆

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Summary: Clear cell renal cell carcinoma is a complex disease with only partial response to therapy and scarce reliable clinical parameters indicative of progression and survival. Fibroblast activation protein expression has been correlated with prognosis in several malignancies but never in renal cancer. We aim to analyze the immunohistochemical expression of fibroblast activation protein in 208 clear cell renal cell carcinomas and to evaluate its impact on the prognosis and survival. A positive cytoplasmic immunostaining of this protein in the stromal fibroblasts associated to cancer cells is associated with large tumor diameter (≥4 cm), high-grade (G3/4) tumors, and high-stage (≥pT3) tumors. Fibroblast activation protein–positive cases had significantly shorter survivals after 5 (P = .00015), 10 (P = .0000042), and 15 (P = .000043) years of follow-up, with a hazard ratio of 0.31. Multivariate analysis showed that fibroblast activation protein (P = .00117) was stronger than grade and stage in predicting clinical aggressiveness in clear cell renal cell carcinoma. This study confirms the usefulness of fibroblast activation protein detection in the stromal fibroblast associated to cancer in clear cell renal cell carcinoma and adds a new immunohistochemical marker to predict clinical behavior in these patients.

1. Introduction

Renal cancer is a common neoplasm and a leading cause of cancer death in Western countries, and its incidence is increasing in recent years with more than 62 000 new cases estimated in the United States in 2016 [1]. Clear cell renal

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cell carcinoma (CCRCC) is by far the most common histological subtype, accounting for approximately for 75%-80% of the cases in most series [2]. CCRCC is a paradigmatic example of an intrinsically heterogeneous and aggressive neoplasm [3], and this fact explains the poor results obtained by modern personalized therapies. Actually, surgery remains nowadays as the only effective treatment in these patients.

Fibroblast activation protein–α (FAP) is a cell surface glycoprotein with dipeptidyl peptidase (DPPIV) and collagenolytic activity highly expressed on cancer-associated fibroblasts (CAFs) from several malignancies, including carcinomas of the oral cavity [4,5], esophagus [6], stomach [7], pancreas [8–10], colon [11], breast [12,13], ovary [14], endometrium [15], and lung [16], as well as in bone and soft tissue sarcomas [17,18] and in malignant melanoma [19]. Very recently, a study has shown that CAFs promote CCRCC progression in vitro [20], although the molecular basis of such activity remains unveiled. However, a clinical study analyzing the impact of FAP expression in CCRCC is still lacking.

The aim of this study was to evaluate the expression of FAP and its clinical significance in a retrospective series of 208 CCRCC.

2. Materials and methods

The authors declare that all the experiments carried out in this study comply with current Spanish and European Union legal regulations. Samples and data from patients included in this study were obtained from the medical records and archives of the pathology laboratory. All patients were informed about the potential use for research of their surgically resected tissues and accepted this eventuality by signing a specific document approved by the Ethical and Scientific Committees (CEIC 2015/060, CEIC-E PI2015101).

A total of 208 CCRCCs retrieved in 2 medical institutions were included in the study in a retrospective way. The series included 179 total nephrectomies and 29 partial nephrectomies. Follow-up was obtained from the clinical histories and was closed at December 31, 2014. Cases were reviewed by 2 pathologists (J. I. L., R. G.), who assigned Fuhrman grade [21] and 2010 American Joint Committee on Cancer stage [22] on hematoxylin and eosin sections from tumor samples obtained following standard protocols. Immunohistochemistry was previously performed using carbonic anhydrase IX (Epitomics, ref. code AC-0137RUO, dilution 1: 100), CK7 (Ventana, ref. code 790-4462, ready to use), and CD117 (Ventana, ref. code 790-2951, ready to use) to confirm as CCRCC those cases that were histologically unclear.

Tissue microarrays were performed for the evaluation of FAP expression. One core (2.5 mm in diameter) of well-preserved tumor tissue obtained at the front of invasion into the renal parenchyma was selected for tissue microarray in each case. FAP antibody (Abcam, ref. ab53066, dilution 1:70) was evaluated in the stromal fibroblasts adjacent to neoplastic nests. Immunohistochemical stainings were performed in automated immunostainers (EnVision FLEX, Dako Autostainer Plus; Dako, Glostrup, Denmark, and BenchMark Ultra; Ventana Medical Systems, Tucson, AZ) following routine methods. Tris-EDTA was used for antigen retrieval in all cases. Negative controls were slides not exposed to the primary antibody, and these were incubated in phosphate-buffered saline and then processed under the same conditions as the test slides. The analysis was performed using a Nikon Eclipse 80i microscope (Tokyo, Japan).

The evaluated parameters were age, sex, Fuhrman grade, tumor diameter, staging, and FAP expression. A data-mining analysis was performed using Waikato Environment for Knowledge Analysis [23]. Multiple parameters were selected to obtain meaningful rules for the classification of the FAP-positive/-negative response. Also, an attribute selection turning out if the parameter was relevant or irrelevant to explain the data was performed. For such a purpose, different search methods were used such as the best-first, rank-search, or random-search algorithms.

R software was used for statistical analysis. Kaplan-Meier (KM) curves and log-rank *P* are displayed after performing a

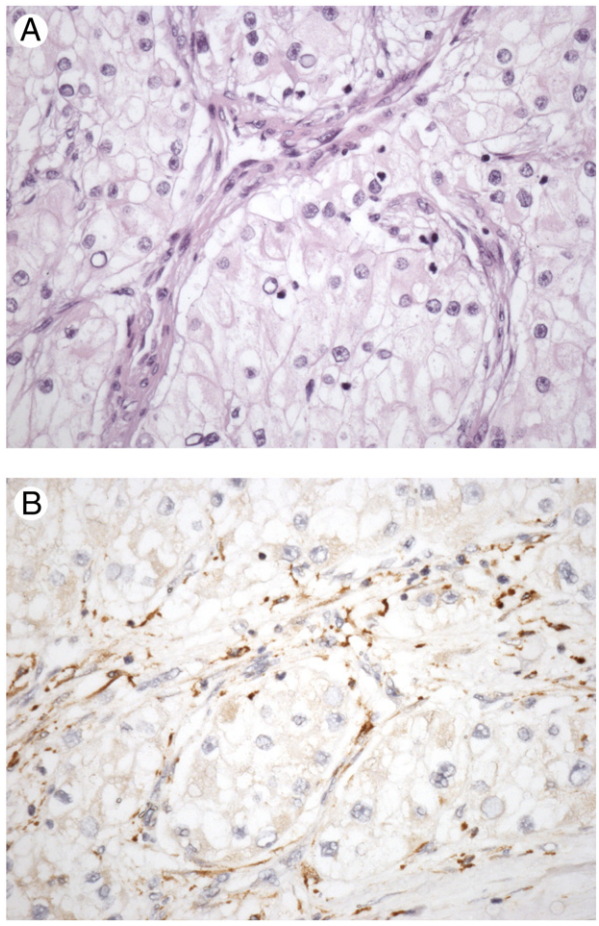

Fig. 1 Nested pattern of growth in CCRCC (A) with peripherally located stromal fibroblasts immunostained with FAP (B) (original magnification ×400).

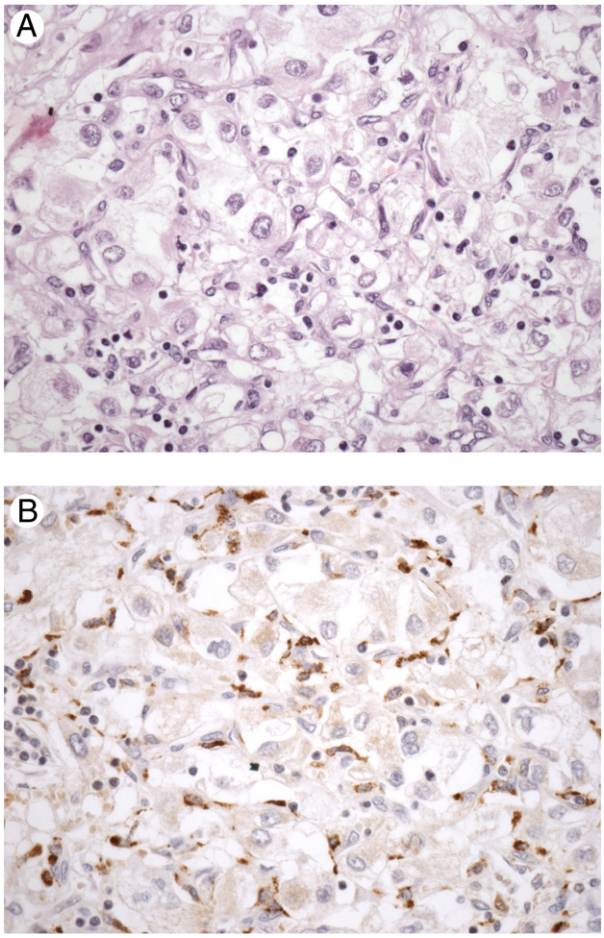

Fig. 2 Diffuse solid pattern of growth in CCRCC (A) with stromal fibroblasts intermingled with tumor cells immunostained with FAP (B) (×400).

univariate analysis to compare 5-, 10-, and 15-year survivals. Hazard ratio (HR) was also computed. R's "survplot" module was used to create the KM curves, and "coxph" function was used to calculate the HR and log-rank *P*. Cox regression multivariate analysis was performed to identify which variables will remain significant if all variables were considered altogether. Classic histopathologic parameters (Fuhrman grade, tumor diameter and staging, and FAP expression) were included in the analysis. Grade was grouped as low (G1/G2) and high (G3/G4), tumor diameter as small (≤4 cm) and large (>4 cm), and stage as low (pT1/2) and high (≥pT3).

3. Results

Men predominated in the series (157 men/51 women) with an average age of 66 years (range, 25-93 years). Follow-up data were obtained for 177 (85%) patients and ranged between 1 and 240 months (average, 89.7 months). A total of 80 patients died of disease (38.5%). Average tumor diameter was 6.22 cm (range, 1-19 cm), 67 (32.2%) cases being ≤4 cm and 141 (68.8%) cases >4 cm. Furhman grade distribution was as follows: 35 G1 (16.8%), 99 G2 (47.6%) 47 G3 (22.6%), and 27 G4 (13%), 134 cases (64.4%) being low grade (G1/2) and 74 (35.6%) high grade (G3/4).

Histologically, FAP expression was restricted to stromal fibroblasts adjacent to epithelial tumor cells. No immunostaining with this antibody was detected in neoplastic epithelial cells. Two different patterns were observed depending on the neoplastic architecture of CCRCCs. Tumors with predominantly nested arrangement showed FAP-positive stromal fibroblasts surrounding solid tumor nests, a distribution reminiscent of the *zellballen* pattern described in paragangliomas (Fig. 1). Tumors with diffuse, nonorganoid growth pattern showed FAP-positive stromal fibroblasts intimately intermingled with neoplastic epithelial cells without any identifiable pattern (Fig. 2). These 2 different patterns depend on tumor architecture and are not related with grade or other cytologic characteristic of neoplastic cells.

Statistical analysis showed, as expected, that tumor substratification by grade, stage, and diameter displayed significant differences in patients' survival after 5, 10, and 15 years of follow-up (Table 1). Sex did not show significant differences in survival.

All attribute search methods tested to know which variables determine better the response of FAP showed that grade and stage were relevant. This result was verified using an a priori association method that gave as result the following rules: when stage was low (pT1/2) and FAP was negative (117 cases met these attributes), 84% of the cases were low-grade tumors (G1/2), and when tumor diameter was small (≤4 cm) and FAP was negative (111 cases), 92% of the cases were low-stage (pT1/2) tumors. On the other side, when stage was high (≥pT3) and FAP was positive (21 cases), grade was high (G3/4) in 90% of tumors, and when tumor diameter was large (>4 cm) and FAP was positive (20 cases), grade was high (G3/4) also in 90% of the tumors. Finally, 83% of low-grade and 79% of low-stage tumors were FAP negative.

FAP-positive immunostaining is associated with tumor aggressiveness and poor survival in CCRCC. KM survival curves and multivariate regression analysis were performed in

Table 1 Log-rank *P* for 5-, 10-, and 15-year survival

	Grade [a]	Stage [b]	Diameter [c]	FAP [d]
5 y	.0000087	.00000000085	.0000001	.00015
10 y	.00000025	.000000031	.000013	.0000042
15 y	.000000083	.000000001	.0000082	.000043

[a] Fuhrman grade, low (G1/2) versus high (G3/4).
[b] American Joint Committee on Cancer 2010 stage, low (pT1/2) versus high (≥pT3).
[c] Tumor diameter, small (≤4 cm) versus large (>4 cm).
[d] FAP expression, positive versus negative.

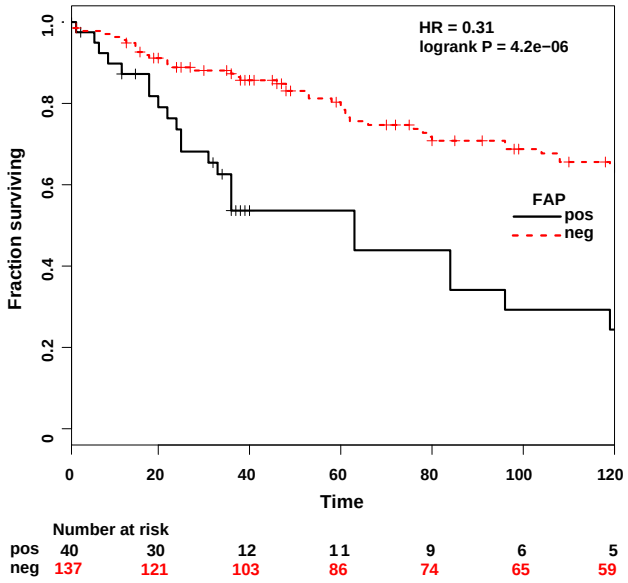

Fig. 3 Ten-year KM survival curves showing significant differences between FAP-positive and FAP-negative cases.

177 patients, 137 of them being FAP negative and 40 FAP positive, and showed a strongly significant difference in survival between FAP-positive and FAP-negative cases after 5 (P = .00015), 10 (P = .0000042), and 15 (P = .000043) years of follow-up (Table 1 and Fig. 3) with an HR = 0.31. Significant differences in survival were detected as early as after the first 20 months of follow-up. Probabilistically, there is a 76% of chance for FAP-positive patients to die before FAP-negative patients.

Univariate analysis displayed significant results for grade, stage, tumor diameter, and FAP expression (Table 2). Finally, Cox regression multivariate analysis showed that FAP (P = .00117) remained as the highest significant variable when considering all variables together, both grade and stage appearing also significant to a lesser degree (Table 3).

4. Discussion

Renal cancer ranks within the top 10 list of the most frequent malignancies in the United States [1]. Its incidence is increasing in recent years in both Europe and the United States [1,24]. As for Spain, the incidence rate is also increasing, with 15.7 cases per 100,000 inhabitants per year expected in 2022 [25]. CCRCC represents an aggressive histological subtype and by far the most frequent renal cell carcinoma variant [2]. Traditionally considered chemo- and radioresistant, the survival improvement in recent years for this tumor is mainly linked to early detection and surgery [26].

Cell biology and carcinogenesis are related to complex and poorly understood disturbances of the intracellular metabolism [27]. CCRCC is typically a heterogeneous tumor made of multiple neoplastic cell clones developing independently in a branched model of temporal and spatial evolution [3]. This peculiarity of CCRCC is the main obstacle nowadays for the successful development of targeted personalized therapies [28].

Cancer development and progression rely not only in neoplastic cells themselves but also in their interaction with the microenvironment [29]. Strong experimental evidence has shown that CAF can promote tumorigenesis and tumor progression through multiple mechanisms, including induction of proliferation, survival, angiogenesis, invasion and epithelial-to-mesenchymal transition, and suppression of immune cells [30]. A very recent study has demonstrated that the interaction of renal cancer cell lines with CAF stimulates proliferation, survival, and migration of tumor cells in correlation with ERK1/2 and Akt activation [20]. These results indicate that CAFs have an important role supporting and promoting renal cancer.

A hallmark of the activation of CAF in tumor microenvironment is the expression of FAP in the cell surface [31]. FAP promotes angiogenesis, cell adhesion, motility, and invasion in several neoplasms by degrading and remodeling the extracellular matrix [30,32]. The overexpression of this peptidase in CAF has been associated with higher risk of metastases and worse survival in several tumors [4–19]. The present study also supports the association between FAP immunostaining in stromal fibroblasts and poor prognosis in 5-, 10-, and 15-year tumor-related survival in CCRCC patients. For this reason, FAP immunohistochemical detection may be very useful in clinical practice selecting tumors with aggressive behavior.

FAP is closely related to the enzyme DPPIV, another serine peptidase. FAP and DPPIV share 70% of the sequence identity in the catalytic domain and show similar activity [31]. It has also been described that both peptidases may form complexes that facilitate extracellular matrix

Table 2 Univariate regression analysis

Variable	P
Grade	.00000124
Stage	.000000000666
Tumor diameter	.000028
FAP expression	.000000764

Table 3 Multivariate regression analysis

Variable	P
Grade	.04162
Stage	.02106
Tumor diameter	.64408 [a]
FAP expression	.00117

[a] Not statistically significant.

degradation [30,33] and support tumor aggressiveness. In this sense, we have seen that DPPIV activity was increased in high-grade and advanced-stage CCRCC [34] and that higher DPPIV activity was associated with poor survival rates in these tumors [35]. These data suggest that FAP and DPPIV are homologous enzymes and may have complementary roles in renal carcinogenesis, pointing to these enzymes as potential targets for therapy.

FAP expression in renal cell carcinomas has not been previously documented in the literature. Although primarily related with CAF, FAP expression has been also detected in neoplastic epithelial cells of carcinomas arising in breast, pancreas, stomach, large bowel, and uterine cervix [5]. The acquisition of this capacity by epithelial tumor cells in these neoplasms is right now a matter of debate. However, as far as we have observed in this study of 208 cases, neoplastic cells in CCRCCs do not express FAP.

Studies in renal cancer cell lines have shown that CAF confers drug resistance to everolimus [20] and that the induction of epithelial-to-mesenchymal transition contributes to resistance to sunitinib [36]. These evidences point to CAF as an important target in renal cancer therapy that may complement mTOR and tyrosine kinase inhibitors. Because FAP is not found in normal adult tissues and its expression is mostly associated to cancer-related stroma, this enzyme could be a potential therapeutic target in cancer [37]. In this way, Brennen et al [38] have tested FAP-activated prodrugs in prostate and breast cancer with promising results.

5. Conclusions

The immunohistochemical evaluation of FAP status in CAF is a reliable tool predicting the clinical behavior of CCRCC. Taking into consideration that CCRCC is an intrinsically heterogeneous neoplasm with only partial response to targeted therapies, the addition of FAP to the list of potential therapeutic targets would open new opportunities for these patients.

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