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Relationship Between Expression of p53 Protein and Tumor Subtype and Grade in Renal Cell Carcinoma

Hayat Mombini,* Majid Givi, Iran Rashidi

Department of Urology, Jundishapour University of Medical Sciences, Golestan Hospital, Ahwaz, Iran

ABSTRACT

Introduction: Our aim was to evaluate the overexpression of p53 protein, product of mutated *TP53* gene, in histologic sections of the kidneys with renal cell carcinoma (RCC) and its association with tumor grade and subtype.

Materials and Methods: A total of 66 histologic sections of the kidneys of patients with the diagnosis of RCC were re-evaluated and tumor grade, tumor subtype, and p53 expression were determined.

Results: Of the total 66 histologic sections with the diagnosis of RCC, 34 (51.5%), 27 (41%), and 5 (7.5%) were conventional, papillary, and chromophobe subtypes, respectively. Fifty-one (77.3%), 14 (21.2%), and 1 (1.5%) of tumors were grade 2, 3, and 4, respectively. Thirty (45.4%) sections were positive for p53 immunohistochemical staining. In 7 cases (20.6%) of the conventional tumors, p53 staining was positive, while 18 papillary (66.6%) and 5 chromophobe tumors (100%) had a positive staining for p53 ($P < .001$). Seventeen out of 51 grade 2 tumors (33.4%) and 12 out of 14 grade 3 tumors (85.7%) were positive for p53. The single case of grade 4 tumor was positive for p53 protein, too ($P = .001$).

Conclusion: Increased expression of p53 protein is rather prevalent in RCC. This factor is associated with tumor grade and subtype. According to our findings, it is generally accompanied by nonconventional subtypes and higher tumor grades.

KEY WORDS: renal cell carcinoma, p53 protein, tumor grade, tumor subtype

Introduction

The most common mutated gene in human malignancies is *TP53*. The mutation of this gene is reported in most of human malignancies such as astrocytoma, mesothelioma, sarcoma, leukemia, and colon, bladder, lung, and breast carcinomas.[1,2,3] Wild-type protein product of this gene, called p53, weighs 53 000 d and has a short half-life (6 to 30 minutes). This normal protein product does not accumulate in cells enough to be detected by immunohistochemical methods[4]; however, the mutated protein has a longer half-life, accumulates in the tissues, and can be easily detected in cell nucleus.[1] The relationship between the increased expression of this protein and urogenital cancers (bladder and prostate carcinomas) has been well demonstrated[3,5-7]; while its relationship with renal cell carcinoma (RCC) is still a matter of debate. Increased expression of *TP53* has been reported to be 20% to 32% in different studies.[8-14] Also, in some studies, a relationship has been demonstrated between the expression of p53 and the tumor subtype (increased p53 expression in papillary tumors comparing with other tumor types),[8] while in other studies, such a relation has not been detected.[13,14] The same controversy exists about the association of p53 expression and the tumor grade; while some investigators have found

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**Corresponding author: Department of Urology, Jundishapour University of Medical Sciences, Golestan Hospital, Ahwaz, Iran.*
Tel: +98 611 334 9293, Fax: +98 611 334 9293
E-mail: moombeni_h@yahoo.com.

no association,[14] a strong relationship has been demonstrated between them by some others and it has been regarded as a potential marker in determining the prognosis of patients with RCC.[11] We conducted this study to evaluate the relationship between the overexpression of p53 tumor suppressor protein and the grade and subtype of RCC.

Materials and Methods

In a retrospective study, all cases of radical nephrectomy due to RCC between 1995 and 2005 in Golestan and Imam Khomeini hospitals in Ahwaz were reviewed. A total of 66 patients were selected. The paraffin-embedded blocks of their tumor specimens were available. After their reblockage, 2-μm-thick sections were stained again by hematoxylin-eosin and were evaluated regarding the latest tumor subtype classification[15,16] and Fuhrman's grading system.[17] Immunohistochemical staining was performed to evaluate increased p53 protein expression. Catalyzed signal amplification (CSA) system (Dako, Carpinteria, CA) was used for immunohistochemical visualization; skin squamous cell carcinoma specimens were used as controls. Sections of RCC with 10% or more of the tumor cell nuclei stained were considered positive for p53.

Chi-square test was used to analyze the relationship between p53 protein expression and pathological variables of RCC. Values for P less than .05 were considered significant.

Results

Of the total 66 histologic sections with the diagnosis of RCC, 34 (51.5%), 27 (41%), and 5 (7.5%) were conventional, papillary, and chromophobe subtypes, respectively. None of the specimens was reported to be collecting duct, medullary cell, or oncocytoma subtypes. There was no grade 1 tumor, while 51 (77.3%), 14 (21.2%), and 1 (1.5%) were reported to be grade 2, 3, and 4.

Thirty (45.4%) sections were positive for p53 immunohistochemical staining (Table 1). In 7 cases (20.6%) of the conventional tumors, p53 staining was positive, while 18 papillary (66.6%) and 5 chromophobe tumors (100%) had a positive staining for p53 ($P < .001$). Seventeen out of 51 grade 2 tumors (33.4%) and 12 out of 14 grade 3 tumors (85.7%) were positive for p53. The single case of grade 4 tumor was positive for p53 protein, too ($P = .001$).

Discussion

The relationship between p53 protein overexpression and tumor subtype and grade has not been well known in RCC. In our study, the overexpression of this protein was seen in 45.4% of the histologic sections with the diagnosis of RCC. Zigeuner and coworkers studied 184 sections with the diagnosis of primary RCC and 56 sections with the diagnosis of metastatic RCC. Overexpression of p53 protein was detected in 22.8% and 51.8% of primary and metastatic tumors, respectively.[8] Other studies have reported this rate to be 20% to 32%.[9,13,14] In our study, the increased p53 protein expression was relatively high. We found that p53 overexpression was more frequent in nonconventional tumor

TABLE 1. *Immunohistochemical staining results for p53 protein in histologic sections of renal cell carcinoma cases**

Renal cell carcinoma	p53 positive	p53 negative	Total	*P* value
Subtypes				
Conventional	7 (20.6)	27 (79.4)	34 (51.5)	< .001
Papillary	18 (66.6)	9 (33.4)	27 (40.9)	
Chromophobe	5 (100)	-	5 (7.6)	
Grades				
1	-	-	-	
2	17 (33.4)	34 (66.6)	51 (77.3)	.001
3	12 (85.7)	2 (14.3)	14 (21.2)	
4	1 (100)	-	1 (1.5)	
Total	30 (45.4)	36 (54.6)	66 (100)	

*Values in parentheses are percents.

subtypes. Thus, our higher rate of p53 positive tumors is, probably, due to our higher frequency of nonconventional subtypes. It has been shown in different studies that p53 overexpression is higher in nonconventional tumor subtypes. Zigeuner and colleagues detected p53 overexpression in 70%, 27.3%, and 11.9% of papillary, chromophobe, and conventional subtypes of RCC.[8] However, in some studies, no correlation has been found between the increased protein expression and the tumor subtype.[13,14]

Increased p53 protein expression was accompanied by higher grades of the tumor in our study which is in agreement with other studies. Leonardi and colleagues have suggested that the strong relation between the p53 expression and the tumor grade, stage, and size found in their study can affect the prognosis of the patients with RCC.[11] In a study by Uhlman and colleagues, it has been also demonstrated that increased p53 expression is seen in higher tumor grades and stages.[13] However, in a study by Bot and coworkers, no relation was found between the tumor grade and the increased p53 protein expression.[14]

Although we could find the above associations of p53 with pathologic characteristics of RCC, our study lacked a multivariate analysis. Furthermore, we could not investigate all grades and subtypes of these tumors due to the relatively small sample size. However, this limited data mandates more investigation to elucidate the role of *TP53* and p53 protein in RCC.

Conclusion

Increased p53 protein expression seems to be rather prevalent in RCC as it was seen in half of the histologic sections of our patients. Also, there is a significant association of p53 overexpression with the tumor subtype and grade. We found that p53 overexpression is more prevalent in nonconventional subtypes and higher grades. However, to date controversial findings have been reported warranting more investigation.

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