Acta Urológica Portuguesa. 2015;32(2):64–70

ACTA Urológica Portuguesa

www.elsevier.pt/acup

ORIGINAL ARTICLE

MST1R methylation as a diagnostic biomarker in renal cell tumors

Ana Sílvia Pires-Luís[a,b,e], Francisco Lobo[c], Márcia Vieira-Coimbra[a,b], Pedro Costa-Pinheiro[a], Luís Antunes[d], Jorge Oliveira[c], Rui Henrique[a,b,f,◊], Carmen Jerónimo[a,f,*,◊]

[a] *Cancer Epigenetics & Biology Group, Research Center, Portuguese Oncology Institute – Porto, Portugal*
[b] *Department of Pathology, Portuguese Oncology Institute – Porto, Portugal*
[c] *Department of Urology, Portuguese Oncology Institute – Porto, Portugal*
[d] *Department of Epidemiology, Portuguese Oncology Institute – Porto, Portugal*
[e] *Department of Microscopy, Institute of Biomedical Sciences Abel Salazar (ICBAS), University of Porto, Portugal*
[f] *Departments of Pathology and Molecular Immunology, Institute of Biomedical Sciences Abel Salazar (ICBAS), University of Porto, Portugal*

Received 28 October 2014; accepted 6 January 2015
Available online 21 July 2015

KEYWORDS
Kidney neoplasms;
Epigenetics;
Biomarkers

Abstract
Introduction: Renal cell tumors comprise both benign – oncocytoma – and malignant – clear cell renal cell carcinoma, papillary renal cell carcinoma, and chromophobe renal cell carcinoma – entities. Since the differential diagnosis among renal cell tumors is sometimes difficult on clinical, imaging and pathological grounds, and prognosis is quite dissimilar, epigenetic-based diagnostic biomarkers, specially promoter methylation, might be useful for accurate diagnosis and therapeutic planning.
Materials and methods: EpiTect Methyl II PCR Array was used to screen methylation status of 22 genes, involved in epithelial to mesenchymal transition. Quantitative real-time methylation specific polymerase chain reaction was performed for candidate gene validation, and methylation levels of renal cell tumors subtypes and normal kidney were determined and compared.
Results: MST1R promoter methylation level was significantly higher in clear cell renal cell carcinoma (median: 5367) compared to other renal cell tumors (median: papillary renal cell carcinoma – 1084, chromophobe renal cell carcinoma – 1023, oncocytoma – 1337) and normal kidney (median: 1125), allowing for accurate discrimination from other renal cell tumors with high sensitivity (>96.7%) and specificity (86.7%).

* Corresponding author.
E-mail addresses: carmenjeronimo@ipoporto.min-saude.pt, cljeronimo@icbas.up.pt (C. Jerónimo).
◊ Joint senior authors.

http://dx.doi.org/10.1016/j.acup.2015.01.004

Conclusion: Quantitative MST1R promoter methylation may be useful as biomarker for accurate diagnosis of clear cell renal cell carcinoma in problematic cases.

PALAVRAS-CHAVE
Neoplasias renais;
Epigenética;
Biomarcadores

Metilação do gene MST1R como biomarcador de diagnóstico em tumores de células renais

Resumo
Introdução: Os tumores de células renais englobam neoplasias benignas – oncocitoma – e malignas – carcinoma de células renais de tipo célula clara, papilar e de células cromófobas. Uma vez que o diagnóstico diferencial entre eles não é linear do ponto de vista clínico, imagiológico e patológico, e que o prognóstico de cada subtipo é distinto, o desenvolvimento de biomarcadores de diagnóstico com base em alterações epigenéticas, nomeadamente a metilação do promotor de genes, poderá ser útil para o diagnóstico e planeamento do tratamento.
Material e métodos: A presença de metilação do promotor de 22 genes envolvidos na transição epitélio-mesênquima foi avaliada através da plataforma comercial EpiTectMethylIIPCR Array. Os resultados foram validados, no gene candidato, por ''polymerase chain reaction'' quantitativo em tempo real específico para metilação. Os níveis de metilação de cada tipo histológico de tumores de células renais e de tecido renal normal foram calculados e comparados.
Resultados: O nível de metilação do promotor do gene MST1R foi significativamente mais elevado nos carcinomas de células renais de tipo célula clara (mediana: 5.367) comparativamente com carcinomas de células renais papilares (mediana: 1.084), carcinomas de células renais de células cromófobas (mediana: 1.023), oncocitomas (mediana: 1.337) e rim normal (mediana: 1.125), permitindo identificar carcinomas de células renais de tipo célula clara com elevada sensibilidade (> 96,7%) e especificidade (86,7%).
Conclusão: O nível de metilação do promotor do gene MST1R poderá constituir um biomarcador útil para o diagnóstico de carcinomas de células renais de tipo célula clara em casos problemáticos.

Introduction

Renal cancer has an estimated age-standardized incidence and mortality rate respectively of 4.4/100,000 and 1.8/100,000 worldwide.[1] In Europe, renal cancer incidence ranks seventh and eighth among all non-cutaneous malignant neoplasms, and in North America kidney and renal pelvis cancers account for 65,150 estimated new cases and 13,680 deaths in both genders in 2013, with men being more affected than women.[2] Besides the classical presentation as metastatic disease, mostly because kidney cancer is asymptomatic at its earliest stages, an increasingly higher number of tumors are being incidentally discovered as small masses, frequently posing diagnostic challenges in what concerns the distinction between benign and malignant tumors.[3]

Renal cell tumors are the most common neoplasms of the kidney (80–85%), followed by urothelial carcinoma of the renal pelvis (15–20%).[4] Renal cell tumors (RCTs) are heterogeneous at the genetic, morphological and clinical levels, comprising both benign and malignant entities.[5,6] Underscoring the high heterogeneity of RCT, malignant tumors – renal cell carcinomas (RCC) – might have different responses to novel targeted therapies.[7] The most frequent malignant RCT is clear cell renal cell carcinoma (ccRCC), followed by papillary renal cell carcinoma (pRCC) and chromophobe renal cell carcinoma (chRCC), accounting respectively for 70%, 10–15% and 5% of all RCT.[4] Oncocytoma, the most common benign tumor, accounts for approximately 5% of all RCT.[5]

Histological subtyping provides relevant prognostic information, independent from tumor pathological stage and grade: ccRCC is the most aggressive subtype, displaying lower cancer-specific survival than pRCC and chRCC, whereas no differences in cancer specific survival are apparent between pRCC and chRCC.[8,9]

Usually, information on histological subtype is available only after pathological evaluation of the nephrectomy specimen, and thus this valuable diagnostic and prognostic data cannot be taken into account for planning the best time for surgery, especially in cases of small renal tumors (<4 cm) that should benefit from nephron sparing therapy.[3,10] For these small tumors, limitations of imagiological techniques and core biopsy histopathological examination preclude accurate characterization of some lesions, seriously limiting the pre-operative information about the biological behavior of the tumor available for the urologist.[3,10] Moreover,