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REVIEW ARTICLE

Role of mitogen-activated protein kinase (MAPK) in the sporadic renal cell carcinoma☆

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Abstract

Context: Only on the basis of the involvement of the *vhl* suppressor gene in the cases of renal cell carcinomas (RCC), the involvement of the signaling pathway between the pVHL and the hypoxia inducible factor 1 alpha (HIF-1α) has been evaluated because of the need to find new diagnostic and prognostic response to drugs markers.

Evidence synthesis: The overexpression of HIF-1α confers better prognosis in clear cell type RCC (ccRCC). Furthermore, HIF-1α regulates other genes, specifically that of the carbon anhydrase IX (CA-IX), whose overexpression is practically only one of the ccRCC and its determination is useful for this subtype. However, the involvement of the CA-IX has not been demonstrated in the prognosis or in the response to immunomodulators or antiangiogenics. Therefore, it is necessary to make a global evaluation of all this pathway: pVHL → HIF-1α → CA-IX, and even the analysis of other proteins and signaling pathways that also control the HIF-1α activity. In the latter case, the MAPK are critical in the HIF-1α activation, there being evidence on the experimental level of the control on its activity. Although the role of the MAPK in the phenomena of resistance to conventional chemotherapy and radiotherapy has been demonstrated, it has not been demonstrated in response to sorafenib, an important piece of information if we consider that it is an inhibitor of several protein kinases. Recently, it has been observed that the MAPK may be involved in the responses to different therapies, included those based on tyrosine kinase inhibitors.

Conclusions: The confirmation of these data would suppose an explanation of the variation observed between patients who, with the same functional alteration of the *vhl* gene, have a different biological, clinical behavior and better selection of non-surgical therapies.

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Tratamiento

Papel de las proteínas quinasas activadas por mitógenos (MAPK) en el carcinoma de células renales esporádico

Resumen

Contexto: Últimamente, basándose en la implicación del gen supresor *vhl* en los casos de carcinoma de células renales (CCR), se ha evaluado la implicación de la ruta de señalización entre pVHL y el Factor Inducible por Hipoxia 1 alfa (HIF-1α), ante la necesidad de encontrar nuevos marcadores diagnósticos, pronósticos y de respuesta a fármacos.

Síntesis de evidencia: La sobreexpresión de HIF-1α confiere mejor pronóstico en pacientes afectos de CCR de tipo células claras (ccRCC). Además HIF-1α regula otros genes, concretamente el de la anhidrasa carbónica IX (CA-IX), cuya sobreexpresión es prácticamente exclusiva de los ccRCC y su determinación útil para el diagnóstico de este subtipo. Sin embargo, no se ha demostrado la implicación de CA-IX ni en el pronóstico, ni en la respuesta a inmunomoduladores o antiangiogénicos. Ello hace necesario la evaluación global de toda esta ruta: pVHL $\rightarrow$ HIF-1α $\rightarrow$ CA-IX, e incluso el análisis de otras proteínas y vías de señalización que también controlan la actividad de HIF-1α. En este ultimo caso, las MAPK, son criticas en la activación de HIF-1α, existiendo evidencias a nivel experimental del control sobre su actividad, aunque no se ha establecido su papel clínico como biomarcador. Si bien está demostrado el papel de las MAPK en los fenómenos de resistencia a quimio y radioterapia convencional, no lo está en la respuesta a sorafenib, dato llamativo si tenemos en cuenta que es inhibidor de varias proteín quinasas. Recientemente se ha observado que las MAPK pueden estar implicadas en la respuesta a distintas terapias, incluidas las basadas en inhibidores de tirosin quinasa.

Conclusiones: La confirmación de estos datos, supondrá una explicación a la variación observada entre pacientes, que con una misma alteración funcional del gen *vhl*, presentan un distinto comportamiento biológico y clínico, y a una mejor selección de terapias no quirúrgicas.

Context

Renal tumors account for approximately 3% of all neoplasias, renal cell carcinoma (RCC) being the most common malignant tumor in the adult kidney.

Both generally and in our environment, the incidence of RCC has increased about 126% since 1950, producing a progressive annual increase in incidence rates of 2.3–4.3%, mainly due to increased use of image techniques. However, in parallel, mortality has increased by 36.5% annually, so the incidental detection alone does not fully explain this increased incidence, which leads us to believe that other factors such as environmental, dietary, or genetic seem to be involved as well in the growing diagnosis of this tumor.[1] Within the RCC, the most common is the clear cell carcinoma (ccRCC), which represents about 70%.

The RCC can occur in the context of hereditary diseases or sporadically, classified, thus, in family kidney tumors and sporadic tumors. The sporadic form accounts for 96% of the cases, hence the great interest in understanding the molecular mechanisms that start its formation. Among the hereditary forms, the best characterized one is that associated with the Von Hippel Lindau syndrome, which is characterized because the affected individuals are at risk of developing tumors in different organs, including the kidneys, the cerebellum, the spinal column, the inner ear, the adrenal glands, and the pancreas. In this syndrome, genetic alterations particularly affecting chromosome 3 have been found. Specifically, in recent years, the *vhl* gene has been identified, located on the short arm of chromosome 3 (3p), classed as a tumor suppressor gene and establishing a close relation between this gene and the Von Hippel Lindau syndrome, in such a way that this is altered in more than 70% of the cases.[2] However, the involvement of this gene has also been verified in the occurrence of sporadic RCC cases, a remarkable relation between alterations in the *vhl* gene with the RCC being found, mainly in clear cell type,[3] something also ratified by previous studies by our group.[4]

In recent years, and given that the diagnostic criteria based solely on the histological architecture are insufficient, we are trying to perform a molecular characterization of the RCC to establish new tumor markers useful both in the histological diagnosis and in the prognostic prediction and drug response that are now being developed. In this regard, and based on the aforementioned involvement of the *vhl* suppressor gene in sporadic RCC cases, we evaluated the involvement of the signaling pathway between VHL and the hypoxia-inducible factor 1 alpha (HIF-1α) in the RCC.

Evidence synthesis

pVHLpathway $\rightarrow$ HIF-1α $\rightarrow$ CA-IX

The *vhl* gene encodes a protein (pVHL) binding to the HIF-1α in normoxic conditions, favoring its degradation, mediated by ubiquitination and by a mechanism dependent on prolyl hydroxylases (hydroxylation of prolines 402 and 564). Herein lies part of the suppressor function of the *vhl* gene. The absence of a normal function of the pVHL (either by mutation or by hypermethylation of the gene) creates a situation similar to hypoxia, so the HIF-1α is not