Kidney: Clear cell renal cell carcinoma

Eva van den Berg, Stephan Störkel

Clinical Cytogeneticist, Department of Clinical Genetics, Academic Hospital Groningen, Ant. Deusinglaan 4, 9713 AW Groningen, the Netherlands (EvdB, SS)

Published in Atlas Database: July 2004
Online updated version: http://AtlasGeneticsOncology.org/Tumors/ClearCellRenalCC5020.html
DOI: 10.4267/2042/38117

This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 2.0 France Licence.
© 2004 Atlas of Genetics and Cytogenetics in Oncology and Haematology

Identity

Alias
Common renal cell carcinoma; Conventional renal cell carcinoma; Non papillary renal cell carcinoma

Classification
Clear cell renal cell carcinoma (cRCC) is a distinct subtype of renal cell carcinoma, possibly originating from mature renal tubular cells in the proximal tubule of the nephron.

Clinics and pathology

Epidemiology
It comprises 70-75% of cases. They show a male preponderance of 2:1.

Pathology
The tumor mass of cRCC is multicolored, with a predominantly yellow surface with white or gray foci. It usually shows a solid growth pattern, but in some cases cystic or alveolar appearance is seen. The cytoplasm is clear, due to an intensive intracytoplasmatic accumulation of glycogen and lipids. The nuclei are condensed and hyper-chromatic. Electronmicroscopical features resembling the proximal tubule can be found i.e. brush border formation and basal infoldings. Tumor cells express antigens of the proximal tubule. Variants can be assigned which are characterized by augmentation of mitochondria leading to a stronger eosinophilia or granularity, respectively, of the cytoplasm. Spindle-shaped/pleomorphic variants as a result of sarcomatoid transformation can also be found.

Cytogenetics

Cytogenetics Morphological

cRCC is characterized by loss of (part of) the short arm of chromosome 3 due to (a) deletion(s) or unbalanced translocation(s) and restricted to this type. Regions frequently lost are 3p12-14, 3p21 and 3p25. Loss of at least two of these regions is necessary for kidney cells to develop into clear cell renal cell carcinoma, and loss of 3p21 is obligatory. Therefore, if a tumor shows only one deletion at 3p, either 3p14 or 3p25, it should be designated common type renal cell adenomas. Other aberrations frequently found in common RCC are (partial) trisomy of chromosome 5, especially the 5q22-qter segment. Trisomy 12, and 20, and loss of chromosomes 8, 9, 13q, 14q, and structural abnormalities of the long arm of chromosomes 6 and 10 are also found and correlated with progression. In general, cRCCs are sporadic tumors but also syndromic in patients with the von Hippel-Lindau (VHL) disease (germ line mutations in the VHL tumor suppressor gene assigned to 3p25). Also familial cRCC has been reported. All have in common the presence of abnormalities involving chromosome 3.

Genes involved and proteins

Note
Based on allele-segregation, LOH and mutation analyses, a step-wise model for cRCC tumori-genesis was put forward in which the loss of the translocation derivative chromosome 3 may lead to chromosomal mosaicism. Subsequently, cells lacking this chromosome may suffer a second hit resulting in full blown tumor development.
Loss of heterozygosity (LOH) and comparative genetic hybridization (CGH) analyses of cRCCs revealed that allelic (interstitial) losses predominantly occur in the chromosome 3p21 region in combination with either 3p25 or 3p13-14, or with both, and these allelic losses were restricted to the cRCC. These results suggest that loss of the 3p21 region is a prerequisite for malignant development of cRCC and indicate that several regions (and thus several genes) on human chromosome-3 contribute to cRCC tumor development.

Until today no tumor suppressor gene responsible for, or at least contributing to, cRCC has been identified - except for VHL-, in the different regions, although many candidate genes have been suggested such as FHIT (fragile histidine triad); TTRC1 (two-three-renal-cancer-1; DUTT1 (deleted in U-twenty-twenty); locus NCR-1 (nonpapillary renal cell carcinoma 1) and RASSF1A (RAS association family 1).

The gene in the 3p21 region involved in cRCC development is the von Hippel Lindau (VHL) tumor suppressor gene. Somatic mutations and LOH of the VHL gene were also found in primary sporadic cRCCs. Occurrence of mutations in this gene in both sporadic as well as hereditary forms of cRCC suggests a key role of the VHL gene in oncogenesis. However, VHL is inactivated in only 30-50% of sporadic cRCC, suggesting involvement of another tumor suppressor gene located on 3p.

Loss of heterozygosity on chromosomes 8p or 9p provide diagnostic significance in patients with locally advanced cRCC and PTEN/MMAC1 (chromosome 10) inactivation may play a role in the progression of cRCC.

To be noted

Some first array studies on RCC have recently been published showing that specific gene expression patterns could be associated with various tumors (types) including cRCC and other disease states.

References


Kidney: Clear cell renal cell carcinoma

van den Berg E, Störkel S


This article should be referenced as such: