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Cytogenetic Classification of Renal Cell Cancer

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ABSTRACT: *Cytogenetic and molecular genetic investigations in cancer are important tools to address problems of oncogenesis and tumor progression, of classification, and of diagnosis of tumors. A combination of advanced molecular genetic, cytogenetic, and (immuno) histopathologic analysis will contribute significantly to the elucidation of the oncogenic steps that lead to immortalization and subsequent malignant behavior. In this review written on the occasion of Dr. Avery Sandberg's 75th anniversary, we will present a model for the pathogenesis of renal cell tumors based on a new cytomorphic classification and our (cyto)genetic analysis of about 175 renal cell tumors, together with the accumulated data in the literature. © Elsevier Science Inc., 1997*

INTRODUCTION

Renal Cell Cancer

Renal cell adenomas (RCA) and carcinomas (RCC) constitute a heterogeneous group of tumors and this heterogeneity is a well-known complicating factor in the diagnosis. The histogenesis of renal cell cancer has been controversial for a long time, especially in terms of the thesis originally expressed by Virchow and advocated by Grawitz [1] that certain clear cell epithelial renal tumors are derived from ectopic adrenocortical elements. This has led to the term "hypernephroma" or Grawitz tumor and finally also to the term "hypernephroid renal carcinoma." Although true hypernephrogenic tumors do rarely occur in the kidney, the hypernephrogenic theory of the clear cell epithelial renal tumors has been questioned for a long time and preference is given instead to the renal tubular histogenesis. The evidence that the usual (nonembryonic) renal adenomas and carcinomas in all their variants derive, in principle, from the mature uriniferous tubule has been promoted and consolidated by animal experiments with carcinogens and observation of prestages and early stages of epithelial renal tumors in human kidneys [2-4].

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CLASSIFICATION OF RENAL CELL CANCER

The aim of a histopathologic classification is to use morphologic criteria to identify biologically distinct disease states, the recognition of which are of clinical value [5]. Therefore, modern tumor classifications generally are cytologically orientated, i.e., emphasizing histogenesis and differentiation. The formation of such a classification for epithelial renal tumors has proved difficult. Previous attempts have been "closed" systems using histology as the basis both for the classification and for the recognition of the distinct species [5].

Currently two morphologic classifications are used: one according to the WHO/AFIP [6] and one according to Thoenes et al. [7] and Störkel [8]. As stated in the latter, eight different subtypes of RCA/RCC can be distinguished, related to the basic cell types of the nephron from which they are derived: (1) RCCs of the clear cell type, (2) RCAs/RCCs of the chromophilic cell type, (3) RCAs/RCCs of the chromophobic cell type, (4) RCCs of the duct Bellini cell type, (5) RCCs of the transitional cell type, (6) RCCs of the neuroendocrine type, (7) RCAs of the oncocytic type, and (8) RCAs of the metanephroid type. These types show phenotypical/histogenetical relations to different parts or cell types, respectively, of the nephron collecting duct system [8].

Basically three growth patterns, which can be deduced from the tubule, are distinguished: (1) compact (subtype: acinar); (2) tubulopapillary, and (3) cystic. Principally, in a given tumor, all growth patterns can occur simultaneously, but generally one of them predominates. There are relationships to the cell types, although not exclusive: clear cell and chromophobe type are predominantly related to compact growth, chromophilic to tubulopapillary growth, oncocytic (true 'renal oncocyoma') is related to acinar, and Bellini duct to both compact and tubulopapillary growth.

The renal cell carcinomas are graded with respect to nuclear atypia, including the size of nucleoli, supplemented by cytoplasmic features, e.g. diminution of basic features, augmentation of eosinophilia/granularity (mitochondria), and spindle/pleomorphic cell form. Presently, according to these parameters three grades (G1, G2, G3/4) are distinguished [7].

CYTOGENETIC AND MORPHOLOGIC CORRELATIONS

Cytogenetics allows the classification of tumors with respect to their genotypic differences. Figure 1 summarizes and correlates both morphology and cytogenetic data with respect to histogenetic aspects of most of the basic tumor subtypes mentioned above. RCCs of the transitional cell type, neuroendocrine type, and RCAs of the metanephroid type are not mentioned in Figure 1 because of the limited data available. One of the first genetic alterations in tumor development, associated with the epithelia of the proximal tubule, are trisomy 7 and loss of the Y chromosome, probably resulting in hyperplastic and dysplastic changes.

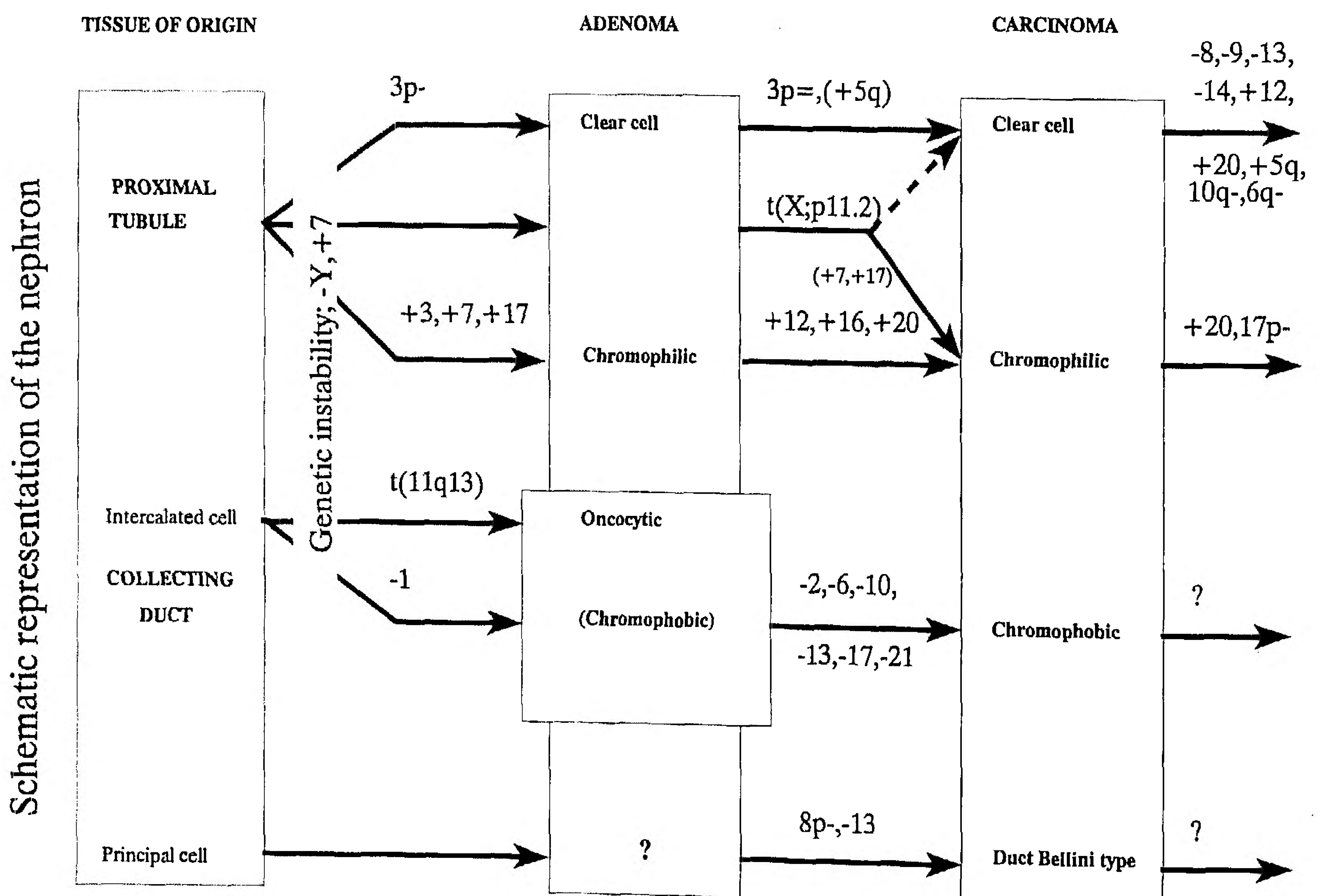
But trisomy 7 and loss of Y may have limited or no significance with respect to RCC development and progression, because these chromosomal alterations have been demonstrated to be present in normal cells of tumor-adjacent kidney parenchyma rather than in the tumor itself [9] and trisomy 7 and trisomy 10 can be found in subpopulations of tumor-infiltrating lymphocytes [10]. Recently, occurrence of trisomies 5, 8, and 18 has also been reported for non-neoplastic kidney tissue [11, 12]. A gain of chromosome 7 may confer growth advantage to some malignant

cells, because of the presence of the epidermal growth factor receptor on this chromosome [13]. The loss of one sex chromosome has been observed frequently. The non-random loss of the Y chromosome in RCC remains obscure and is possibly age-related [14, 15]. The most frequent finding in RCCs of the clear cell type is a deletion or unbalanced translocation involving the short arm of chromosome 3 [16–18].

The breakpoints appear to cluster in region 3p11-p21, usually at 3p14. Involvement of the long arm has seldom been described. Recently, the relevant tumor suppressor gene responsible for the hereditary forms (von Hippel-Lindau disease) has been identified [19]. This gene seems also to play a role in the development of the sporadic forms, probably in combination with other gene(s) [20, 21]. Moreover, a recent report suggests the presence of clear cell RCAs, showing only one deletion at 3p (3p- in Fig. 1), either 3p14 or 3p25, whereas subsequent loss of the 3p21 region results in clear cell RCCs (3p= in Fig. 1) [22]. Also a (partial) trisomy of chromosome 5, especially the 5q22-qter segment, is frequently found in the clear cell tumors as well as trisomy 12, and 20, loss of chromosomes 8, 9, 13, 14, and structural abnormalities of the long arm of chromosomes 6 and 10 [18, 23–26, own observations].

RCAs of the chromophilic type show a typical pattern of numeric aberrations: i.e. -Y, +7, (+7), +17. Trisomy 3 is also frequently found [27–31]. Trisomy of chromosomes 12, 16, and 20 has been associated with the progression from the adenoma into the carcinoma stage, i.e. RCCs of the chromophilic type [28, 32]. Conflicting data exist

Figure 1 Proposed oncogenetic model for renal cell tumors.



about papillary RCC showing rearrangement of the critical 3p segment, at least at a molecular level [33, 34].

Several human renal cell carcinomas with X;autosome translocations have been reported in recent years (see for review [35]). The t(X;1)(p11.2;q21) appears to be a specific primary anomaly, suggesting that tumors with this translocation form a distinct subgroup of chromophilic RCC, showing clear cell features. These tumors preferentially occur in male patients [36–39], although one female case has recently been described [40].

Chromophobic carcinomas show multiple losses of entire chromosomes, i.e. loss of chromosomes 1, 2, 6, 10, 13, 17, 21, and the Y chromosome, leading to a low chromosome number. They also show quantitative as well as qualitative changes in mitochondrial DNA [41, 42].

Two reports with cytogenetic data from collecting duct carcinomas revealed conflicting findings of monosomy for chromosomes 1, 6, 14, 15, and 22 in one case [43] and trisomies 7, 12, 16, 17, and 20 in the other [44]. Schönberg et al. [45] reported involvement of the short arm of chromosome 8 related to poor prognosis and loss of the long arm of chromosome 13, both in three out of six cases.

There are no cytogenetic data on RCCs of the transitional cell type. Only one case with cytogenetics of RCC of the neuroendocrine type has been published revealing structural and numerical aberrations of chromosome 13 [46]. Molecular analysis of another case showed LOH on 3p21 [47]. Both transitional cell RCCs and neuroendocrine RCCs are not mentioned in Figure 1. RCAs of the oncocyctic type seem to be characterized by mitochondrial DNA changes [48,49], a feature they share with the chromophobic carcinomas. At least two subgroups can be distinguished: one characterized by translocations involving 11q13 [50] and one by the combination of $-Y, -1$ [51, 52]. Loss of chromosomes 1 and Y is also observed in chromophobic carcinomas. From a cytogenetic point of view, oncocytomas showing $-Y, -1$ might progress to chromophobic carcinomas through additional chromosome losses (see Figure 1). This might explain why oncocytomas, which are considered to be benign neoplasms, occasionally show malignant behavior. One case of RCA of the metanephroid type (not mentioned in Figure 1) revealed a normal (46,XY) karyotype [53].

A strong correlation between pronounced telomere shortening and the appearance of telomeric associations of chromosomes was found in three renal cell tumor subtypes (RCAs of the oncocyctic type, RCAs/RCCs of the chromophobic type, and RCCs of the chromophilic type), suggesting an etiologic role of the loss of telomeric DNA repeats in the formation of telomeric associations and a possible involvement of this mechanism in the pathogenesis of chromosome aberrations [54].

CYTOGENETICS AND TUMOR PROGRESSION

In the clear cell RCCs, monosomy 8, 9, 13, and 14, and trisomy of chromosomes 12 and 20 seem to correlate with a higher grade, and thus progression. Also structural aberrations (and probably loss of heterozygosity) of chromosomes 5q, 6q, 8p, 9, 10q, and 14q are associated with tumor progression [18,55, own observations]. In RCAs/RCCs of the

chromophilic type polysomies 12, 16, and 20 are associated with progression from adenoma into carcinoma stage. The loss of the extra chromosome 17p in RCCs of the chromophilic type tend to be related to the higher grade neoplasms, in which also a higher frequency of trisomy 20 is found [56]. It seems that tumors derived from the proximal tubule (RCAs/RCCs of the clear cell and the chromophilic cell type) share secondary karyotypic changes and this might suggest that many of the tumor suppressor loci involved may be common to the etiology of both forms [57].

Sarcomatoid transformation in RCC represents the highest form of dedifferentiation [7]. Sarcomatoid variants of RCC can in principle be deduced from all the basic cell types. Cytogenetic data on sarcomatoid RCC is scarce. Grammatico et al. [58] reported a sole case of pleuric effusion of sarcomatoid RCC with structural abnormalities of chromosomes 1, 5, 16, and 19. Others have found a relation between p53 mutations and sarcomatoid RCC [59]. Because it is not clear which basic cell types are involved in the above mentioned cases, these data are not included in Figure 1.

CONCLUSION

Renal cell cancers (RCCs) are epithelial neoplasms that demonstrate a diversity of morphologic characteristics and clinical manifestations. The classification of the heterogeneous group of RCC is still a matter of debate.

Different subtypes of renal cell carcinoma might originate from cells of the different parts of the renal tubulus. Taken together, cytogenetic and molecular genetic studies of recent years have demonstrated that certain specific chromosomal abnormalities correlate with different histologic subtypes of renal tumors. Chromosomal abnormalities are believed to be responsible for neoplastic transformation, tumor growth, and tumor progression [60]. Oncogenetic studies might reveal the cell of origin, oncogenetic steps, and relationship of tumors. The view of a relation between renal cell adenomas and carcinomas is strengthened by the fact that oncocytomas and adenomas occasionally show a malignant behavior. A reasonable explanation for this exceptional behavior is that oncocytomas and adenomas probably represent the benign side of a spectrum of renal cell tumors, with renal cell carcinoma at the other extreme. If the "spectrum" concept for adenomas and carcinomas is correct, then it may be expected that there would also exist an overlap in some of the characteristics of these benign and malignant tumors. Referring to this concept, the chromophobic carcinoma could be the malignant counterpart of the oncocytoma. Both show marker proteins and ultrastructural features of the distal nephron, thus disproving the broadly accepted hypothesis that all renal cell cancers are related to the proximal tubulus.

At the (cyto)genetic level, this oncogenetic sequence might be envisaged as depicted in Figure 1.

Thus, (cyto)genetic studies of renal cell adenomas, various subtypes of carcinomas, and oncocytomas will contribute to a better understanding of the biology of these tumors, and reveal key information on the process of tumorigenesis and tumor behavior. This information may open new opportunities for (early) diagnosis and specific therapy.

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