Review

Human renal cancer carcinogenesis: A review of recent advances

W. Stadler & N. J. Vogelzang
Section of Hematology/Oncology, Department of Medicine, University of Chicago, Chicago IL, U.S.A.

Key words: renal cancer, molecular biology, cytogenetics, carcinogenesis

Introduction

Renal cell carcinoma has fascinated the medical profession for many years. It has been called the internist's tumor because of its unusual patterns of metastases, its numerous associated paraneoplastic syndromes (see Table 1), and its well documented spontaneous regressions [1-4]. For the oncologist, it has been a frustrating disease to treat. Patients presenting with locally unresectable or metastatic disease have a median survival of less than 1 year [5]. Chemotherapy and radiotherapy have had little effect on this natural history [5]. Yet, a small percentage of patients are long term survivors, despite metastatic disease. In the mid to late 1980s the immunotherapy of this tumor using IL-2 with or without LAK (lymphokine activated killer) cells or TILs (tumor infiltrating lymphocytes) generated great enthusiasm [6-9]. Even here, though, the response rate in most large trials has only been 12%-16% and median survival of the patients has not demonstrably improved [10-13]. Altering the IL-2 schedule or route of administration has not convincingly increased the response rate [14-16]. Combination IL-2 and interferon-α (also an active agent) has likewise failed to increase the response rate [17].

Many investigators therefore have come to realize that better treatments will depend on a better understanding of the biology of renal cancer. Thus within the past 5 years there has been a rapid increase in knowledge regarding mechanisms of carcinogenesis of renal cancer. Carcinogenesis has traditionally been investigated with epidemiologic methods supplemented by traditional pathology as well as by studies with animal models, whose tumors tend to be chemical carcinogen induced. More recently, molecular biologic methods have successfully been directly applied to spontaneous human tumors in an effort to elucidate mechanisms of carcinogenesis. Clinicians, generally more familiar with epidemiology and animal models than molecular biology, do not seem to have shared in this recent knowledge explosion.

In an effort to bridge this gap we briefly review the epidemiology, pathology, and traditional animal models of renal cell cancer and then provide a more in depth review of the exciting new developments in the molecular and cytogenetic aspects of renal cell carcinogenesis.

Methods

MEDLINE, CANCERLIT, and major textbooks were searched for appropriate articles using renal cell carcinoma, renal adenocarcinoma, clear cell carcinoma, and hypernephroma as key words. In addition, the reference lists from the selected literature were reviewed for additional articles. Those consistent with the goals of this review were analyzed in detail and those conforming to generally accepted experimental methods are included here [18-20]. In some cases, articles not meeting these criteria were included because of their historical importance or the lack of additional data. Whenever this was necessary, qualifying remarks are made.

Epidemiology

The incidence of renal cell carcinoma is approximately 7.5 cases per 100,000 representing 2.3 percent of male
renal cell carcinoma usually arises as a single mass in the kidney cortex. In 85% of cases it is highly vascular and thus shows the typical findings of neovascularity, A-V fistulas, and pooling of contrast medium on angiography [60]. On cut section it is surrounded by a fibrous pseudocapsule and is noted to have a variegated appearance with hemorrhage, necrosis, calcification, and cystic change [61]. Extension tends to be local with growth into the perinephric fat, through Gerota's fascia, and then to regional lymph nodes as well as surrounding tissue. In addition, the tumor has a unique propensity to grow in the renal vein with subsequent extension up the vena cava. Metastases are most common in lung and bone. Metastatic disease, however, has been documented in every organ, sometimes giving rise to diagnostic confusion. Although there has been some controversy regarding the existence of so-called benign renal adenomas, current consensus is that these represent true carcinomas at an early stage [21, 61].

Microscopically the tumor is classically composed of cells with clear cytoplasm and glandular differentiation. The histology can, however, vary widely and the tumor is generally classified as a clear cell, granular cell, or spindle cell neoplasm [5, 20, 21, 61]. The histologic pattern can be classified as papillary, tubular, alveolar, or solid [5, 61]. Close examination of both the light microscopic and as at the ultrastructural level suggests that these tumors arise from the proximal renal tubule [21, 62–64]. Immunohistologic studies confirm this hypothesis. For example, at least 80% of renal tumors react with polyclonal anti-brush border anti-serum, a reagent that binds exclusively to the proximal tubules of human kidneys. Anti-Tamm-Horsfall antiserum, which binds to distal tubules, does not bind to renal cell carcinoma tissue [65]. On the other hand, an antiserum which specifically recognizes nephrocalcin, a calcium-binding protein produced by proximal tubules, does bind to renal cell carcinoma tissue [66]. Nephrocalcin is produced by renal cancer cells in culture as well and may be a potential tumor marker [67].

Monoclonal antibody technology has been used to better define the cell of origin for renal cell cancer. Four of six such antibodies produced by immunizing mice with established renal adenocarcinoma cell lines reacted strongly with proximal tubules but not with other regions of normal kidneys [68]. One of these monoclonal antibodies reacted with all 20 fresh spontaneous renal carcinomas and all 100 renal carcinoma cell lines studied. Bander et al. recently isolated two monoclonal antibodies which define mutually exclusive regions of the normal adult proximal tubule. The respective antigens are coexpressed only in fetal proximal tubules and in renal cell carcinomas [69]. Of 50 fresh tumors studied, only one failed to express either antigen, but this tumor did express other proximal tubule antigens. None of the 50 tumors, including one with papillary histology, expressed distal tubule antigens. The renal cell cancer associated with acquired cystic disease has also been suggested to arise from the proximal renal tubule and occurs in conjunction with tubule epithelial cell hyperplasia [35]. Cancers occurring in this disorder are generally less than 3 cm (thus qualifying them as "adenomas" in the older literature) and tend to have a papillary architecture [32, 35]. Cancer associated with autosomal dominant polycystic kidney disease exhibits a similar hyperplasia and papillary histology [37]. Finally, the kidneys of patients with von Hippel-Lindau (VHL) disease also contain cysts lined...
by atypical epithelial cells, often adjacent to the carcinoma [70]. Renal oncogenesis in genetic and cystic renal diseases thus appears to be a continuum of genetic changes, not unlike that seen in cancers of the colon [71]. An analogous continuum in de novo renal carcinoma can be hypothesized but has not been studied.

### Animal models of renal cancer

Renal cell cancer occurs in numerous animals, and several spontaneous tumors have found use as transplantable models or a models of the human hereditary renal cell carcinoma [72–74]. In attempts to find convenient and reproducible animal models, a number of renal carcinogens have been identified (Table 2). Of the chemicals listed only phenacetin has been clinically linked to human renal cancer [47]. The number of cases attributable to phenacetin abuse, though, is small and they are usually transitional cell carcinomas.

Some of the chemically-induced tumors may shed light on the pathogenesis of the spontaneous human counterpart. For example, Dees et al. using the FBPA-induced cancer showed that the initial lesion was characterized by large bizarre nuclei in the cells of the proximal tubule [83]. Interstitial fibrosis and a mononuclear cell infiltrate then appeared, followed by atypical epithelial hyperplasia, dilated cystic tubules surrounded by fibrosis, and ‘foam cells’. It was only then that tumor nodules appeared. DMN-induced tumors also arise from the proximal tubule, and do contain some clear cells [78]. It has been postulated that chemical injury to the tubule along with a secondary monocellular cell infiltrate is the tumorigenic event [78]. Additionally, both the lead [75, 76] and the streptozotocin [89–92] induced tumors are associated with cystic tubule dilatation. Interestingly, heterozygote offspring of rats with a hereditary renal cell carcinoma (the Eker mutation) have a 70-fold increased sensitivity to DMN induced renal carcinogenesis [79]. The analogy to multistep human carcinogenesis is obvious.

Animal models that mimic the clinical finding of a male predominance are the rodent renal cell tumors induced by streptozotocin [90–92], ferric nitrilotriacetate [81–83], and diethylstilbestrol (DES) or other estrogens [93–97]. The DES model has prompted attempts at hormonal treatment for renal carcinoma, usually with little or no success [5]. Although the DES induced tumors were initially reported to arise from epithelial cells of the proximal tubule [94], subsequent work indicated that the precursor cell is probably much earlier in the differentiation pathway, giving rise to tumors with multiple cytologic characteristics [96, 97]. In the ferric nitrilotriacetate model, hormonally dependent differences in toxin-induced proximal tubular lipid peroxidation appear to mediate the observed male tumor predominance [86, 87]. Although the histology of all the above tumors varies in detail it is noteworthy that most contain cells that can be identified as ‘clear cells’, and most demonstrate at least some papillary growth pattern, especially in the early lesions.

A final animal model is the Lucke renal tumor in leopard frogs [98, 99] which is a herpes virus-induced tumor that fulfills all of Koch’s postulates [100]. Although another virally-induced kidney cancer has been reported [101], there is no pathologic or epidemiologic evidence for a human ‘renal cancer virus’.

### Cytogenetics and molecular biology

Modern methods of cytogenetics and molecular biology have revolutionized the study of renal cell cancer. The first important discovery in this era was by Cohen et al. who described a family with hereditary renal cancer associated with a constitutional translocation from the short arm of chromosome 3 to the long arm of chromosome 8 [39]. The initial report assigned the break point on chromosome 3 to band p21, but subsequent reports assigned it to p14 [102–104]. The break point on chromosome 8 was assigned to band q24 in all reports. Although one of the later studies reported a translocation of the myc oncogene from chromosome 8 to the chromosome 3 derivative, no rearrangements in the myc gene or in the flanking sequences were detected [103]. A subsequent report on another family with hereditary renal carcinoma also showed an associated break on the short arm of chromosome 3 (3p13) [40]. This mutation differed from the former in that the deleted chromosomal material was translocated to the short arm of 11 (11p15), and the mutation was limited to the tumor cells. Numerous reports then appeared confirming that the deletion of a segment from the short arm of chromosome 3 was closely associated with sporadic renal cell tumors as well [105–110].

The initial reports were highly variable as to the percentage of tumors containing the 3p deletion, making it unclear whether a 3p deletion was causally related to

---

**Table 2. Renal carcinogens in animal models.**

<table>
<thead>
<tr>
<th>Chemicals</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lead</td>
<td>[75, 76]</td>
</tr>
<tr>
<td>Dimethylolurosine (DMN)</td>
<td>[77, 80]</td>
</tr>
<tr>
<td>Diethylolurosine (DEN)</td>
<td>[81]</td>
</tr>
<tr>
<td>N-(4-Fluoro-4-biphenylacetamide (FBPA)</td>
<td>[82, 83]</td>
</tr>
<tr>
<td>Phenacetin</td>
<td>[84]</td>
</tr>
<tr>
<td>Ferric nitrilotriacetate</td>
<td>[85–87]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Natural Products</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Aflatoxin</td>
<td>[88]</td>
</tr>
<tr>
<td>Streptozotocin</td>
<td>[89–92]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hormones</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Diethylstilbestrol (DES)</td>
<td>[93–94]</td>
</tr>
<tr>
<td>Other estrogens</td>
<td>[95]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Viruses</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lucke renal tumor virus</td>
<td>[98–100]</td>
</tr>
<tr>
<td>MH2 reticuloendothelioma virus</td>
<td>[101]</td>
</tr>
</tbody>
</table>
the development of renal cell carcinoma. Some of the variability in the frequency of deletions can be ascribed to the banding techniques used, tumor cell heterogeneity, contamination with normal cells, and the method or length of cell culture required to obtain sufficient cells for analysis. The latter also made it difficult to elucidate whether the deletions were truly inherent to the tumor or simply a result of selective pressures from cell culture. A recent review of all published cytogenetics in primary renal cancer does however point to consistent deletions within the 3p13-pter segment [111].

Restriction fragment length polymorphism (RFLP) analysis helped to further refine these reported deletions. This technique depends on the inherent variability of defined DNA sequences in the genome. Some of these variations create a sequence recognized by readily available restriction enzymes, while other variations do not create such a sequence. Thus, if a probe for the region of interest is available, restriction enzyme digestion and Southern blotting of the DNA will visualize a different number of bands depending on the presence or absence of a restriction site. In the simplest situation, two bands will be visualized if the individual is heterozygous for the site and only one band (albeit of double intensity if the amount of DNA is standardized) if the individual is homozygous for the site. These sites need not necessarily be within the gene of interest, only closely linked, in order to be informative. RFLP analysis of fresh renal tumors with probes previously mapped to the 3p region showed that 60%-100% of sporadic renal cell carcinomas have a loss of heterozygosity when compared to normal tissue from the same patient [112-121]. The specificity of a 3p lesion is supported by its presence in sporadic, hereditary, as well as von Hippel-Lindau associated renal cancers [122-126]. Also, both early and late stage tumors have such a lesion whereas additional chromosomal abnormalities (by cytogenetics or RFLP analysis) are rare in the absence of a 3p deletion [115, 116-119, 127, 128]. Some of this data is summarized in Table 3. It appears that additional chromosomal abnormalities tend to be limited to later stage disease. The numbers reported are small, statistically insignificant, and are biased by the RFLP probes the investigators chose to examine (which may or may not be closely linked to the genes of interest). Nevertheless, the data suggest that a 3p deletion is an early and critical step in renal cell carcinogenesis, whereas other abnormalities may be important in tumor progression. In fact, the additional losses noted may well be in the region of other tumor suppressor genes (see below) and two recent papers support this hypothesis by demonstrating loss of two known suppressor genes, p53 and the retinoblastoma gene, mainly in advanced stage tumors [127, 128].

Using several RFLP probes, whose linkage and relative order on the 3p chromosome are known, a number of investigators have attempted to more specifically localize the proposed renal cell cancer gene [115, 119-121, 129, 130]. There is relative good consensus, confirmed by the most recent detailed deletion mapping [121], that the minimal region of deletion is in band 3p21.3. One study also suggests a second region of common deletion at 3p13-14.3 [121]. This latter site is within the region of most cytogenetic breakpoints and also contains a fragile site (fragile site 3B) [131]. As such it may only be a common site for DNA damage and rearrangement and may not necessarily be related to a specific tumor suppressor gene (see below). This is supported by close linkage of the 3:8 translocation in the familial renal cancer reported by Cohen to fragile site 3B [104], although it should be pointed out that a correlation between fragile sites and chromosome breakpoints in sporadic renal cancer has not been demonstrated [110]. Interestingly, the von Hippel-Lindau gene has been mapped very closely to the common region of deletion at 3p21.3, and may or may not be the same as the proposed renal cancer susceptibility gene [132-134]. Finally, it is important to note that deletions in the 3p21 region have also been documented in human lung [135-137], breast [138], uterine cancer [139], and head and neck cancer [140]. Chromosomal deletions have also been described in the hereditary renal cancer (Eker mutation) [141], although none of the deleted regions are homologous to human 3p21 [142].

Given the current interest and activity in mapping of human chromosome 3p [143, 144], it is expected that isolation of the gene or genes important in the develop-

Table 3. Chromosome loss by cytogenetics and/or RFLP in nonpapillary renal cell cancer according to stage.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study #</td>
<td>Study #</td>
<td>Study #</td>
<td>Study #</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>I/II</td>
<td>3/5</td>
<td>11/21</td>
<td>10/15</td>
<td>4/5</td>
</tr>
<tr>
<td>III/IV</td>
<td>12/17</td>
<td>5/9</td>
<td>3/6</td>
<td>47/53</td>
</tr>
</tbody>
</table>

Study #1: Bergerheim, et al. [115] – Included 1 papillary.
Study #2: Ogawa, et al. [118] – Included 3 papillary.
Study #3: Monta et al. [117] – Histology not mentioned.
Study #4: Anglard et al. [119] – Included 1 papillary, used 10 RFLP probes for 3p. 8 probes for 11p.
Study #5: Presti et al. [120] – Used both RFLP probes & cytogenetics.
ment of renal cell carcinoma will soon be published. In fact, the expression of a gene localized to the 3p21 region has already been reported to be markedly decreased in cancerous as opposed to normal kidney tissue [145]. This was true even in the one patient who retained heterozygosity for an RFLP mapped to the same site. This gene was later identified as acylpeptide hydrolase or a closely related protein [146]. A similar decrease in expression of two other genes (ACY1 and D8) mapped to 3p21 has been described in small cell lung cancer lines [147, 148]. Another interesting gene localized to the 3p21 region at this time is a tyrosine phosphatase (see below) [149].

Given the above data, it has been postulated that the mechanism of renal tumorogenesis is due to inactivation of a tumor suppressor gene as is the case in retinoblastoma [150]. This tumor arises in both a hereditary and sporadic form [151]. A patient with the former type is at high risk for bilateral tumors and has a much earlier age of presentation than a patient with the latter. Early family studies suggested the presence of a recessive ‘anti-oncogene’ which was genetically deleted or altered in the patients with hereditary disease. These patients then presented with a tumor when the second, normal, retinoblastoma gene became mutated in the somatic cells [152]. Patients with sporadic disease would thus have to have two such mutations in their genetically normal retinal cells. This hypothesis has since been confirmed [153–161]. The retinoblastoma gene (Rb) has been isolated [155, 156], the mutations have been described [157, 158], and the protein product purified [159]. Confirmation of the tumor suppressor activity of Rb has been accomplished by suppression of the malignant phenotype in human cancer cells transfected with a normal Rb gene [160, 161].

Unfortunately, the proposed renal cell carcinoma susceptibility gene(s) has not yet been isolated. When such a gene is cloned, similar investigations will no doubt ensue. One report has already described modulation of the tumorigenicity of a renal cell cancer cell line when a normal 3p chromosome is introduced [163]. Also, recent excitement has been generated with the discovery and characterization of tyrosine phosphatases, which are candidates for tumor suppressor genes [164]. As stated above, one such gene has been localized to the 3p21 region [149].

Although loss of the proposed renal tumor suppressor gene on 3p21 has been reported to be specific for the clear cell subtype, there is not yet a consensus for this claim. It is, however, important to note the lack of 3p deletions in renal tumors with papillary histology, which instead may be associated with a trisomy 17 [120, 165–167]. The interpretation is that papillary tumors are biologically different, an interpretation supported by the somewhat better prognosis of these tumors [168, 169].

As noted above, numerous other chromosomal abnormalities, both by cytogenetic and RFLP analysis, have been described. It is likely that many are markers for genetic aberrations important in multistep carcinogenesis and progression. As such it could be predicted that different tumors as well as different clones of a single tumor developed after different genetic insults. Any specific genetic change would then only be found in a percentage of renal cancers, as has been reported for the p53 and Rb tumor suppressor genes (see above). In general, the rapid pace of advancements in molecular genetics leaves us with a wealth of data for which pathophysiologic and clinical correlates have not yet been determined. One chromosome region that is a possible candidate for further investigation is the reported allelic loss of a 6p centromeric region in 6 of 33 fresh renal carcinomas [171]. Since this is close to the HLA-D locus it may explain the reported abnormal frequency distribution of HLA-DR5 and HLA-DR8 in renal cell cancer patients [172, 173].

Because chromosomal breakpoints often pinpoint oncogene rearrangements in other human malignancies (e.g. c-abl in CML) a similar phenomenon was sought in renal cell cancer. One paper demonstrated a shift of the c-raf 1 locus from the terminal portion of 3p to the breakpoint region using in situ hybridization [174]. As could be expected from this gene’s more telomeric location than the critical 3p21 region, neither a rearrangement nor a change in its mRNA transcript was demonstrated. Although the myc oncogene is translocated to the derivative chromosome 3 in one of the familial renal cell cancers, no rearrangements or amplifications of the myc gene have been noted in sporadic tumors. Increased myc expression, however, has been reported and may correlate with tumor grade [175, 176]. Enhanced expression of the epidermal growth factor (EGF) receptor gene (c-erbB-1) has also been consistently found [177–184] (see below). Decreased expression of HER2/neu (c-erbB-2), which encodes a EGF receptor-like tyrosine kinase [185] has been noted, and may be specific for the clear cell histologic subtype [177, 178]. Either no expression or expression equal to that of normal renal tissue has been found for the N-ras, c-fos, c-raf, c-Ki-ras, N-myc, c-fes, and c-abl oncogenes [176].

Growth factors and their receptors

Most cellular growth and differentiation is presumed to be under the control of various growth factors acting in an endocrine, paracrine, or autocrine fashion. The interaction between a growth factor and its receptor initiates a series of events beginning with membrane signal transduction through proteins such as the G-proteins and culminating in transcription of specific genes in the nucleus. It is suspected that most oncogene products are constituents of this pathway and their dysregulated expression and/or function contributes to carcinogenesis [186]. This has been most clearly defined in hematopoietic cells and malignancies. Similar factors have been suspected to support kidney cell
growth and contribute to the development of renal cell carcinoma.

It has long been known that unilateral nephrectomy leads to compensatory growth of the remaining kidney [187]. Extensive research in this area has elucidated a factor excreted in the urine, but poorly dialyzable, that specifically stimulates kidney cell growth both in vivo and in vitro [187–189]. This factor has not been isolated and its role in renal cell cancer not adequately studied. However, one abstract reports an increased growth rate of metastatic renal cancer nodules in nude mice after nephrectomy as compared to growth rates after partial hepectectomy or sham operation [190].

Three groups have also isolated a heparin binding growth factor from fresh human renal tumors or from the urine of patients with renal cell cancer. The growth factor activity was assayed by using thymidine incorporation into BALB/c 3T3 cells (an immortalized mouse fibroblast line) [191–193]. This activity was higher in cancer cells than in normal kidney tissue [192], stimulated angiogenesis in a chick chorioallantoic membrane assay [191], stimulated endothelial cell growth [192], was similar to basic fibroblast growth factor in size and antigenicity [191, 193], but did not support the growth of a human renal cell carcinoma line [191].

IL-6 has also been reported to act as an autocrine growth factor in cultured renal carcinoma cells [194–196], although this is not universally accepted [197]. In fact serum IL-6 although elevated in patients with metastatic renal cancer, is not an independent predictor of survival as would be predicted if it were a clinically important autocrine growth factor [198]. There is preliminary information that insulin-like growth factor I (IGF-1) may also be an autocrine growth factor, but detailed studies are lacking [199]. In addition, Kochevar reported the partial purification of a 178 kd protein from renal cell carcinoma conditioned media that seemed to act as a growth factor for several renal cancer and fibroblast cell lines [200]. The relationship of this substance to IGFs, which circulate with their binding protein as 150 kd complexes [201], was not investigated. Hypokalemia has also been suggested to be a stimulus for renal epithelial cell growth and cyst generation [202]. This, however, occurs most prominently in the distal tubule and an increased rate of tumor formation in chronically hypokalemic patients has not been reported.

The role of transforming growth factor-α (TGF-α) has also been extensively studied. This growth factor is structurally related to epidermal growth factor (EGF) [203, 204], binds to the same receptor [205, 206], induces a reversible phenotypic transformation in normal rat kidney cells [207], and was first isolated from a renal cell carcinoma line [207]. As mentioned above, the EGF receptor is identical to the c-erbB-1 oncogene [208]. In model systems, TGF-α often acts in conjunction with transforming growth factor-β (TGF-β), a structurally and biochemically distinct molecule [207, 209]. It was initially observed that several renal carcinoma cell lines and 2 of 2 fresh renal tumors expressed increased amounts of mRNA for TGF-α, TGF-β, and the EGF receptor [179]. The overexpression of TGF-α mRNA in tumor tissue in comparison to adjacent normal kidney tissue was confirmed in both early and late stage renal carcinomas [184, 210]. The latter study also demonstrated the overexpression of TGF-β in the malignant tissue. A slight increase in the mRNA [176, 177, 180, 181], and protein [182], expression of the EGF receptor in fresh renal carcinoma tissue has also been confirmed; this increase is not due to gene amplification [183]. A recent report extended these observations by showing enhanced mRNA expression of pre-TGF-α, a membrane-bound TGF-α precursor [211], and the EGF receptor in 33 of 33 renal tumors [184]. A corresponding decrease in expression of pro-EGF, a membrane bound EGF precursor [212], was also demonstrated. Interestingly, in vitro baby mouse kidney tubule growth seems to be dependent on EGF, TGF-α, or one of their homologues [213]. The hypothesis that TGF-α supports renal carcinoma growth through an autocrine loop has been supported by studies with 2 renal carcinoma cell lines [214], although it should be noted that growth stimulation by TGF-α may be dependent on the status (confluent or logarithmic growth phase) of the cells [215].

The family of ras genes codes for membrane-associated guanine nucleotide binding proteins (G-proteins) presumably important in signal transduction [186]. Their mutated or overexpressed forms have been associated with numerous tumors [186]. Activated ras oncogenes have classically been isolated by transfection of NIH/3T3 cells with tumor DNA [216], a method that has demonstrated a number of ras mutations in human urinary tract transitional carcinomas [217]. Because most of the mutations in the ras oncogenes occur in well defined ‘hot-spots’ [218], probes for these regions can be manufactured, the DNA amplified via the polymerase chain reaction [219], and then analyzed for mutations. Both this highly sensitive method, and the classical transfaction assay detect a less than 5% incidence of ras gene mutations in renal cell carcinoma [220, 221].

Conclusions

The goal of this review on the carcinogenesis of renal cell cancer has been to summarize the current data on epidemiology, pathology, animal models, cytogenetics, molecular biology and growth factors in a manner such that a conceptual framework for this fascinating disease can be created. The susceptible renal proximal tubule can be envisioned to undergo an environmental or genetic insult, probably leading to the deletion of important gene(s) on the p21 region of chromosome 3. Although the putative tumor suppressor gene for renal cancer has not yet been isolated, several candidate
genes near or on 3p21, are being actively investigated. Loss of the candidate gene(s), followed by additional chromosomal losses or mutations, may then allow the unregulated growth and expansion of the malignant clone(s), supported by activation of one or several growth factor pathways (TGFα, TGFβ, or IL-6). Such a progression, although at least partially conjectural is clearly amenable to experimental analysis. It also provides a framework for the development of innovative treatment or prevention strategies. Identification of susceptible individuals, earlier diagnosis on the basis of characteristic molecular genetic findings, interruption of growth factor pathways, and even replacement or repair of defective genetic material are all theoretically possible. Thus, renal cell cancer, although currently a frustrating and often devastating disease, may well yield to therapies derived from the elucidation of its unique biology.

Acknowledgement

The authors wish to thank Manuel Diaz, Ph.D for helpful discussions and Charisse Anderson for secretarial support.

References


Vanderbrouk AH, Vandervies P, Wijmenga C et al. The region of common allele losses in sporadic renal cell carcinoma is bordered by the loci D3S2 and THR3B. Genomics 1991; 11: 537-42.


462


Received 12 January 1993; accepted 13 January 1993.

Correspondence to:
Nicholas J. Vogelzang MD, FACP
Associate Professor of Medicine
University of Chicago Hospitals
5841 S. Maryland Avenue, MC 2115
Chicago, Illinois 60637-1470
U.S.A.

---

Book review


The authors present the whole gastrointestinal pathology in a very practical way with an encyclopedic review of epidemiology, staging and therapeutic options.

The textbook on gastrointestinal oncology offers useful and concise information about the role of endoscopy in dealing with patients with malignant diseases of the GI tract. The first chapter includes a short but informative presentation on endoscopic procedures for the general reader.

The chapter on principles of chemotherapy explains in an excellent manner the problem of 'de novo' resistance to anticancer drugs in the treatment of gastrointestinal cancer, explaining the biologic and chemical mechanism which causes the frustrating clinical results. In the same chapter, the pharmacology of 5-FU and its clinical use is discussed, giving a clear rationale for its use in various schedules.

In the chapter on esophageal cancer the parts describing the epidemiologic studies and the discussion of treatment results with the combination of chemotherapy and radiotherapy are of relevance.

It is somewhat surprising to read that upper GI endoscopy 'confirms barium meal studies for dysphagia,' rather than that it is the first-choice investigation, allowing for immediate biopsies and potential therapeutic procedures, such as dilatation. In the gastric cancer section endoscopy is the first-choice procedure, possibly coupled with endoluminal ultrasonography to determine the depth of infiltration. ERCP (endoscopic retrograde colangio pancreatography) is presented in two chapters on pancreatic and biliary tract cancers. Surprisingly, the palliative treatment of tumoral stenosis by stenting is treated somewhat superficially.

In the discussion of colorectal cancer, we especially appreciated the part devoted to prevention, risk factors and screening, including several interesting hints useful for all physicians: the chapter on colon neoplasias reports in detail the performance of flexible sigmoidoscopy and colonoscopy and polypectomies.

For prevention, it is correctly stated that colonoscopy is the gold standard, enhanced when necessary by double contrast barium enema. Searching for occult blood in the feces is accepted 'only' for mass screening. Surprisingly, one reads in chapter 23 that flexible sigmoidoscopy 'is feasible after minimal training,' when every experienced endoscopist knows that most of the technical difficulties in guiding the colonoscope arising during the left colon examination. Endoluminal ultrasonography is briefly dealt with in the chapter on diagnosis and staging of colorectal malignancies.

Despite the brevity of the chapter devoted to the gastrointestinal lymphomas, it contains an appropriate summary of the most common chemotherapeutic regimens used, as well as a thorough discussion of the role of surgery today.

The last sections deal with the more recent developments in G cancer treatment such as the laser application of intraoperative radiation therapy.

Gastrointestinal Oncology is dedicated to promoting an integrated approach to detection, staging and treatment of gastrointestinal cancer by the gastroenterologist, surgeon, and radiation and medical oncologist and can be recommended not only for oncologists, but also for general physicians and for the libraries of every medical school.

B. Miazza & G. Martinelli
Lugano