Cellular Oncology 31 (2009) 57–59
DOI 10.3233/CLO-2009-0459
IOS Press

Letter to the Editor

Multiple numerical chromosome aberrations in carcinogenesis: The kidney cancer model

Dear Sir,

This letter summarizes the talk I gave at the *2nd Conference on Aneuploidy and Cancer: Clinical and Experimental Aspects*, in Oakland, California, after the kind invitation of Peter Duesberg from the University of California, Berkeley. The conference addressed the issue of whether aneuploidy or gene mutations are the driving force behind the development of cancer. I chose to focus on the kidney cancer model because it gives good arguments to both sides of the fence, having therefore the potential to stimulate a fruitful discussion. So, why is the kidney cancer model so interesting?

Malignant tumors of the kidney account for three percent of all human neoplasms and about 85 percent of all kidney cancers are renal cell carcinomas (RCC) [7]. The histological classification of epithelial kidney neoplasias was traditionally based on the type of nephron cell from which it was originated (clear cell, chromophilic or chromophobe carcinoma) and its growth pattern (papillary or nonpapillary). However, overlapping morphologic characteristics can make difficult the differential diagnosis of renal tumors, even to highly experienced pathologists [1]. The more recent classification of renal epithelial tumors has evolved to embrace the new cytogenetic knowledge that most neoplastic entities are characterized by specific karyotypic patterns, which are helpful for differential diagnosis [9]. Interestingly, different renal cell carcinoma subtypes are characterized by disparate patterns of chromosome rearrangements, namely, recurrent deletions, translocations, and multiple numerical chromosome changes without concomitant structural karyotypic alterations.

Clear cell carcinoma (ccRCC) represents approximately 75% of the malignant tumors of epithelial origin in the kidney and most display losses of chromosome arm 3p [9]. The frequent 3p deletion in ccRCC suggests the existence of at least one relevant tumor suppressor gene in this region. The gene *VHL* at 3p25 has indeed been shown to be specifically inactivated in most ccRCC, usually by point mutations but also by promoter hypermethylation [5,6,11]. Another subgroup of renal cell carcinomas, showing clear cells but often a papillary or nested growth pattern, represents a significant proportion of kidney carcinomas of children and young adults and is characterized by specific chromosome translocations that involve members of the *MiTF/TFE* transcription factor family. The t(X;1)(p11;q21) originates a fusion between the basic-helix–loop-helix transcription factor *TFE3* on Xp11 and the *PRCC* gene on 1q21 [14] and the t(X;17)(p11;q25) results in the *ASPL-TFE3* fusion gene [10]. *TFE3* can alternatively fuse with splicing factor genes *PSF* (1p34) or *NonO* (Xq12) [2]. Finally, another cytogenetic subtype of kidney carcinomas arising in children and young adults is characterized by a t(6;11)(p21;q12), which has been shown to result in fusion of the 5' portion of the *Alpha* gene (11q12) with the transcription factor gene *TFEB* (6p21) [3].

The above mentioned genetic changes fit well with the gene-centered theory of carcinogenesis, as they involve mutations in specific tumor suppressor genes or oncogenes that are often the result of isolated karyotypic changes. On the other hand, other kidney carcinoma subtypes are cytogenetically defined by the presence of multiple numerical chromosome abnormalities in the absence of known recurrent point mutations. Papillary renal cell carcinoma (pRCC) accounts for approximately 10% of renal cell tumors in surgical series and the most consistent genetic changes in these tumors are trisomies or tetrasomies of chromosomes 7 and 17 and loss of the Y chromosome (in men), typically together with various combinations of additional trisomies of chromosomes 12, 16 and 20 [9]. On the other hand, chromophobe RCC (chRCC) represent about 5% of renal cell tumors and are characterized by several whole chromosome losses, namely of chromosomes 1, 2, 6, 10, 13, 17, 21, X and/or Y [9]. These tumor types characterized by the presence of multiple numerical chromosome abnormalities with-

out concomitant structural karyotypic changes are less well accounted for by current pathobiological models of tumorigenesis, probably because we do not have equally good gene-level models for what the pathogenetic implications of numerical aberrations might be as we do for structural anomalies. However, the karyotypic data demonstrate no less specific cytogenetic–pathologic correlations than those existing for many structural chromosomal aberrations in neoplastic entities, in many instances becoming their defining feature and constituting highly informative markers for differential diagnosis [15]. Some investigators have claimed that numerical chromosome changes are secondary to some submicroscopic genomic change [8], a view that has also been used for pRCC fuelled by anecdotal reports of *MET* mutations in pRCC with trisomy 7 [16], but this is an oversimplification as at least one such gene-level mutation would have to be postulated for each recurrent extra chromosome. The fact remains that the gene targets of these recurrent karyotypic changes remain unknown, although genome-wide gene expression analyses with microarrays indicate that the downstream consequences of numerical changes may be altered expression of multiple genes located in the affected chromosomes, suggesting a simple dosage effect [4].

Let alone their molecular consequences, the data on how aneuploidy arises are also very scarce. We have recently evaluated the role of mitotic checkpoint defects for the karyotypic patterns characteristic of renal cell carcinomas. The mRNA expression levels of the major mitotic checkpoint genes of the budding unhibited by benzimidazole family (*BUB1*, *BUBR1* and *BUB3*) and of the mitotic arrest deficiency family (*MAD1*, *MAD2L1* and *MAD2L2*) were analyzed by real-time quantitative polymerase chain reaction in 11 chRCC, 19 pRCC, and 36 normal kidney tissue samples [12]. *MAD1*, *MAD2L1* and *MAD2L2* showed significant expression differences in tumor tissue compared to controls. ChRCC presented underexpression of *MAD1* and *MAD2L2*, whereas pRCC showed overexpression of *MAD2L1*. The expression level of the BUB gene family in chRCC and pRCC did not differ significantly from that of normal kidney. On the other hand, the study of 39 ccRCC showed overexpression of *BUB1*, *BUBR1*, and *MAD2L1* and underexpression of *MAD1* [13]. The degree of genomic complexity of ccRCC measured by comparative genomic hybridization was associated with *BUB1* and *BUBR1* overexpression, as well as with tumor grade. One can therefore conclude that expression changes in *MAD1*, *MAD2L1* and *MAD2L2* play a role in renal carcinogenesis characterized by multiple numerical chromosome abnormalities and that *BUB1* and *BUBR1* overexpression is associated with karyotypic complexity in conventional renal cell carcinomas.

Several tumor types of different histogenic origins have as a primary pathogenetic event in their development the acquisition of multiple numerical chromosome abnormalities. These cytogenetic changes may enable, in a single step and through a dosage effect or regulatory disturbances at the supra-genic level, the simultaneous alteration of multiple cancer-relevant genes, reducing the number of independent genomic events necessary for carcinogenesis. Most gene-centered models of tumorigenesis do not take into account the common finding of numerical karyotypic changes and ploidy shifts in cancer cells, and we lack knowledge on their origin and their molecular consequences. The kidney cancer model teaches us that both aneuploidy and structural gene changes are pathogenetically important and that we should integrate the data from both levels of analysis to allow a more detailed understanding of the mechanisms of carcinogenesis.

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