Reviewer's report

Title: Recurrent and multiple bladder tumors show conserved expression profiles

Version: 1 Date: 8 March 2008

Reviewer: Imad Fadl-Elmula

Reviewer's report:

The present manuscript addresses the issue of clonal origin in multifocal and recurrent tumors and also the variability of genetic expression profile. Around 30% of urinary tract TCCs are found as multiple tumors at the time of diagnosis. Of these 70% recur after initial transurethral resection of the primary tumor. The multifocal nature of uroepithelial cancer, together with a propensity for recurrence (polychronotopicity) strongly support the monoclonal view that presupposes a common clonal origin of multifocal and recurrent uroepithelial tumors implying that these macroscopically distinct lesions develop as the result of intraluminal seeding of viable cancer cells shed from the original tumor. However, the dysplastic changes that are usually seen in the mucosa neighboring bladder tumors have been interpreted as strong circumstantial evidence that TCC represents a field disease. According to this field disease theory, the entire epithelium is tumor-prone in the sense that multiple polyclonal primary lesions are likely to emerge from it, either synchronous or metachronous manner. The strong support for monoclonal hypothesis has come from analyses of X-chromosome inactivation patterns, molecular, and cytogenetic analysis (Steffens & Nagel, 1988; Sidransky, 1992; Fadl-Elmula et al., 1999). However, the odd genetic intertumor variability in contrast to the chronological appearance remains poorly understood. Thus the present paper deals with an important and exciting subject not only for uroepithelial carcinoma yet for all other solid tumors.

In fact this observation has been discussed by Fadl-Elmula et al (1999) but due to the limited available genetic information, no conclusion as to whether tumor cell shedding with subsequent implantation and growth is more likely to occur from the first or later (second) primary tumors. However, the possibility of both situations remains present. Sidransky et al (1992) suggested a pathogenetic model based on early intraluminal dissemination of transformed cells followed by the independent growth of each cell, eventually resulting in multiple, clonally related tumors that vary in their pattern of secondarily acquired genetic alterations. Fadl-Elmula et al (1999) suggested in addition to the acknowledge common clonal origin, that seeding is a rather late event and that the similarity between multifocal tumors is hardly compatible with an early splitting up of the monoclonal, neoplastic cell population followed by the acquisition of secondary genetic changes.

I believe the present article constitute important addition work toward better understanding of the complex genetic, transcriptional and genomic level, make up of multifocal and recurrent uroepithelial carcinomas.
My recommendations and comments are the following:

Discretionary Revisions

1. In the abstract, results section (page 2) the first phrase “We use molecular means to demonstrate an incomplete correspondence between genetic evolution and chronology of appearance of urothelial tumors”. This phrase has no place in the result section and should be moved from result section to the discussion section in my opinion.

2. Page 2. The result section needs to be change since I could not see any findings but conclusions e.g., “These findings are incompatible with a direct origin of recurring tumors from the preceding ones. In contrast we show that despite apparent genomic differences, the recurrent and multiple bladder tumors from the same patients display remarkably similar expression profiles”.

I think the author should summarize the findings not the conclusions (interpretation) of the results.

3. Page 4. Mean title “Methods” should change to “Material and Methods”

4. Page 4. The subtitle “Patients, Tissues, and extraction of nucleic acids” the author should change it to “Tumor Material “as separate subheading and “Extraction of nucleic acid” as separate subheading

5. Under the subheading “Tumor material” the author should describes the material in this section not under the “Results” section, page 5, as he did.

6. Page 5. Subheading “Mutation, LOH, and CGH analysis” need to be change to “Mutation, CGH, and LOH analysis” as to follow the order they are presented in the text.

7. Page 5. Subheading “Mutation, LOH, and CGH analysis” the end of the paragraph “Hence both FGFR3 and TP53 mutation may occur independently in meta- and synchronous tumors”. Such statements, present in many places in the Results section, are in fact representing the discussion of the result and hence should be moved to Discussion section

What next?: Accept after minor essential revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests