Reviewer's report

Title: Assessment of the role of transcript for GATA-4 as a marker of unfavorable outcome in human adrenocortical neoplasms

Version: 1  Date: 28 September 2003

Reviewer: David B Wilson

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General

Increased expression of GATA-4 has been shown to accompany adrenocortical tumorigenesis in experimental animal models, including gonadectomized inhibin-alpha promoter T-Ag mice (carcinomas) and gonadectomized DBA/2J mice (adenomas). In these experimental models there is a concomitant increase in LHR expression and decrease in GATA-6 expression.

To explore whether these markers are relevant to human tumors, the authors used RT-PCR analysis to retrospectively survey the expression of GATA-4, GATA-6, and LHR transcripts in adrenocortical tumors [13 non-metastasizing (NM), 10 metastasizing/ recurrent (MR)] from a total of 22 pediatric and adult patients. GATA-4 mRNA was detected in normal adrenal tissue, 8/13 NM tumors and 9/10 MR tumors. LHR mRNA was observed in normal adrenal tissue and in the majority of NM tumors but in only 2 MR tumors (from the same patient). GATA-6 mRNA was seen in normal adrenal tissue, 13/13 NM tumors, and 9/10 MR tumors. GATA-4 expression was more prevalent in virulizing tumors than in those associated with Cushing’s syndrome. The main conclusions of the paper are that: 1) GATA-6 mRNA expression is not altered during human adrenocortical tumorigenesis, and 2) GATA-4 mRNA expression is not predictive of metastatic potential in human tumors.

Strengths of the paper:
1. At present there are no reliable histological markers that distinguish potentially aggressive human adrenocortical neoplasms from more benign variants. Therefore, this is an important topic to study.
2. These Brazilian investigators have examined a relatively large number of these rare tumors. It may be difficult for other investigators to amass such a large series.

Discretionary Revisions (which the author can choose to ignore)

None.

Minor Compulsory Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. Page 8. The authors refer to “rates” of GATA-4 and GATA-6 positive samples. “Prevalence” or “frequency” might be better terms.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. The investigators rely on RT-PCR for all their studies. Obviously, this is not a preferred methodology for quantification. The manuscript would be strengthened considerably by the addition of another method of measurement (e.g., Northern analysis, RNase protection analysis, or immunohistochemistry) for at least a subset of the tumors. There are commercially available...
antibodies that recognize GATA-4, GATA-6, and LHR (to varying degrees of success) in
formalin-fixed paraffin sections.
2. The data in this manuscript yield “negative” results, which limits enthusiasm for the paper.

Advice on publication: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: A paper whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Declaration of competing interests: None