Reviewer's report

Title: Characterization of the prostate cancer lesions developed in heterozygous Men1 mutant mice

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Reviewer: Cornelis Lips

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Major compulsory revisions:

It is missing in this article whether in human prostate cancers cells the menin-encoding gene is expressed at reduced levels (and also whether the AR, p63, CDKN1B and Nkx3.1 genes are expressed at lower levels) as compared to normal prostate tissue.

. The MEN1 gene may have an oncogenic role in prostate cancer. (Paris PL et al. in Prostate Cancer Prostatic Dis. 2009;12(2):184-91.

Results:

Page 12; what about Men1 gene LOH in mPIN lesions which have developed in wildtype mice?
Page 13: what about doublestaining for menin and AR to see whether AR is downregulated in the same cells which have downregulated menin expression?

Discussion:

Page 16: which common partners are there between menin and AR (list them or provide reference)

The question arises whether in man, the AR is present in all prostate cancers. The clinical prognosis may be influenced by activation of the AR. A more favourable outcome may depend on the repression of the AR. Androgens may promote growth and malignant transformation of prostate tissue. This observation provides the rationale for approaches that either prevent the production of androgens or blocks their action. Androgen deprivation therapy (ADT) is the standard initial approach for all patients with metastatic prostate cancer. ADT utilizes either bilateral orchidectomy or medical castration (i.e. a gonadotropin releasing hormone agonist with or without an anti-androgen). This approach may not be very effective, and even highly undesirable, for patients whose prostate tumor is AR-negative anyhow!

It is useful to refer to the article of Imachi et al.:

Menin, a product of the MEN1 gene, binds to estrogen receptor to enhance its activity in breast cancer cells: possibility of a novel predictive factor for tamoxifen resistance.

Menin positive breast tumours had a worse outcome than menin-negative ones. Menin functions as a transcriptional regulator of ER\# and is a possible predictive factor for tamoxifen resistance. Menin-negative patients had a more favourable disease-free survival than menin-positive group by Log-rank-test. On the basis of the results of this study, it can be hypothesized that expression of menin in breast cancer cells might be associated with resistance to anti-estrogens.

In analogy with the presence of ER\# receptor in breast cancer, the presence of the androgen receptor in prostate cancer may be predictive of the outcome and survival and direct medical treatment.

Conclusion:
Page 18:
Do the genetic loci found in reference 18 include the genes studied in the present paper (menin, AR, p63, CDKN1B, Nkx3.1)?

Figure legends:
Page 27 (Figure 3) How was “reduced intensity of AR expression, relative to the average AR staining intensity” defined? How much reduced?? What was average?

For p63 I see hardly a difference between Fig 3B (wildtype mouse) and 3F (adenocarcinoma in Men1 mutant mouse).

Minor essential revisions:
Specific, but general remark:
Many sentences have to be formulated more carefully, throughout the entire paper!
In addition, the English language has to be reviewed

For example:
Abstract:
Background:
Intriguingly, other MEN1-specific lesions in hormone-dependent organs like breast and prostate were observed in the Men1 mutant mice.
Results:
.., while none of the control mice developed cancerous lesions ‘in the prostate’.
Background:
‘Inactivating’ mutations of the MEN1 gene predispose patients to multiple … high frequency (which frequency?) sex-cord stromal cell tumours
Intriguingly, we have found three cases of breast cancer in heterozygous MEN1 mice. (3 out of how many mice?)
Dreijerink et al. ‘have’ in stead of ‘has’

Level of interest: An article of importance in its field

Quality of written English: Not suitable for publication unless extensively edited

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