Reviewer's report

Title: Decrease in thyroid adenoma associated (THADA) expression is a marker of dedifferentiation of thyroid tissue

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Reviewer: Giuseppe Damante

Reviewer's report:

In this paper authors investigated expression of THADA gene in different normal tissues as well as in hyperfunctioning thyroids and thyroid carcinomas. Comparison among various normal tissues was performed by using snap-frozen samples whereas comparison among specimens of thyroid normal and pathological tissues was performed by FFPE samples.

Authors report two majors findings:
1. In normal thyroid THADA expression is higher than in other types of normal tissues.
2. In anaplastic carcinomas THADA is reduced compared to normal thyroids and different other thyroid pathological tissues.

Overall the research is well planned, performed in a detailed way and written in an easy-to-read style.

However, this referee rises several criticism.

Major criticism.

Authors claim that THADA is a marker of dedifferentiation of thyroid tissue. They support this statement with two observations:
- THADA is reduced in anaplastic carcinomas compared to other (more differentiated) thyroid neoplasms.
- By comparing the present results with those of HMGA2 expressions (previously published), they found a significant negative correlation.

Both these issues are quite weak to demonstrate that THADA expression is a marker of dedifferentiation in thyroid tissues. Authors should correlate THADA expression of papillary and follicular carcinomas (in which the degree of differentiation is quite heterogeneous) with a very much recognized marker of thyroid differentiation (i.e. NIS or TPO gene expression).

Minor criticisms.

1. Page 7, line 7. “18S rev_1” should be “reverse”.
2. Page 8, line 8 from the bottom. Source of snap-frozen tissues must be better specified; “taken for diagnostic purposes” is not sufficient.
4. Page 11, paragraph “transcription factors binding to THADA”. Since the
transcription factor HEX plays a role in thyroid-specific gene expression, information on the presence of putative HEX binding sites is required.

5. Page 12, line 11. Authors state “clear indication for a role of THADA in maintaining thyroid differentiation is presented”. These statement is not correct; authors show evidence THADA expression “is associated to thyroid differentiation” (provided that the major criticism is addressed).

In the case authors address the above criticism, this referee recommends publication of this research in BMC Clinical Pathology.

**Level of interest:** An article whose findings are important to those with closely related research interests

**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 interest