Reviewer's report

Title: Implication of Intracellular Localization of Transcriptional Repressor PLZF in Thyroid Neoplasms

Version: 2 Date: 20 May 2014

Reviewer: Alessandra Care'

Reviewer's report:

In this paper Matsuzawa and coauthors describe the expression level and delocalization of PLZF associated with thyroid carcinoma progression. Although technically sounding, results are not properly discussed.

In particular, PLZF is described to translocate from the nucleus into the cytoplasm in advanced carcinomas, whereas it remains mostly nuclear in normal cells or primary tumors. Although not evaluated in thyroid carcinoma, the mechanism underlying PLZF regulatory function was previously reported by different groups in various cellular systems (i.e. colorectal cancer, melanoma, leukemia). In fact PLZF can be bound by HB-EGF-CFC, the C-term fragment of the main ligand of the EGF receptor, and exported from the nucleus. This removal from different promoter binding sites (i.e. c-myc, cycA, microRNA-222) prevents PLZF negative transcriptional role exerted on a number of genes critical for cell proliferation thus reversing PLZF tumor suppressor role.

It is then absolutely improper that the authors ignore this regulation, as they say "There are no previous articles describing the significance of PLZF expression in the cytoplasm. The reason why PLZF is highly expressed in the cytosol of papillary thyroid carcinoma cells remains unclear. And we could not clarify why PLZF translocates to the cytoplasm and shows high expression in malignant tissues."

Major compulsory revision

• The authors should analyze the actual role of HB-EGF-CFC in cell lines stabilized from thyroid carcinoma. In particular they should confirm in this cellular system the HB-EGF-CFC binding to PLZF, their translocation from the nucleus into the cytosol, as a consequence of stimuli like TPA, and the parallel increase of cell proliferation.

• Obviously they should cite one or more paper reporting this issue in other cancers (Nanba JCB 2003, Nanba 2008, Hieda JCB 2008, Felli PlosOne 2013, Ozeki PlosOne 2014) and discuss this issue.

• Finally, before being published, this paper needs some corrections being repetitive and a little bit confused.

Level of interest: An article of importance in its field
Quality of written English: Needs some language corrections before being published

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.