**Reviewer's report**

**Title:** Balanced re-arrangement of chromosomes 5 and 17 points to a role for sex steroid hormones and carbonic anhydrase-related protein X in chondroblastoma pathogenesis

**Version:** 1  **Date:** 4 August 2009

**Reviewer:** Bertha Brodin

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Mononuclear cells of chondroblastomas and suggest that sex steroid hormones like ER alpha and carbonic anhydrase might be involved in chondroblastoma pathogenesis.

This is a very interesting observation with a high potential of identifying a possible mechanism for chondroblastoma genesis in relation to its natural localization: i.e. the epiphysis of the long bones.

The genetic data do not support the expression data. and a deeper investigation has to be performed to prove this:

1. The chromosomal translocation t(5;17) was found in 1 out of 14 chondroblastomas, no fusion gene was identified, and there is not data that prove that this aberration points towards sex steroid hormones and CA-RX in the pathogenesis of chondroblastoma.

2. Sex steroids play a crucial role in the longitudinal growth of the plate; there chondrocytes are recruited proliferate and differentiate. Oestrogen Rc signaling as well as aromatese play an important role in these process (See Chagin AS, Sävendahl L: Genes of Importance in the Hormonal Regulation of Growth Plate Cartilage. Horm Res 2009;71(Suppl.2):41-47 (DOI: 10.1159/000192435)

The observation that, most of of chondrosarcomas analyzed express high levels of SRD5, ER alfa and other sex hormones (supplement 3) may be related with a "benign" grading of chondroblastoma that may resemble normal chondroblasts of the growing plate and not associated to abnormalities in chr 5 or 17.
3. The literature presented in table 1: “cytogenetic findings in condroblastoma”; do neither support an association of chr 5 and 17 aberrations in chondroblastomas. It rather points towards no consensus in the findings, aberrations in chromosome 5 are relatively frequent, though not in the same regions or ch arms. This resembles a more chaotic genetic aberration pattern, like in other bone tumors.

4. To uncover a possible and exclusive role for sex steroid hormones in chondroblastoma genesis, other studies have to be performed, ex: expression studies of sex steroid hormones and carbonic anhydrase in normal chondrocytes/cartilage, vs benign and malignant chondroblastoma, and other cartilage tumors.

ER alpha signaling in experimental models of chondroblastoma, Ex transgenic models of ER alpha and CA, are today available.

If transcriptional regulation is suspected, maybe microRNA arrays can provide interesting information.

5. The conclusions stated in the abstract: giant cells in chondroblastoma are probably a reactive population as they do not harbour the translocation is not correct:

A translocation that is found in 1 of 14 chondroblastomas do not seem to be important for the transformation process. Giant cells may have other aberrations of relevance for the pathogenesis of these tumors.

GUIDELINES FROM THE EDITORS

1. Is the question posed by the authors well defined?

YES

2. Are the methods appropriate and well described?

YES, but more studies need to be performed.

3. Are the data sound?

YES

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?

YES

5. Are the discussion and conclusions well balanced and adequately supported
by the data?
No. See comments above
6. Are limitations of the work clearly stated?
YES
7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?
More discussions on previously published data should be included (ex discuss the data presented in Supplement fig 1.
8. Do the title and abstract accurately convey what has been found?
The title do not support the data presented, It needs to be changed. The abstract is very well summarized