Author's response to reviews

Title: Notch signaling in pediatric soft tissue sarcomas

Authors:

Rossella Rota (rossella.rota@opbg.net)
Roberta Ciarapica (roberta.ciarapica@yahoo.com)
Lucio Miele (lmiele@umc.edu)
Franco Locatelli (franco.locatelli@opbg.net)

Version: 2 Date: 24 September 2012

Author's response to reviews: see over
Roma, 24 of September, 2012

Re: MS 3001062807751690 Revision

Rebuttal letter for the Review entitled “Notch signaling in pediatric soft tissue sarcomas”.

Here we report a point by point description of our revisions in response to the comments. To make easier for the Editor and the Reviewers to check the corrections, the new version of the manuscript shows highlighted revisions in those sections that have been extensively revised. Moreover, all the revisions made in response to the Reviewers’ concerns have been also highlighted.

Authors’ information: This section has been revised including relevant information about the authors and eliminating the list of Institutions.

Response to the Referee’s comments:
Reviewer: Heinrich Kovar

We thank the Reviewer for his positive comment on the value of our Review.

He has a number of minor revisions:

1. Even though direct evidence for NOTCH involvement in synovial sarcoma is missing, a recently closed NCI sponsored phase II study at MSCC (NCT01154452) of a hedgehog inhibitor combined with a gamma secretase inhibitor (RO4929097) included adult patients with advanced synovial sarcoma. It would be nice if the authors mentioned that in their review (text and/or Table 2).

We agree with the Reviewer on the importance of this study in the view of combination studies even if in adults. Therefore, we have mentioned the study in the text, since the Table 2 reports only pediatric patients-involving clinical trials, on page 21, lines 19-25.
2. On page 11, second paragraph, the authors refer to a paper by Schaefer et al. with “In a recent report, Schaefer et al. showed that, in a global gene expression profile on 27 primary samples of ES, the Notch signaling is among the most represented de-regulated pathways besides to be over-represented in metastatic tumors [41]”. It is true that this paper says so in the text, but the Table to which Schaefer et al. refer does not support this statement, instead it lists the Hedgehog pathway. Since it is not clear where the mistake occurred, in the Table or the text, I would recommend omit reference to this paper in the context of NOTCH in Ewing sarcoma. The same is true for Table 1, in which the authors refer to reference 41 by NOTCH signaling to be “overexpressed in primary tumors”. Even if Schaefer et al. meant that genes of the NOTCH signaling pathway were over-represented in a comparison between localized and metastatic tumors, it does not necessarily mean that they were overexpressed but differentially expressed.

The reference has been omitted from the text and Table 1.


We have revised this point and added the reference (n. 55).

4. Figures 2 and 3 are common text book knowledge and almost every NOTCH review presents very similar figures. Since no new aspect is added to these figures they should be omitted.

We have eliminated Figure 1 and 2 and reported in the text: (reviewed in…), Page 6, line 12 and Page 7, line 3.

5. Several grammatical errors and a few typos make substantial proofreading by a native English speaker necessary.

The manuscript has been extensively revised and checked for typographical errors and language by a native English speaker.

Reviewer: Isabella Screpanti

We wish to thank the Reviewer for her positive evaluation of our Review.

She has some concerns:

1. page 10 lane 2, in the paper by Graziani et al, cited by the authors there is no evidence that Notch/RBP-Jk axis directly repress PTEN expression additionally the current view is that Notch
signaling represses PTEN expression through a HES-1-dependent mechanism (see the commentary of Bailis and Pear, Blood 2012). The text should be modified to clarify this issue.

We agree with the Reviewer and, therefore, the text has been changed accordingly inserting the sentence: “…even though no evidence for a direct CSL/RBP-Jk-dependent effect was reported.” Moreover, some clarifying sentences have been added together with the Reference of Bailis (n. 47) and additional clarifying references (n. 45-46). Page 10, lines 18-25 and Page 11, lanes 1-2.

2. page 11 lane 24, the role of Numb in sustaining Notch3 degradation is controversial (see Beres et al. Mech Dev 128:247, 2011), the authors should mention that.

The point has been revised (Page 12, lanes 16-18) and the Reference has been added (n. 53).

3. In this review the main subject approached is the role of Notch signaling in STSs tumors whereas the targeting of Notch signaling for the treatment of pediatric soft tissue sarcomas is only discussed as a possible perspective, therefore the title should be modified in order to keep the title in focus with the review topic.

The title has been revised in: “Notch signaling in pediatric soft tissue sarcomas”

Minor points
- to avoid misunderstanding, when the acronym CSL (derived from CBF-1/RBP-Jk/Su(H)/Lag2, as stated on page 6) is used, it would be better writing CSL/RBP-Jk

We have done it.

- a number of sentences should be shortened and better focused to make easier the reading

The manuscript has been extensively revised and checked for typographical errors and language by a native English speaker.

During the revision we have also added the following new references: 10, 11, 22, 23, 25, 26, 27, 28, 55, 83, 84, 85, 89, 90, 94

We hope the changes we made to the manuscript and the responses to the Reviewers’ expert concerns will prove sufficient to favorably incline you towards publication of our manuscript.

Rossella Rota PhD
Laboratory of Angiogenesis
Dept. of Oncohematology
Ospedale pediatrico Bambino Gesù
Piazza S. Onofrio 4
00165 Rome
Italy
rossella.rota@opbg.net
rossella_rota@yahoo.com
Ph:+39-06-6859.2648 office
Ph:+39-06-6859.2651/52 labs
Fax:+39-06-6859.2904/2101
mobile:+39-335-6175500