

Reviewer 2:

The manuscript is a review entitled "the YAP/TAZ pathway in osteogenesis and bone sarcoma pathogenesis" by Kovar et al.

This review is a dense (maybe too dense) review on the current knowledge about YAP/TAZ signaling in bone and the related disease: bone sarcoma. It is well written, and the overall structure intelligible.

Thank you for positively considering our manuscript.

However I would recommend couple of changes to make this review more comprehensive for a broad readership.

Main points :

In the first part, in which the authors discuss signaling pathway :

- Addition of figures to support the text would be useful.

New Figure 1 provides a simplified overview of the main components and outputs of the pathway.

- 1 paragraph would require some changes to make the authors point more evident. There is a lot of information but the reader is left without a clear picture.

To address this point, we have extended the last paragraph of section 1 to read (Lines 77-85) :

“Adaptation to microenvironments of different tissue architecture plays a particularly important role in bone cancers which tend to metastasize through the hematogenous route and home primarily to bone and lungs, which are organs of completely different stiffness, extracellular matrix composition and oxygen supply. It is therefore not unexpected that the YAP/TAZ signaling pathway is prominently involved in bone cancer pathogenesis and metastatic spread. As this aspect has been poorly addressed so far, we will here first highlight key aspects of the growing complexity of YAP/TAZ signaling and ensuing phenotypes, and then address their impact on normal bone development, bone cancer and metastasis with a focus on chondrosarcoma, osteosarcoma, and Ewing sarcoma.”

- Line 81 the word ‘integrate’ is not appropriate, YAP and TAZ transmit signals from the plasma membrane or metabolic cues to the nucleus.

Text changed accordingly.

- Line 98 “14-3-3 σ ” is restrictive, to the best of my knowledge the binding of YAP/TAZ is not restricted to this protein, but rather shared by other 14-3-3 members.

Text changed accordingly.

- Latter in this paragraph, the authors discuss the role of FAK and downstream signaling. Here there is a bench of data from literature that are missing that would be important to incorporate. Indeed, it starts to become clear integrin integrate extracellular matrix cues by activating a pathway in which the Src non receptor tyrosine kinase has a major role (Lamar et al., Sabra et al. etc...). A more complete description of this pathway is important, as Src is emerging as a potential therapeutic targets in oncology.

To address this reviewer’s request, we have extended the discussion of the roles of FAK and SRC in YAP/TAZ signaling (lines 152-162 and 170-173).

- Paragraph 2.2 and 2.3. I don’t really understand why the authors discuss these issues. Is that relevant for bone or bone sarcoma. Please either remove or make the link more obvious.

Following this reviewer’s suggestion, we have made the link of Wnt signaling to osteogenesis and bone sarcoma more obvious by briefly referring to its role in bone remodeling, osteosarcoma and

Ewing sarcoma at the beginning of section 2.3 (previously 2.2.; lines 189-191). Section 2.4. (previously 2.3.) has been renamed (Role of micro-RNAs in YAP/TAZ regulated circuitries) and extensively revised to mention specifically YAP/TAZ regulatory microRNAs playing a role in bone development and osteosarcoma (lines 206-214).

- 4 : YAP and TAZ are not sensor they are relays of mechanical stimulation. Sensor are at the plasma membrane. They transmit those informations from the integrin and likely cadherins to the nucleus.

Title of the section rephrased: YAP and TAZ as relays of mechanosensors.

- 5. This is an important issue that is poorly addressed in many other reviews. The authors should consider to incorporate and discuss the recent work from Lu et al. NCB, 2020.

We have incorporated a discussion of this important reference into the text (lines 331-336).

In the part YAP and TAZ in osteogenesis.

- Here my main concerns is the poor consideration of the osteoblastic population. While a short introduction is presented on bone formation, very few to discuss the relative contribution of different bone cells function (osteo-formation vs osteo-resorption).

To address this point, we have now included a paragraph on reciprocal regulation of osteoblasts and osteoclasts in bone remodeling mediated by YAP regulatory mechanisms (osteoclast derived exosomal microRNAs, PIEZO1) in lines 539-551.

Minor point :

- I am wondering why the authors left behind important emerging findings such as metabolic state and autophagic process in YAP/TAZ biology. This could have been relevant in particular when tumor is on the table.

To address this point, we now mention YAP regulation by AMPK in response to metabolic and energy stress in lines 163-165, and the role of YAP/TAZ in autophagy in lines 236-263.