

## Peer Review File

Article Information: <https://dx.doi.org/10.21037/tau-23-602>

### Reviewer A

The manuscript is interesting, generally well written and illustrated.

**Comment 1:** Lines 55-61: it deserves to be pointed out that metformin can also improve the sensitivity to chemotherapeutics (see PMID: 36361682)

**Reply 1:** Page 2, paragraph 2. We have added this information and have added the reference suggested. References numbers have been updated accordingly.

#### Addition in the text (highlighted):

“It also exerts antiangiogenic effects (9) and can also improve the sensitivity to chemotherapeutics (10).”

New reference added

10. Tossetta G. Metformin Improves Ovarian Cancer Sensitivity to Paclitaxel and Platinum-Based Drugs: A Review of In Vitro Findings. *Int J Mol Sci.* 2022;23:12893.

**Comment 2:** Lines 63-66: Although authors highlighted the role of metformin in modulating ROS, they did not introduce the role of ROS in prostate cancer onset and progression. In fact, ROS play a key role in prostate cancer onset (see PMID: 36335520). Moreover, chemoresistance and castration resistance occurrence is favored in prostate cancer cells expressing high antioxidant capacity (see PMID: 37525922, 37296999). These are important points to add since are involved in prostate cancer onset and progression, and metformin could play an important role in their modulation

**Reply 2:** Page 2, paragraph 2 and beginning of page 3. We have added the information provided by the reviewer. With this addition, to have a more fluid paragraph, we have exchanged the last two sentences of the paragraph, with detailed description of ROS at the end of the paragraph. We have added the references suggested. References numbers have been updated accordingly.

#### Addition in the text (highlighted):

“Of note, ROS play a key role in prostate cancer onset (20) and castration resistance occurrence is favored in prostate cancer cells expressing high antioxidant capacity (21,22).”

New references added:

20. Marzioni D, Mazzucchelli R, Fantone S, Tossetta G. NRF2 modulation in TRAMP mice: an in vivo model of prostate cancer. *Mol Biol Rep.* 2023;50:873-881.

21. Tossetta G, Fantone S, Marzioni D, Mazzucchelli R. Cellular Modulators of the NRF2/KEAP1 Signaling Pathway in Prostate Cancer. *Front Biosci* 2023;28:143.

22. Tossetta G, Fantone S, Marzioni D, Mazzucchelli R. Role of Natural and Synthetic Compounds in Modulating NRF2/KEAP1 Signaling Pathway in Prostate Cancer. *Cancers.* 2023;15:3037.

**Reviewer B**

**Comment:** The authors have submitted a well-rounded editorial on a relevant article published recently in European Urology linking the expression of a prostate differentiation marker, NKX3.1 and response to metformin. The editorial is both a generous and critical review of the published work. There is little to add in terms of strengthening the review.

**Reply:** No change made to the manuscript as none were requested