Peer Review File

Article information: https://dx.doi.org/10.21037/tlcr-23-621

Reviewer A

This is a comprehensive review, but it is somewhat confusing.

1) In particular, an illustration(s) of the structure of survivin to correlate with lines 93-116 the relative locations of the BIR and CDE domains would be helpful to the reader.

   Thanks for the suggestion. We have added detailed schematic illustrations for better understanding of structure and function of survivin after appropriate review of literature.
   Changes in the text: Figure 1a & 1b

2) In a like manner, a table of the survivin regulating miRNAs described in the paragraph beginning with line 117 should be added.

   Thanks for the valuable suggestions. Table describing the role of microRNAs in survivin regulation added with an appropriate illustration and appropriate labels.
   Changes in the text: added table 2.

3) Sheperdin appears misspelled as "sheperdine" in line 243 and should not be capitalized.

   On multiple verifications, the spelling seems appropriately written according to different sources. I am assuming there is a misunderstanding due to ‘hesperidin’ which is also tested for its role in lung cancer treatment but is unrelated to survivin and its related pathways.

4) In lines 291 and 299 the references that are listed as "et al" oddly have the author's first initial in them. These should be Schmitz et al, and Xiang et al, respectively.

   Thanks for correction. Appropriate corrections made and rest of the references checked for formatting errors.
   Changes in the text: corrected in line 314, 321 and other places.

Reviewer B

The authors presented an interesting and well-focused manuscript. The authors make an adequate presentation of the state of the art. However, it is necessary for the authors to make small changes before final acceptance:
-The title of the manuscript is simple and lacks a translational perspective.

Thanks for your suggestion. Although our intention was to keep the title simple and straight forward, we agree that the title of the manuscript is too simple and does not give the full idea of what is covered in the review. We have discussed with peers and decided to change it to a more descriptive title.
Changes in the text: Updated the title.

-The authors have to justify the translational novelty in the introduction to the state of the art.
Thanks for your suggestion. We have added explanations to justify the novelty of the topic covered in the review. We wrote briefly about the kind of progress that happened due to the identification of such markers earlier and what can be expected if survivin is truly established as a molecular marker for lung cancer.
Changes in the text: added lines 79-83 for underline the translational importance.

-The authors must improve the quality of the figures. The figures should be more self-explanatory.
Thanks for the suggestion. We have added multiple illustrations with appropriate labels, titles, legends, expanded abbreviations and sources where appropriate. Added an additional table expanding all the abbreviations in the review.
Changes in the text: Tables-3,4, 6 figures 1 & 2.

-The authors must discuss the discussion from a translational perspective, they must include the manuscripts doi: 10.3390/jpm13020167. and doi: 10.3892/ijo.2022.5444.
Thanks for suggesting such well-rounded and articulate articles. We included one of the above the article as reference, given the discussion is based on similar areas of molecular markers and targeted therapies.
Changes in the text: Added lines 79-82 referring to the above-mentioned articles.

-The authors must justify the limitations of the drugs and the clinical trials.
Thanks for suggestion. We agree that adding limitations of the previous clinical studies is important, considering very few of them are pursued into phase I/II studies. We added a brief segment describing the limitations.
Changes in the text: Added lines 299-308 describing the limitations of the trials and the agents

used.

-The conclusions must be eminently translational.
Thanks for the suggestion. The translational applications of the study have been discussed in conclusion.
Changes in the text: Added lines 341-348 in the conclusion as advised to stress on the translational novelty of the study.

-Authors must include a graphic summary.
Thanks for the suggestion. We have added multiple illustrations and tables for better understanding of the multiple complicated pathways of survivin.
Changes in the text: Added figures 1a,1b, 2 for summarizing various aspects of survivin.

-The authors must improve the use of English grammar.
Thanks for the suggestion. We verified the grammar and improved sentence framing and structure We have proofread the paper of grammatical errors and flow of contents.

Reviewer C

This manuscript by Pachimatla and colleagues discusses the IAP survivin and its normal function and potential role in lung carcinogenesis. They go on to discuss the work done to explore the possibility of targeting survivin for therapeutic benefit. The manuscript is interesting and topical, and would likely be of interest to the readership if the following points were addressed:

1. In the abstract (line 52) they mention that survivin has been 'confirmed' as a biomarker of advanced NSCLC. I think this is overstated. While there is data that it is highly expressed in this context it is not yet a clinically useful biomarker. I think at best it can be considered a 'potential' biomarker.

   Thanks for suggestion. We agree that it cannot be 'confirmed' biomarker with current level of evidence and that it is not a clinical biomarker yet. We made the changes accordingly.
   Changes in the text: Changed confirmed to potential in line 51.

2. Line 76-77. Expression in a cell line cannot be associated with prognosis. This study

showed that expression in tumor samples correlated with prognosis.

Thanks for the suggestion. We have corrected the wording error.
Changes in the text: Corrected the error in line 71.

3. While the reporting of search terms and other parameters is interesting, it is not necessarily required as this is not a meta-analysis but a literature review.

   Thanks for the suggestion. We let the methods and search terms remain to maintain transparency with the readers and to let the reviewers and editors know the process of data collection.

4. More specific details about the function of survivin would be helpful in the 'structure and function' section. For example, what are the precise mechanisms that underly the role of survivin in the processes discussed in lines 100-101.

   Thanks for the suggestion. We have added illustrations of the structure and function of survivin, which can be applied for better understanding of the therapeutic pathways. Our interest was to gather and streamline the evidence in using survivin as therapeutic and preventive target, due to which the fundamentals of structure and function have not been described in detail.
   Changes in the text: Added figures 1a& 1b.

5. The authors frequently discuss that survivin is correlated with cancer progression and later stage disease. This does not prove a causal relationship. Therefore, using these data to conclude that survivin has a causal role in carcinogenesis is not appropriate. Are there any studies that show that genetic or pharmacological knockdown of surviving reduces cancer progression? If so, these should be discussed implicitly to support the conclusions.

   Thanks for the suggestion. It is true that correlation does not imply causation. We discussed about articles which discussed effect of survivin knock down in various cancer cell lines.
   Changes in the text: Added lines 199-205.

6. The statement on line 169-170 regarding angiogenesis, metastasis and growth requires more detail. Please discuss the data in these studies to support this statement.

Thanks for the suggestion. Although the effect of on VEGF-related pathways are well known, this is one of the few studies which examined the in-vivo effect and found that the number of blood vessels in the tumor increased with survivin expression. We have added more details from the study, explaining the statement.
Changes in the text: Added lines 195-198.

7. The studies discussed in line 171-182 outline the normal function of survivin and would be better placed in the prior section 'structure and function'. This would help address point 4.

   Thanks for the suggestion. Rearranged accordingly for better flow of contents and added illustrations.
   Changes in the text: moved the section to the structure and functions section as suggested.

8. The statement in line 187 requires a reference.

   Thanks for the suggestion. We have added the appropriate reference to the statement.
   Changes in the text: added reference number 46.

9. The study discussed in line 200 – it is not clear how these data suggest survivin is a good therapeutic target. Please could this be discussed further.

   Thanks for the suggestion. The study suggests that since survivin is exclusively expressed in cancer cells, survivin can be potentially targeted for therapeutic options. We clarified the same in the review.
   Changes in the text: Added lines 219-221.

10. In the 'Therapeutic target' section, the authors refer to table 1. In the manuscript there is table 2 and 3. Could this be corrected please. Furthermore, in table 2 (which I believe should be table 1) could further labelling be added to mirror what is seen in the next table (for example mechanism of action, pathway etc).

    Thanks for pointing out the error. Table 1 (in primary manuscript) is about the search terms and placed in the methods section. Table 2 and table 3 are about therapeutic agents and were misquoted in the text as Table 1 and Table 2. All the errors have been cross-

checked and rectified.

11. On a few occasions throughout the manuscript ‘surviving’ is used instead of ‘survivin’. Could this be corrected please.

    Thanks for pointing out the error. Manuscript thoroughly checked for such errors and corrections made accordingly.

Reviewer D

The manuscript entitled, “Role of Survivin in Lung Cancer: A narrative review” is interesting. The authors used highlighted the functional significance of survivin in prognosis, treatment response and resistance, including immune-targeted therapies and survivin inhibitors in lung cancer. Overall, the review is nicely presented. However, inclusion of a schematic figure highlighting survivin’s function and mechanisms involving cell signaling pathways would greatly benefit the readers. Also, please add another table to include the ongoing phase I/II clinical trials based on survivin.

Thanks for the valuable suggestions and feedback. We have added illustration for survivin-mediated pathways for better understanding. We also added another table with all the ongoing phase I/II clinical trials based on survivin-related agents in lung cancer.
Changes in the text: Added figures 1a & 1b, Table 5 as advised.