

## Peer Review File

**Article Information:** <http://dx.doi.org/10.21037/tlcr-20-1298>

**Comment 1:** *What is the main issue of this review? There are plenty of information, but in my opinion, it is hard to follow the text. Sometimes it seems that authors just took information from multiple manuscripts and prepare this review. Are you going to present data on molecular mechanisms on cell lines, animal models, clinical data? It is all mixed, and I found it to be difficult to found some important messages from this review.*

**Comment 2:** *Additionally, the title is too general*

**Respond to Comment 1 & 2:** Thank you for pointing this out. We would like to respond Comment 1 and 2 together as we find them similarly. Our main purpose for writing this manuscript is to sort out and summarized information and researches regarding relationship of Clusterin and lung cancer in different fields of study and also researches conducted recently. Therefore, a general title is needed as it included a tremendous amount of information. We hope that this manuscript will be a helpful reference to various fields of scientists and researchers who are interested in this topic as the last review article related was published in 2009 as mentioned in the previous reply letter.

In additional, we have also changed the name of the title to "The Multiple Roles and Therapeutic Potential of Clusterin in Non-Small Cell Lung Cancer: A narrative review".

**Changes in the text:** The Multiple Roles and Therapeutic Potential of Clusterin in Non-Small Cell Lung Cancer: A narrative review

**Comment 3:** *Some tables or figures (e.g. for role of clusterin in tumorigenesis and metastasis, especially in lung cancer) could be helpful to follow the text.*

**Respond to Comment 3:** We agree with this comment and have added 1 table and 1 figure for assisting reading.

**Comment 4:** *Please carefully check the text, there are some English style errors, and other editing mistakes like e.g. line 176, double "in", lung cancer cell (should be cells), line: 151-152 - high levels seem not seems, sometimes it is clusterin while sometimes there is CLU (shortcut). Please unify the text.*

**Respond to Comment 4:** Thank you again for pointing this out. We have incorporated the suggestion throughout the manuscript. However, we are truly sorry for not finding the error mentioned, double "in" and "lung cancer cell" in line 176 (old version). But we have discovered similar error in subsection 3.6, paragraph 2, line 353 (new version) and we have corrected it. As to the error mentioned "high levels seem not seems", we find that it is not in line 151 – 152.

We apologized for not noticing the issue about lines number changes due to different versions of Word software. We will submit a PDF version of this new manuscript (with track change) together with the word document as your kind reference.

**Changes in the text:** In vitro, Fu's team found out that high levels of sCLU **seem** to correlate with tumor angiogenesis through inducing the expression of vascular endothelial growth factor (VEGF). Corrected line is at subsection 2.2, paragraph 3, line 149.

**Comment 5:** *Please, carefully check the citations, e.g. Cristina et al. - Cristina is the name of the*

*first author, please cite the surname of the first authors. Additionally, please include the number of citations right after the cited authors, not at the end of the sentences. While reference 61 is written with capital letters? Sometimes all journal-title is written with capital letters, but sometimes only the first word of the title, please unify this.*

**Respond to Comment 5:** Thank you for your detailed comment. We have revised the surname of all the cited first authors and included the number of citations right after cited authors. Reference 61 has been deleted (detailed information mentioned at Respond to Comment 7).

**Comment 6:** *In line 93 it is written that relevant studies from 2015 to 2020 were cited in this review, while in the reference list there are many manuscripts cited published before 2015.*

**Respond to Comment 6:** Thank you for this suggestion, we agree and have changed the text as below.

**Changes in the text:** The information used to write this review was collected from PUBMED database (date of the last search 14 March 2021), using combinations of search terms including “lung cancer”, “clusterin”, “apolipoprotein J”, “chemotherapy”, “radiotherapy” and “antisense oligonucleotide”. Reference lists of identified articles were searched manually to find other relevant studies. We present the following article in accordance with the narrative review reporting checklist.

**Comment 7:** *There are some factual errors, e.g. line 198 - differentiation of T cell did not intensify colitis and colon tumorigenesis.*

**Respond to Comment 7:** We regret the oversight in the manuscript reference number 61 (old version) and discovered the contradiction between the title and the result of the manuscript, so we decided not to apply reference 61.

**Comment 8:** *In the subsection concerning tobacco smoke there are only 2 citations on the relationship between smoking and CLU, in my opinion, it is too little to present it as a separate subsection.*

**Respond to Comment 8:** The subsection 3.1 Tobacco smoking and clusterin has been updated, additional information about benzo(a)pyrene and clusterin have been added into it.

**Changes in the text:** Subsection 3.1, paragraph 2 – 3, line 238 – 251.

In addition to the above comments, additional information also added at subsection 3.7, paragraph 4, line 415 – 421. We have read thoroughly the manuscript to correct all spelling and grammatical errors.