**Peer Review File**

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## Reviewer A

This is a well described review. The manuscript has a good relevance to the field.

The authors Liu and colleagues investigate the role of LOXL4 in human malignant tumors. In this narrative review they focused on LOXL4 expression among solid tumors including human grastric cancer, breast cancer, esophageal carcinoma and colorectal cancer.

This is an interesting review, well organized and described. The authors have focused on a hot topic.
The manuscript would benefit from the followings:
The role of LOX family as drugguble biomarkers in solid malignancies has been already reported. In this regard the author should include the following reference for proper discussion:
Lysyl oxidase engineered lipid nanovesicles for the treatment of triple negative breast cancer. Sci Rep. 2021 Mar 3;11(1):5107. doi: 10.1038/s41598-021-84492-3. PMID: 33658580; PMCID: PMC7930284.

Reply1: Thank you very much for your suggestions on this manuscript, which are crucial to improving the quality of our article. According to your suggestion, we have modified our text as advised.
Changes in the text: We have discussed the value of the LOX family as druggable biomarkers in solid malignancies (see line 584-589).

## Reviewer B

This is a narrative review concerning LOXL4, one of the LOX-family of proteins in the pathogenesis and development of human malignant tumors.

Major comments:
I have a few comments to avoid confusion and eliminate some misleading information.
Line 78. The authors need to replace “structure” with “primary protein structure”.
Line 107 – Line 110: We do not know the importance of CRL domains to LOX catalytic activity yet.
Line 115: lack SRCR domains have pro-peptides.
Line 117: Citation 14 is not appropriate.
Line 119 – 120: can be glycosylated expected to be glycosylated.

Line 139: It is not clear what “different mutation rates” means.
Line 152: It is not clear what “cell surface-associated locations” mean.
Line 156 – 159: should be omitted. Repetitive.
Line 162: “between” should be replaced with “among”
Line 176: “LOXL4 catalyzes the oxidation of lysine residues in its substrate to produce hydrogen peroxide (H2O2)”. The authors should mention the predicted or proposed substrates for LOXL4. The product is not just H2O2 but also substrate-derived aldehyde.
Line 246 – 247: LOX, LOXL2 and LOXL3 are reported to be under the control of TGF-β1. This leads to major concerns. Although this paper concerns LOXL4, it is better to briefly summarize the overlapping evidence or hypothesis for the roles of other members of the LOX family in metastatic tumors. It does not need to be long but the authors should include a subsection to discuss this matter.
Similarly, miRNAs that are under the control of LOXL4 or controls the expression of LOXL4 should be discussed together with miRNAs that are involved in other members of the LOX family and HIF factors.

Reply2: Thank you very much for your suggestions on this manuscript, these comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our research. We have modified our text as advised.
Changes in the text:
(1) We have replaced “structure” with “primary protein structure” (see lines 30, 70, 846 and 865).
(2) We do not know the importance of CRL domains to LOX catalytic activity yet, so we added the description "No function has been associated with this domain so far" in the manuscript (see line 104-106).
(3) We add the description "LOX and LOXL1 lack SRCR domains but have pro-peptides" in the manuscript (see line 110).
(4) Citation 14 is not appropriate, so we update the original reference (14) to (15-17) (see line 112-114).
(5) "different mutation rates" was inappropriately described and was changed to “the frequency of mutation, amplification, and deep deletion of the LOXL4 gene in various types of human malignant tumors were different” (see line 134-136).
(6) “cell surface-associated locations” was inappropriately described and was re-described (see line 145-150).
(7) Lines 156-159 in the original manuscript have duplicate descriptions and have been deleted.
(8) We have replaced “between” with “among” (see line 156).
(9) We provide an additional description of predicted or proposed substrates of LOXL4 (see line 171-175).
(10) By reviewing the literature, we found that LOXL2, LOXL3 and LOXL4 are reported to be under the control of TGF-β1 in HCC, which has been supplemented in the manuscript (see line 247-248).
(11) We have briefly summarized the roles of other members of the LOX family in metastatic tumors. (see line 513-519).

(12) We also believe that it is necessary to discuss the miRNAs controlled by LOXL4 or controlling LOXL4 expression together with the miRNAs of HIF factors, so we have supplemented this section in the Discussion (see line 534-572).

Minor comment:
Although the authors obtained the AJE editing certificate, the first paragraph under tissue-specific expression of LOXL2 (line 126-130), the usage of “the” should be revised.
Line 109 remove residues after (LTQ)
Line 111 remove hyphen in between Tyr & 693, Lys & 638
Line 168 – 169: “cell metastatic potential” should be replaced with “metastatic potential of tumor cells”
Line 175: Ref 19 should be cited instead of 18.
Line 186: “immune microenvironment suppression” immune suppression of tumor microenvironment.
Line 197: “the low-isoelectric point” “the acidic region”

Reply3: Thank you very much for your suggestions on this manuscript. We have modified our paper as advised and the full text has been checked and reconciled. Incorrect descriptions and inappropriate references have been revised and replaced. Modified sections are marked in red in the revised paper.