Dear Editor,

Thank you for carefully reviewing our manuscript previously titled "**Overexpression of Ubiquilin4 is associated with poor prognosis in patients with cervical cancer**" for possible publication in the ***World Journal of Clinical Cases***. We are grateful to you and your reviewers for their constructive critique. We have revised the manuscript, highlighting our revisions in red. and have attached point-by-point responses detailing how we have revised the manuscript in response to the reviewers' comments below.

Thank you for your consideration and further review of our manuscript. Please do not hesitate to contact us with any further questions or recommendations.

Yours Sincerely,

Hai-Yan Cheng

Reviewer Comments:

I think that the manuscript is well written. I ask the authors to read my suggestions and to include a few important facts in the introductory part of the paper. I wrote in which direction to discuss. After that the paper could be accepted for publication.

- I suggest that authors point out in the introductory part of the paper that ubiquilines are important factors for maintaining proteostasis in cells, because they function as adapters for the delivery of poly−ubiquitinated proteins in proteasome and it is important to note that they participate in autophagosome formation, as well as in the endoplasmic reticulum−associated protein degradation pathway.
- Please comment that the human genome encodes five major ubiquitine proteins (UBQLN 1, UBQLN 2, UBQLN 3, UBQLN 4 and UBQLNL) which belonging to the non−proteasomal UBL−UBA family, by containing a domain similar to ubiquitin at the N−terminus and a domain associated with ubiquitin at the C−terminus! UBQLN1, UBQLN2 and UBQLN4 are ubiquitous, while UBQLN3 is exclusively expressed in the testes.
- I think that authors should explain that there is a lot of evidence that linking ubiquilines (UBQLN) with neurodegenerative diseases, such as Alzheimer ' s disease or other forms of dementia with locomotor dysfunction and other proteinopathies, such as amyotrophic lateral sclerosis.
- It is also important to point out that ubiquilines exhibit activities in the modulation of important players in the cell cycle, apoptosis, membrane receptors, DNA repair, epithelial−mesenchymal transition and miRNA.

  (First part)

  Use the following reference: Jantrapirom S, Piccolo LL, Pruksakorn D, Potikanond S, Nimlamool W. Ubiquilin Networking in Cancers. Cancers (Basel). 2020; 12(6):1586. doi: 10.3390/cancers12061586.

- Clarify the fact that the ubiquilin proteins are included in tumorigenesis and cancer progression in one sentence! Also comment that UBQLN4−p53 has a role in the gastric cancer cell line! Compare with the role of UBQLN4−p53 in the cervical cancer cell line, if you can! Authors well explained that high expression of UBQLN4 was associated with short overall survival and progression free survival when we discuss about cervical cancer. All praise for a good and exhaustive discussion!
- I advise the authors to note in the introductory part of the paper that overexpression of UBQLN4 induces cell aging and arrest of the G1−S phase of the cell cycle via the p53/p21 axis.

(**Second part)**

Use the following reference: Huang S, Li Y, Yuan X, et al. The UbL-UBA Ubiquilin4 protein functions as a tumor suppressor in gastric cancer by p53-dependent and p53-independent regulation of p21. *Cell Death Differ.* 2019;26(3):516-530. doi:10.1038/s41418-018-0141-4

Consider and discuss the following facts: Stabilization of p53 by overexpression of UBQLN4 gives p53 a great chance to transcriptionally regulate p21. In addition, the acetylated tumor protein p53 activates a cyclin−dependent kinase 1 inhibitor, a gene encoding p21. Note that p21 protein level can be controlled translationally and posttranslationally, especially by ubiquitination!

- Just mention the following fact: Several E ubiquitin ligase complexes including SC^{FSkp2}, MKRN1, $CRL4^{CDT}$, APC / C^{CDC20} and RNF114 promote p21 ubiquitination and degradation.
- Also write that UBQLN4 as BAG−6 binding factor is necessary for the elimination of incorrectly localized proteins of the cytosolic transmembrane that failed to reach on the exact destination on the endoplasmic reticulum membrane. UBQLN4 recognizes cytosol

mislocalized transmembrane proteins and also targets on mislocalized proteins for proteasomal degradation.

(Third part)

Use the following reference: Huang S, Li Y, Yuan X, et al. The UbL-UBA Ubiquilin4 protein functions as a tumor suppressor in gastric cancer by p53-dependent and p53-independent regulation of p21. *Cell Death Differ.* 2019;26(3):516-530. doi:10.1038/s41418-018-0141-4

Reviewer #1:

Response:

First part: This section is arranged in the first and second paragraphs of the introductory part.

Second part: This section is arranged in the third paragraph of the discussion part.

Third part: This section is arranged in the third paragraph of the discussion part and the third paragraph of the introductory part.