Peer Review File
Article information: https://dx.doi.org/10.21037/gpm-23-13

Reviewer Comments

Introduction.

1. *First paragraph, remove "famous" before immune checkpoint programmed death …*

Reply 1: we had removed the word "famous" in the Line51 in the introduction part.

2. *Second paragraph: the relationship between DOCK6, GEFs, and Rho GTPase family is not well written, very confusion. Higher DOCK6 leads to higher Rho GTP?, and then what?*

Reply 2: The DOCK6 works as atypical GEFs to participate in the cell activities. And DOCK6 is a member in the downstream of Rac1 and Cdc42 signaling pathway. Rac1 and Cdc42 belong to the Rho GTPase family, which are important in cell activities including tumorigenesis, angiogenesis, invasion, and metastasis. Thus, DOCK6 may be correlated with the tumor, which was reported in gastric cancer. Sorry for causing confusion, we had modified our language in this section.

Material:

1. *Only patieitns wihtou chemo or radiotherapy before surgery was enrolled. However, most of them were stage IIB, according to NCCN guideline, should be getting chemoRT as you stated in the results paragraph 1. So, how many of them were treated with surgery, how many by chemoRT?*

Reply 1: in our research, all the patients were treated with surgeries, where we got the CC samples. All of the patients were fully informed with the efficacy of chemoradiotherapy before surgery and they signed the consent. Among the 94 patients, 82 of them who had stage ≤IIB still chose to have surgeries. The other 12 patients who had should have advanced stage over IIB radical chemoradiotherapy rather than surgeries. However, some of them had revised stage because of more positive findings during surgery, and other patients chose to have surgeries for some personal concerns.

2. *"Patients with neoadjuvant chemo or combined with tumors in other organs were excluded". Not*

clear what you mean.

Reply 2: Patients who had neoadjuvant chemotherapy before surgeries were exclude from this research and Patients who had tumors in other organs were also excluded. The neoadjuvant chemotherapy may prevent the prognosis of CC, which may bring bias in the detection of DOCK6 expression. The tumors in other organs may be associated with patients' survival, which would bring bias in the assessment of DOCK6 expression and prognosis of CC.

3. *"The telephone follow ups were completed with two individual staff". What does that mean? Is this how you got the survival data? So you do not have the recurrence data? What is the median and range of follow up time when you made the phone call, in comparison with the diagnosis date? How many patients did not respond to the phone call?*

Reply 3: the overall survival time was followed up with telephones by two independent staffs. I and Quyou Wang made the phone calls to collect the survival information of every patient. We reached the patients or her family members through the numbers (normally two individual numbers) they recorded in our Hospital Information System. We collected the information regarding the follow-up visits or treatments after surgery, the time of recurrence and the survival time through the phone calls. The median follow-up period was 56 months (ranging from 11 to 74 months) at the time. The total median survival time was 75.83±1.69 years and the overall 5-year survival rate was as high as 90.42%. Those data were elaborated in the manuscript.

Results:

1. *Dividing patients to groups of > 65 and <65 is has no strong basis, and the screening age does not matter. This division makes the group with >65 having too few patients.*

Reply1: According to the NIH recommendations, CC screening should be taken up to 65-year-old. Therefore, we divided our patients into two groups (≤65 years, n= 91, 96.81% and >65 years, n=3, 3.19%). However, no difference in the DOCK6 expression in those two groups. Though it was a negative result, it helped us expand our knowledge about the cervical cancer and DOCK6 expression.

2. *Again, Here should mention the patients' treatment data, and a clear division of stages, with stage 1, 2, 3.*

Reply2: Our patients got diagnosis and treatment between June 2006 and June 2012. At that time, the primary division of the CC stage followed the FIGO staging for carcinoma of the cervix uteri (1994) and we added this reference in the manuscript. Compared with the revised FIGO staging (2018), there was no much difference with the Stage IIb division. Thus, our following analysis results still work if the latest FIGO staging were applied. Patients with stage IA had extrafascial hysterectomy or modified radical hysterectomy. The other patients who had CC over stage IA had radical hysterectomy. Adjuvant treatment is indicated after radical hysterectomy depending on surgical findings and disease stage.

Survival analysis

Medial survival is 75 years, but the curves indicates months

Without PFS data, survival can have all different causes of death, may not be related. Maybe there should be cervical cancer specific death data.

Reply3: thanks for your reminder. We made some clerical error in the manuscript, and now it had been revised. The total median survival time was 75.83±1.69 month and the overall 5-year survival rate was as high as 90.42%. during the follow-up period, only 8 patients died from CC and the others were divided as censored in the analysis. The 8 patients had relapse and 3 of them had experienced metastasis before death, and this information was added into the manuscript. Thus, our survival analysis could be also regarded as CC- specific death data.

Discussion:

The second paragraph has no relationship with this study

The first paragraph repeats what is stated in the introduction, I am not sure if that is related to the DOCK 6 testing.

How does DOCK 6 serve as a biomarker for prognosis through WNT/b catenin pathway should require more explanation.

Paragraph from line 258-283

The data did not show higher expression of DOCK 6 with higher stages of tumor. So the statement in the title is not accurate.

"Those results suggested DOCK 6 may be associated with the progress of tumor cells, which means

tart on DOCK6 could be a good choice against disease progression." I do not think the study can make such a conclusion. You do not have progression data. It only showed association with some poor prognostic markers at the time of diagnosis. It may be an independent biomarker only. Because the validity of the survival data is questionable, to make a conclusion of this statement is questionable.

Line 288-295. Making too strong predictions or statements. ".. providing the possibility that DOCK 6 works as a potential target for CC immunotherapy". What basis it this?

Reply: The first paragraph was a short introduction for CC including its etiology and signaling pathway for development and progression. The DOCK6 was associated with the WNT/β-catenin signaling pathway and PI3K/Akt pathway signaling pathway. Thus, the first paragraph was a background for our research on DOCK6.

The second part described the current immunotherapy for cervical cancer, indicating the possibility of immunotherapy in this disease. Our research was about the expression of DOCK6, which participated in the development and progression of CC, could be a potential biomarker for the immunotherapy.

As you mentioned, our data did not show higher expression of DOCK 6 with higher stages of tumor. We changed the title into "The dedicator of cytokinesis 6 (DOCK6) is a novel indicator for prognosis in cervical cancer". According to our analysis, the high DOCK6 expression in tumor tissue possibly was associated with a poor prognosis. Referred to other research, DOCK6 was in the downstream of the WNT/β-catenin signaling pathway and PI3K/Akt pathway signaling pathway, which was important in the CC development and progression. Thus, we have such statement that "DOCK 6 may be associated with the progress of tumor cells". According to your suggestion, in L271-273, we changed the statement into "DOCK6 could be a potential target for therapy for CC in the future" instead of "immunotherapy". in the last part of the manuscript, we mentioned, DOCK6 expression was highly correlated with the tumor-specific survival of cervical cancer and it was identified as an independent prognostic factor for the prediction of poor survival in CC. We emphasized DOCK6 could be a potential target for therapy for CC in the future. But the efficacy of DOCK6 blocking should be verified in the subsequent experiments *in vitro* and *in vivo*.