Response to reviewer

The authors reviewed the tight junction proteins and the PKC signaling pathway in relation to their potential diagnostic and therapeutic use in pancreatic cancer. The structure of this review is clear. However, some modifications are necessary.

We modificated and rewrote following the comments of reviewer.

1. Minor language polishing is required. The following two sentences are examples. “In pancreatic cancer, some tight junction proteins, including claudins, are abnormally regulated and therefore are promising molecular targets for diagnosis is prognosis and therapy” “The current review will focus on the roles of tight junction proteins, including claudins, and PKC signaling with regard to the potential applicability for diagnosis is prognosis and the therapy during EMT in pancreatic cancer”.

We corrected some sentences of our manuscript.
“In pancreatic cancer, some tight junction proteins, including claudins, are abnormally regulated and therefore are promising molecular targets for diagnosis, prognosis and therapy.” (Abstract)
“The current review will focus on the roles of tight junction proteins, including claudins, and PKC signaling with regard to the potential applicability for diagnosis, prognosis and the therapy during EMT in pancreatic cancer”.(Introduction)

2. C-CEP: It would be good to provide some details about C-CEP. For example, how many amino acids?

The functional domains of CPE can be separated into a receptor-binding region (C-terminal of CPE, C-CPE) and cytotoxic region (N-terminal of CPE). C-CPE is a C-terminal fragment composed of the CPE amino acids 184 to 319 (Katahira et al., 1997). The receptor binding region of CPE has been reported to be in the C-terminal 30 residues (amino acids 290 to 319) of CPE (Hanna et al., 1991).
We added the sentences in the paragraph “The effect of C-CPE targeting claudin-4 against pancreatic cancer”.

3. It would be good to have a picture to show the locations of the tight junctions in pancreas. It is also necessary to point out that the tight junctions and the PKC pathway

are not only related to pancreatic cancer.

We added a new figure (Figure 3) about the localization of tight junctions in normal human pancreas.
Tight junction proteins are regulated by various cytokines and growth factors via distinct signal transduction pathways including PKC (Gonzalez-Mariscal et al., 2008; Kojima et al., 2009). In various cancer cells, the regulation of tight junctions via PKC pathway is reported. The assembly of ZO-1 and occludin is involved in PKC-dependent signaling in gastric cancer cells (Yoshida et al., 2005). The activation of c-Abl-PKCdelta signaling pathway is critically required for the claudin-1-induced acquisition of the malignant phenotype in human liver cells (Yoon et al., 2010). PKC activation causes an increase in claudin-1 transcription and claudin-1 appears to contribute to cell invasion in human melanoma cells (Leotlela et al., 2007). PKCε activation regulates an alpha5 integrin-ZO-1 complex and correlates with invasion and unfavorable prognosis in lung cancer cells (Tuomi et al., 2009).
We added the sentences in the paragraph “The role of PKC in tight junctions during EMT in normal pancreatic duct and cancer”.

4. Conclusion. The conclusion of this review is too high, not fully supported by the evidence stated in the manuscript.

We agreed your comments and changed to short sentences.