Reviewer 1: The manuscript is described the review of epigenetic change (histone methylation) in pancreatic cancer, and its probability of therapeutic target. I think the manuscript is overall well-written, however, genetic mutation such as K-ras, TP53 and SMAD4 are the more critical issues we should overcome than epigenetic abnormalities. The authors should discuss or address the importance of epigenetic change rather genetic mutation.

Response to reviewer: Thank you for your suggestion. In the introduction section, the causes of pancreatic cancer (PC) at the genetic level are simplified. We add the effect of genomic instability on the development of cancer to connect genetic mutations with epigenetic modifications. Therefore, the prospect of epigenetic research in the treatment of PC is raised.

Reviewer 2: Most of the abstract part is used to explain epigenetics and common malignant cancers. Therefore, the readers may not predict that much information related to PC is provided in this review by this abstract alone. To increase the number of readers of this review, I suggest that the authors minimize the background part for general epigenetics and cancer and provide pancreatic cancer (PC)-specific information about epigenetic regulation and diagnosis, the current situation of the chemotherapy using epigenetic reagents, and about what is expected as advanced PC treatments based on future epigenetic research.

Response to reviewer: Thank you for your suggestion. In the abstract section, we delete the basic concept and classification of epigenetics. The

introduction of histone modification is also deleted. More information of the effect that histone methylation has on the diagnosis and treatment of pancreatic cancer (PC) is added to make this abstract focused on PC. We then state current situation of the study and clinical application of writers, readers and erasers and points out the prospect of epigenetic research in PC.

Reviewer 2: Tables 1-4 have much information and are plentiful. However, rows and groups are difficult to recognize. How about reorienting for more space, reducing the font size, and separating groups with thin lines or grey-and-white columns?

Response to reviewer: Thank you for your suggestion. The font size in Table1-4 has been changed from 10 to 8 in order to create more space. And the author also separates groups with thin lines, which makes rows and groups easier to recognize.

Reviewer 2: Minor points:

1) P3, line 7: Therefore, some researchers have turned to (are focusing on?) epigenetics,….
2) P5, line 10: “trypot-phan-aspartic acid 40 domain”…. The "tryptophan-aspartic acid 40 (WD40) domain" may be appropriate for this part.
3) P7, line 1: PRMT5…leading to the silencing of the cell cycle. Is this description correct? This is the opposite of the PRMT5 feature mentioned in the following statement.: PRMT5 overexpression improves cancer cell survival, proliferation….

4) P8, line 20: The following statement is inconsistent with evidence that FBW7 inhibits EZH2 function through its ubiquitin-mediated degradation : EZH2 and FBW7 protein levels are negatively correlated in human PC specimen. The authors may want to say that EZH2 and FBW7 protein levels are oppositely regulated in human PC specimens.
5) P10, line 14: FBXL10 should be described as KDM2B for the reader's convenience.
6) P17, line 16: Is it correct that EZH2 is not expressed in normal pancreatic cells? P18, lines 14–15: The expression of EZH2 in PC cells is significantly higher than in normal pancreatic duct cells and fibroblasts. These two are a bit inconsistent.
7) P20, line 30: Jarid1b should be described as KDM5B for the reader's convenience.

Response to reviewer: I am sorry for that. To improve the accuracy and clarity of the manuscript. We have changed these sections of text.

1) P3, line 7: Therefore, some researchers have turned to (are focusing on?) epigenetics,….

Response to reviewer: P3: We replaced the phrase 'have turned to' with 'are focusing on'.

2) P5, line 10: "trypot-phan-aspartic acid 40 domain"…. The "tryptophan-aspartic acid 40 (WD40) domain" may be appropriate for this part.

Response to reviewer: P5, line 14: We replaced 'trypot-phan-aspartic acid 40

domain' with 'tryptophan-aspartic acid 40 (WD40) domain'.

3) P7, line 1: PRMT5…leading to the silencing of the cell cycle. Is this description correct? This is the opposite of the PRMT5 feature mentioned in the following statement.: PRMT5 overexpression improves cancer cell survival, proliferation…

Response to reviewer: P7, line4-line8: Thank you for your suggestion. We have deleted it in the revised manuscript.

4) P8, line 20: The following statement is inconsistent with evidence that FBW7 inhibits EZH2 function through its ubiquitin-mediated degradation : EZH2 and FBW7 protein levels are negatively correlated in human PC specimen. The authors may want to say that EZH2 and FBW7 protein levels are oppositely regulated in human PC specimens.

Response to reviewer: P8, line24: Thank you for your suggestion. We have changed the sentence, which shows the relationship between FBW7 and EZH2: downregulation of FBW7 induces high EZH2 protein expression, promoting tumor progression in PC.

5) P10, line 14: FBXL10 should be described as KDM2B for the reader's convenience.

Response to reviewer: P10, line18: We replaced 'FBXL10' with 'KDM2B'.

6) P17, line 16: Is it correct that EZH2 is not expressed in normal pancreatic cells? P18, lines 14–15: The expression of EZH2 in PC cells is significantly higher than in normal pancreatic duct cells and fibroblasts. These two are

a bit inconsistent.

Response to reviewer: P17, line24-line27: After consulting literatures, we confirm that EZH2 is expressed at high levels in PC and at low levels in normal cells. So we deleted the statement 'EZH2 is not expressed in normal pancreatic cells'. (line)

7) P20, line 30: Jarid1b should be described as KDM5B for the reader's convenience.

Response to reviewer: We replaced 'Jarid1b' with 'KDM5B'. (KDM5B)

In this review, we also correct some errors and simplify some statements to avoid lengthy.