Response to Reviewer 1 Comments

Comments and Suggestions for Authors

The authors proposed an article focused on the different epigenetics mechanisms that may participate in the development of idiopathic pulmonary fibrosis and chronic obstructive pulmonary disease. This work offers an exhaustive view of the main epigenetic modifications that occur in these pathologies. In the second part of the manuscript, they developed a very interesting paragraph on the therapeutics leverage that could be used to correct the aberrant epigenetic landscape observed in these pathologies. I suggest some minor comments to the manuscript:

General comments:

- **Point 1:** please justify the text all along the document.

  Response 1: The text was checked one more time all along and the missing parts were added.

- **Point 2:** for the methylation part (2.1 and 2.2), please describe the localization of the methylation change of the genes you cite (promoter, gene body, enhancer).

  Response 2: We went through the references and added the information available from the publications. Updates can be found in the 2.1 and 2.2 sections. Please see the change via 'track changes' function in word file.

- **Point 3:** authors Contribution, Funding, and Institutional Review Board Statement have not been completed.

  Response 3:

  Author Contributions

  E.A., P.S. and S.S.P. contributed to the development of draft. R.S. and W.S. revised the draft. All authors have read and agreed to the published version of the manuscript.

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  Institutional Review Board Statement

  Not applicable.

  Informed Consent Statement

  Not applicable.

  Data Availability Statement

Not applicable.

Conflicts of Interest

The authors declare no conflict of interest.

Specific comments

Point 1: Line 19-20: this part of the sentence is not clear for me: “which cultured ex vivo characterized and showed to maintain the disease phenotype”.

Response 1: The sentence is rebuilt as “isolated fibroblasts and smooth muscle cells from patients with pulmonary diseases such as IPF and PH, which were cultured *ex vivo* maintained the disease phenotype.” Please see the change via ‘track changes’ function in word file.

The intention of this sentence is to highlight that these isolated cells from the patients were cultured and they maintained the hyper-proliferative and apoptosis resistance phenotype as well as increased level of EMC in *ex vivo* conditions.

Point 2: Line 33: please add information on the time course of this pathology (survival, death rate,…)

Response 2: The paragraph down below is added. Please see the change via ‘track changes’ function in word file.

“According to the World Health Organization (WHO) mortality database, the mean age of the mortality rates from IPF across Europe in 2001–2013 were 3.75 per 100,000 for males and 1.50 per 100,000 for females (7). The median survival among 65 year-old or older adults with IPF in the United States was 3.8 years (8).”

Point 3: Line 47: please correct: “(Fig.)1”

Response 1: Corrected as (Fig.1). Please see the change via ‘track changes’ function in word file.

Point 4: Line 48: I suggest to moderate this sentence by changing “responsible for” by “participating to”.

Response 4: Corrected as ‘participating to’. Please see the change via ‘track changes’ function in word file.

Point 5: Line 50: the end of sentence is missing.

Response 5: The sentence is revised as “Moreover, the pathogenesis of other pulmonary diseases such as asthma and chronic obstructive pulmonary disease (COPD) has been already linked to epigenetics (14, 15)”. New reference order is 16,17 for this sentence. I believe the place of the figure was shifted and covered the end of the sentence.

Point 6: Line 71-72: You refer to WHO records from 2019 in this sentence, please find a most recent publication to justify “the prevalence continues to increase by 2021”.

Response 6: The typo mistake is corrected as ‘2019’. Please see the change via ‘track changes’ function in word file.

Point 7: Lines 82-85: the causes and consequences are not differentiated. For example in this sentence "apoptosis and inflammation" are molecular mechanisms that may participate in the phenotypes changes such as "remodeling of blood vessels as well as extracellular matrix".

Response 7: The sentence was changed according to the reviewer suggestion as below. Please see the change via 'track changes' function in word file.

"Given damage due to generated free radicals/oxidants results in alveolar epithelial injury, inactivation of pulmonary surfactants and anti-proteases, membrane lipid peroxidation, dysregulated mitochondrial function, apoptosis and lastly inflammation. These molecular mechanisms eventually participate in phenotypic changes such as remodelling of blood vessels as well as extracellular matrix (24)." New reference order is 26 for this sentence.

Point 8: Lines 85-86: "Inflammation itself is a major influencer of the ROS response in the cells" please add a citation.

Response 8: The reference is added. Please see the change via 'track changes' function in word file.

Chelombitko M. A., Role of Reactive Oxygen Species in Inflammation: A Minireview. Moscow University Biological Sciences Bulletin volume 73, pages199–202 (2018).

Point 9: Line 121-122: DNA hypermethylation is associated with an altered level of gene expression, not to a systematic suppression of its expression. Indeed, It has been shown that over-methylation could be associated with an increased expression of some genes (see D. Anastasiadi et al. 2018 in *Epigenetics & Chromatin*).

Response 9: We went through the suggested article regarding DNA hypermethylation and we agreed that epigenetic gene regulation based on tissue and species are diverse. Thus, as suggested by the reviewer, we can´t generalize DNA methylation based on only a suppression of regulatory genes. This was the main reason for us to write the sentence down in a neutral tone in IPF and COPD disease concept. Here, we only highlight 'altered gene expression' and do not discuss increased or decreased gene expression in IPF and COPD. Please see the sentence kindly again.

"DNA methylation is shown to associate with altered expression of genes and pathways important to lung diseases such as IPF (31, 32)." New reference order is 34, 35 for this sentence.

In the next sentence, we only discussed the correlation between DNA hypermethylation and decreased gene based on existed research papers in only IPF context. We are not aware of any new study directly referring to hypermethylation and increased gene expression in IPF. Please kindly see the sentence down below.

"In addition, DNA hypermethylation is considered a crucial contributing factor for down-regulation of the IPF suppressor genes such as THY1 (Thy-1 Antigen), CAV1 (Caveolin 1), PTEN (Phosphatase and Tensin Homolog), and PTGER2 (Prostaglandin E Receptor 2), which are known to regulate important cellular processes."

Point 10: Line 124: transfer the information on COPD methylation "and COPD (33, 34)" in the "2.2. DNA methylation in COPD" paragraph.

Response 10: Transferred into '2.2. DNA methylation in COPD' paragraph. Please see the change via 'track changes' function in word file.

Point 11: Line 144-145: Changing “expression” by a synonym (i.e. production) may avoid confusion with the previous sentence that describes no change in the expression of DNMT3A.

Response 11: ‘Expression’ word is exchanged by ‘production’. Please see the change via ‘track changes’ function in word file.

Point 12: Line 152: please correct “d pendent” by “dependent”.

Response 12: Corrected as ‘dependent’. Please see the change via ‘track changes’ function in word file.

Point 13: Line 196: precise that the study of Liu *et al* is focused on chronic CSC exposure (up to 9 months)

Response 13: Time point (up to 9 months) is added to the sentence according to reviewer’s suggestion. Please see the change via ‘track changes’ function in word file.

Point 14: Line 284-285: please add a reference.

Response 14: Reference was added before. Please kindly see the original text down below.

“These multiprotein complexes can interact with other proteins such as nuclear receptors, transcription factors, and other epigenetic gene modifiers, such as histone methyltransferases (HMTs), DNA methyltransferases (DNMTs), and methyl-CpG-binding proteins (MBDs) to regulate gene expression (83).” New reference order is 86 for this sentence.

Point 15: L307-318: It could be interesting to discuss the opposing results obtained by Adenuga (102) on HDAC2 expression and activity when compared to other authors (103).

Response 15: We revised the text as these are no opposing result. Both research studies are concordant to each other. Please kindly see the original text down below and the change via ‘track changes’ function in word file.

“Decreased HDAC2 activity is associated with glucocorticoid resistance and elevated oxida-tive stress as well as pro-inflammatory mediators in smoke induced COPD”

New reference order is 105, 106 for these research papers.

Point 16: Line 351: please add a short paragraph introducing the mechanisms of action of the miRNAs as you did for others epigenetics mechanisms.

Response 16: Original text we provided to the journal contains a chapter with the name of “microRNAs in IPF” before microRNAs in COPD chapter. This IPF part was somehow excluded from the journal manuscript. Since we mentioned mechanisms of action of the microRNAs briefly in IPF, we preferred not to be repetitive in COPD section.

IPF part is added again into the manuscript which describes the mechanisms of action of the miRNAs. Please see the change via ‘track changes’ function in word file.

Point 17: L355-356: please add a reference.

Response 17: The sentence was initiation step to the specific research paper, which is indicated as reference 126 in the following sentence. However, the reference was added once again in the line as the reviewer suggested. Please see the change via 'track changes' function in word file. New reference order is 129 for this sentence.