Response to reviewer 2:

We thank the Reviewer for pointing out that "It's an interesting topic. The author described the endogenous retrovirus elements in the genome, which were not well investigated."

We are also grateful for the cues provided to improve our manuscript. All the concerns have been addressed as detailed below.

1. In line 132, the author mentioned that 'there is no RNA-seq data available for normal mesothelium', which is not really the case. Because there are some GEO datasets, where RNA-seq was done for both normal pleura and mesothelioma tissues, such as GSE2549 (From Bueno's group), although there are only several normal pleura tissues. Besides, a paper has been published with single-cell RNA sequencing of human pleura 'https://www.nature.com/articles/s41586-020-2157-4#Sec2, Construction of a human cell landscape at single-cell level'. In addition, scRNA-seq of human pleura has been done in this pre-print paper 'Single-cell transcriptomic analysis of human pleura reveals stromal heterogeneity and informs in vitro models of mesothelioma'. Therefore, it would be great if the author has a look at ERVs by the datasets. Maybe these data could help to understand the 'ERVs' in normal pleural and mesothelioma.

We thank the reviewer for commenting on this crucial point of availability of RNA-seq data for normal mesothelium. Unfortunately GSE2549 is a dataset based on Affymetrix Human Genome U133A Array, meaning that it is not RNA-seq data. The second study mentioned (Han et al, Nature 581:303, 2020) reports indeed adult pleura single cells mRNA-seq. In these study 4 clusters are identified in adult pleura: 3 defined as mesothelial cells and one unknown, interestingly characterized by the expression of interferon induced genes. We speculate that this last cluster might correspond to what we have recently defined as monocyte-derived small peritoneal/pleural macrophages (Wu et al, Proc Natl Acad Sci U S A. 2023;120:e2210836120). Because Han et al used a polyA RNA-seq protocol it is not possible to use the available data to interrogate ERVs expression since this method has been shown to fail to detect several classes of repeat RNA (Solovyov A, Vabret N, Arora KS, et al. Global Cancer Transcriptome Quantifies Repeat Element Polarization between Immunotherapy Responsive and T Cell Suppressive Classes. *Cell Rep* 2018;23:512-521). However we edited the text to include this comment (see below). Finally, we thank the Reviewer for pointing to the bioRxiv preprint 'Single-cell transcriptomic analysis of human pleura reveals stromal heterogeneity and informs in vitro models of mesothelioma'. There the data is not available yet.

To address the concern we have edited the text in the revised manuscript, lines 131-134:

"Indeed, for the time being the only RNA-seq data available for normal mesothelial cells is provided in a single cell mRNA-seq study in the context of a human cell atlas [33]. The polyA RNA-seq protocol which was used has been shown to fail to detect several classes of repeat RNA[34]."

2. Study of ERVs in mesothelioma seems quite rare, while only two studies from the author. So not so many descriptions of ERVs in mesothelioma can be written in a review. Not sure if it's necessary to write a review about ERVs in mesothelioma. It will be helpful to add a table to describe the specific ERVs to show whether they can be used for prognostic or immunotherapy biomarkers, based on the author's work and the study about the functions of ERVs in other types of cancer. The author can predict the potential functions of ERVs in mesothelioma based on research in different types of cancer. In other words, a summary table for sections 3 and 4.

According to Reviewer's suggestion we have extended the analysis of ERV expression in other cancer types and included a table (Table 2) to describe the specific ERVs that can be used for prognostic or immunotherapy biomarkers, based on our work and the study about the functions of ERVs in other types of cancer.

The following text has been added to section 4, lines 290-300:

"In an additional clear cell renal cell carcinoma study, *ERV_4700* (or *ERVmap_4700*) expression predicted response to immunocheckpoint blockade and association with translation, meaning the production of neoantigens [95]. In another clear cell renal cell carcinoma study, RNAseq performed on more than 100 formalin-fixed paraffin embedded patient samples from the two clinical trials (CheckMate-010 and CheckMate-025), identified a link between *ERV_2282* (or *ERVmap_2282*) expression with better overall survival in the group treated with anti-PD-1[96]. Differences between the different studies in this cancer type have been suggested to be linked not only to RNA sequencing approaches, as previously mentioned, but also to cohorts differences and ERV mapping and annotation (reviewed in [97])."

Comments on the Quality of English Language

English is good. Some grammar mistakes need to be checked and corrected. For example, in the last sentence 'Finally, besides ERV, other TE such as selected LINE1 are overexpressed in mesothelioma', TE should be TEs (plural).

We thank the Reviewer for the correction, which has been implemented