In this manuscript by Qian et al, the authors performed secondary analyses for lncRNA genes on previously generated RNA-seq data for protein-coding genes and uncovered distinctive expression profiles of lncRNA genes. They further validated their findings by activating NLRP3 inflammasome in THP-1 cell line and performed loss-of-functional assays of the inflammasome-regulated lncRNA, ENSG00000273124 and showed its role in polarization of macrophage-like cells to pro-inflammatory macrophage-like cells. Finally, they have built InflammasomeDB web application with expression profiles of protein-coding and lncRNA genes related to the NLRP3 inflammasome activation. Though the focus of the study was interesting in terms of highlighting the functional roles of lncRNA, the authors may consider few concerns that the authors might consider strengthening their work.

Response: Thank you very much for your valuable comments.

1. The authors reported in the introductions (Lines 31-35) that "Upon activation by various danger signals or cellular stressors, the NLRP3 inflammasome assembles and triggers the conversion of pro-interleukin (IL)-1β and pro-IL-18 into their mature and biologically active forms, IL-1β and IL-18, respectively. The release of IL-1β and IL-18 leads to the recruitment and activation of immune cells, such as neutrophils and macrophages, initiating an inflammatory response and pyroptotic cell death". These lines sounds as if NLRP3 inflammasome assembly and activation is happening elsewhere and consequences of this inflammasome activation is recruiting immune cells and killing them by pyroptotic cells death, which is not true to its context. These lines are misleading and needed much attention. In fact, their predominant presence in the immune cells emphasizes its significant role in immune response.

Response: The above paragraph was rewritten as follow:

"Inflammasomes are complex protein assemblies found in macrophages, dendritic cells, and neutrophils [1-5]. They control the activation of cysteine protease caspase-1. This enzyme then regulates the maturation of pro-interleukin (IL)-1β and IL-18, leading to a process called pyroptosis. The NLRP3 inflammasome, comprising NLRP3, the adaptor molecule caspase-recruitment domain (ASC), and the cysteine protease caspase-1, plays a crucial role in regulating inflammation and immune responses. In the context of infections or injuries, this response is crucial for host defense and tissue regeneration. However, in sterile inflammatory situations, excessive or prolonged activation of the NLRP3 in-flammasome and subsequent production of IL-1β and IL-18 may contribute to chronic inflammation and tissue damage [2]."

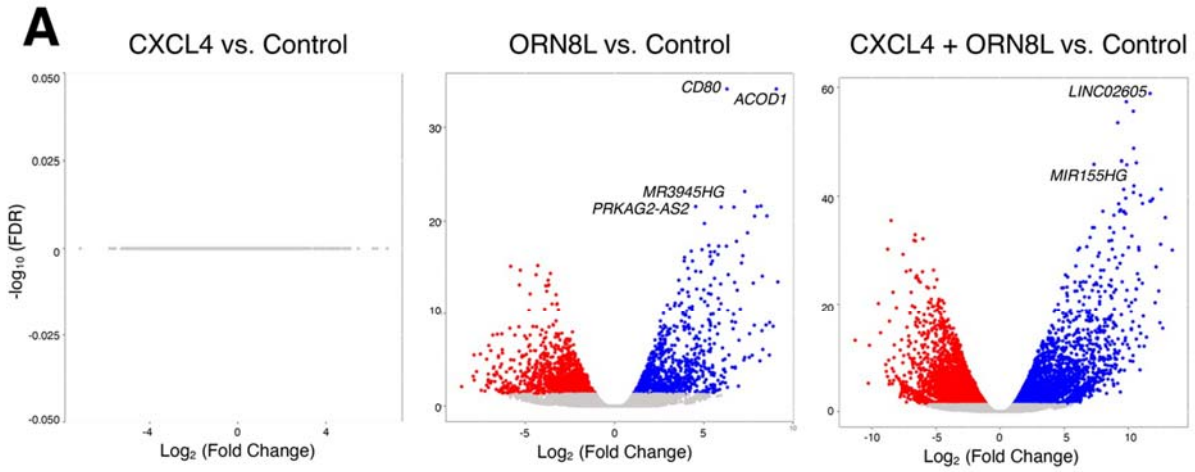
2. Again, in lines 75-76, is it true that IL-1B activate NLRP3 activation? In fact, NLRP3 inflammasome-mediate IL-1β production can be primed by TLRs activation.

Response: The above mentioned part was removed in the revised manuscript.

3. What the authors mean when said "Volcano plots compared to the control" in figure 1A. It would be more informative to show the up and down regulated genes of

interest in the volcano plot. Moreover, the x-axis and y-axis are unclear in Figure 1A and 2A

Response: Both figures were modified.



B

Up-regulated	CXCL4 vs. Control	ORN8L vs. Control	CXCL4+ORN8L vs. Control
protein_coding	0	851	2,101
lncRNA	0	146	713
Others	0	51	275
Total	0	1,048	3,089

Down-regulated	CXCL4 vs. Control	ORN8L vs. Control	CXCL4+ORN8L vs. Control
protein_coding	0	1,148	3,122
lncRNA	0	168	459
Others	0	26	96
Total	0	1,342	3,677

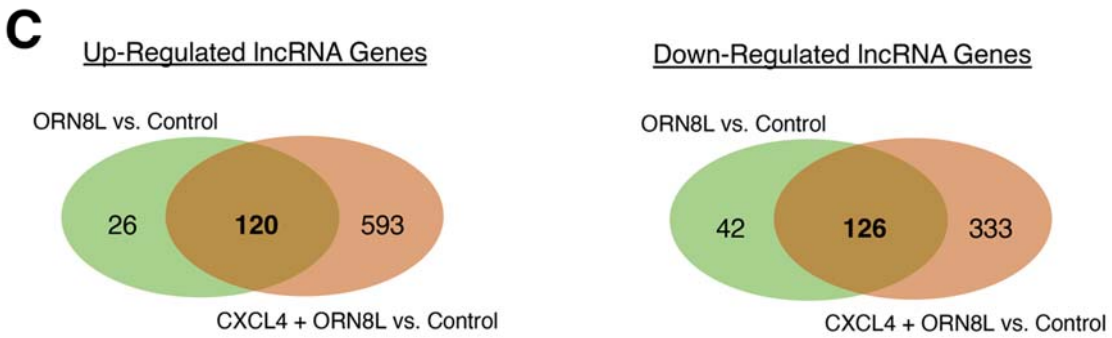
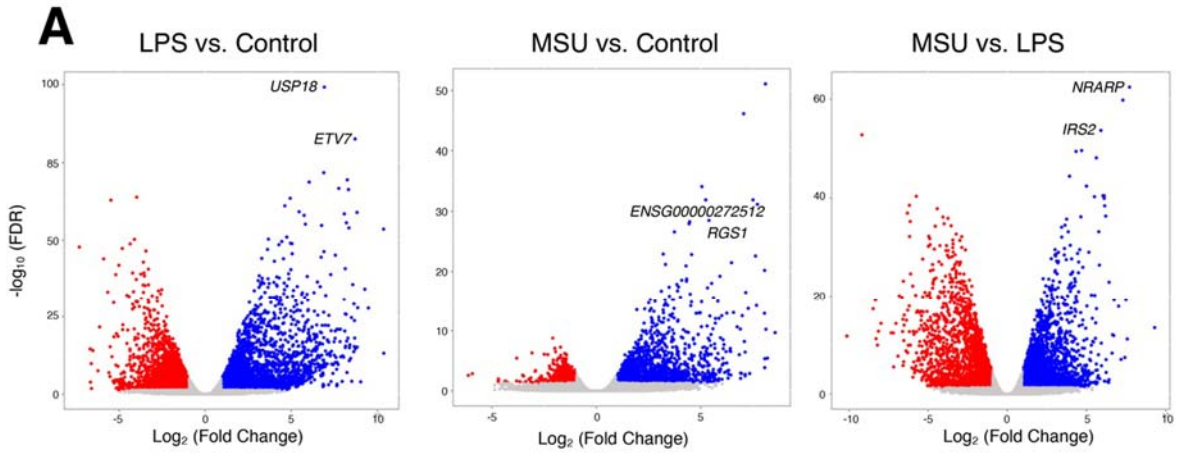


Figure 1



B

Up-regulated	LPS vs. Control	MSU vs. Control	MSU vs. LPS
protein_coding	1,963	1,028	1,915
lncRNA	386	267	465
Others	121	56	84
Total	2,470	1,351	2,464

Down-regulated	LPS vs. Control	MSU vs. Control	MSU vs. LPS
protein_coding	1,926	463	1,778
lncRNA	446	48	218
Others	89	13	85
Total	2,461	524	2,081

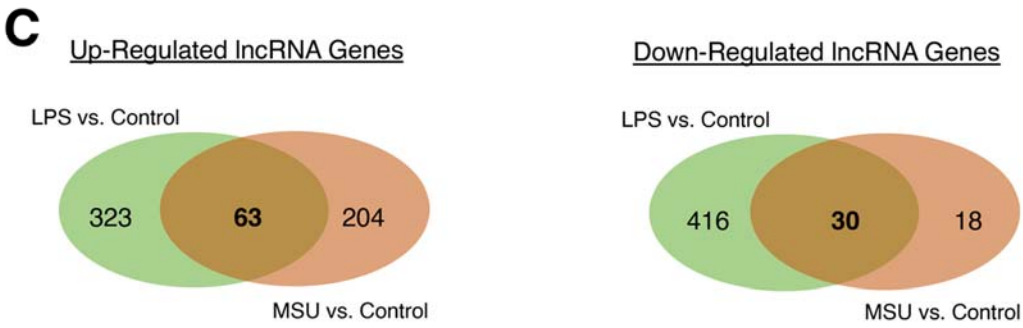


Figure 2

4. The info. presented in Fig 6 need clarity for better understanding.

Response: The figure legend for Figure 6 was modified as follow:

"Figure 6. The InflammasomeDB web database. (A) Home page of InflammasomeDB. InflammasomeDB can be accessed freely without the need for username and password. (B) "Explore Results" page. The user-defined threshold values allow the generation of the Result Table and volcano plot. Both the table and volcano plot are generated based on the user-defined threshold values. (C, D) Categorization of the DEGs by enriched (C) GO terms and (D) KEGG pathways for inspecting global changes in signaling pathways. (E) lncRNA page. The detailed information about lncRNA genes is provided as a table along with the information obtained from the Lnc-Book 2.0 database. By

selecting a lncRNA of interest in the table, the list of possibly bound miR-NAs and the information about GWAS are dynamically generated in the gray box in the right-hand side of the window.”