Dear Editor

We are submitting a manuscript entitled “Cxxc finger protein 1 coordinates histone H3 lysine-4 trimethylation of Innate Lymphoid Cell Related to Aging” for your consideration for publication as an article in Nature.

The gut is considered a pervasive and important player involved in an array of biological events, including digestion, absorption, and immune modulation. Disturbances along the brain-gut-microbiota axis even significantly contribute to the pathogenesis of neurodegenerative disorders. Similar to other organ systems, the gut also undergoes senescence. Aging enhances intestinal disease incidence and exerts a profound impact on individual health. Elucidating age-related changes in gut epithelial function is fundamental to understanding the underlying mechanisms. In this study, we found that gut $CCR6^+$ ILC3s in aged mice exhibited dysregulated differentiation and function, which led to susceptibility to bacterial and fungal infection. The enrichment of H3K4me3 modification at promoter regions in $CCR6^+$ ILC3s of aged mice was selectively declined when compared with young mice. We showed that Cxxc1 was comparatively higher in $CCR6^+$ ILC3s and conservatively acted as the dominant histone lysine methyltransferase mediating H3K4me3 in aged gut ILC3s. Deletion of Cxxc1 in young mice led to similar premature aging-related phenotypes, including the reduction of $CCR6^+$ ILC3s, coupled with decreased H3K4me3 modification, as well as their impaired ability to secret IL-22 and IL-17A. *Cxxc1*-deficient and aged gut ILC3s showed great similarity in genome-wide Cxxc1-binding sites and H3K4me3 modification level. We found that Cxxc1 bound to Klf4 and Maf by maintaining the appropriate H3K4me3 modification of their promoter regions. Moreover, over-expression of Klf4 could partially rescue the differentiation and function defects seen both in aged intestinal and *Cxxc1*-deficient $CCR6^+$ ILC3s. Collectively, these data underline effects of aging on innate lymphoid cell development and function, and indicate that targeting tissue-resident ILC may pave the way for new strategies to improve persistent inflammation in the elderly.

Taken together, our findings revealed an unknown role of Cxxc1-induced H3K4me3 in the homeostasis, function, and senescence of gut ILC3s. To our knowledge, this is the first report revealing the biological effects of H3K4me3 in aged gut ILC3s, which will be of great interest to the readership of Nature.

The work described has not been submitted elsewhere for publication, in whole or in part. All the authors have approved this submission and certify that there are no conflicts of interest.

We would do feel honored if you feel that the manuscript is appropriate for your journal.

We deeply appreciate your consideration of our manuscript, and we look forward to receiving comments from the reviewers. We would do feel honored if you feel that the manuscript is appropriate for your journal. If you have any queries, please don’t hesitate to contact me at the address below. And we look forward to hearing from you soon.

Sincerely,

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