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Response to comment on: "Ligature-induced periodontitis promotes *Dnmt3a*^{R878H}-driven clonal hematopoiesis"

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Author Contributions

Qiao Yuan, Min Liao and Fuhua Yan contributed to the conception, data analysis, and critical editing of the manuscript. All co-authors have reviewed and given final approval to the submitted version.

Disclosure

The authors declare no conflict of interest.

We are grateful for Dr. Cheng and Dr. Wu's interest in our paper, "Ligature-induced periodontitis promotes *Dnmt3a*^{R878H}-driven clonal hematopoiesis," published in *Haematologica*.[1,2] Their perspectives touch upon three critical dimensions-mechanistic triggers, distant metastatic potential, and clinical translational management. These perspectives offer invaluable direction for broadening the scope of our ongoing investigations. In the responses below, we address each of these issues in detail and look forward to continued discussion with them.

Firstly, their question regarding the upstream triggers of the CCL17 chemokine storm is critically important. Specifically, they raised the need to distinguish between dysbiosis driven by microbiota and sterile mechanical injury in the ligature induced periodontitis (LIP) model. We greatly appreciate this opportunity to clarify the issue. The LIP model was originally designed to create a plaque-retentive environment around the teeth by placing ligatures, thereby inducing periodontitis. We totally agree that the LIP procedure itself introduces an initial mechanical trauma. To control for this potential confounder and to exclude its influence, we clearly described in the "Ligature induced periodontitis" subsection of the Methods that control (CTL) animals underwent sham ligation, in which sutures were tied and immediately removed. This approach effectively eliminated the possible impact of sterile mechanical injury on our experimental outcomes. Our results consistently demonstrated that, in comparison with the true ligature group, the sham ligation group showed a markedly attenuated elevation of CCL17 and subsequent clonal expansion, indicating that the observed inflammatory feedback loop is driven predominantly by sustained plaque accumulation rather than by transient surgical trauma itself.

Furthermore, given that periodontitis is currently recognized as a plaque-initiated disease, our primary aim was to recapitulate the natural pathophysiology as closely as possible. We therefore chose to use conventional (non-germ-free) mice, which more closely mirror the complex oral microbial community present in human disease.[3,4] Nonetheless, we entirely agree with their insightful suggestion that employing germ free mice or administering targeted antibiotics would elegantly separate mechanical

trauma from maladaptive immune training, thereby pinpointing the principal source of the signals that sustain this specific inflammatory feedback loop. This certainly represents a promising avenue that merits thorough exploration in future studies.

Secondly, Dr. Cheng and Dr. Wu's perspective from the clinical oncology viewpoint regarding the systemic expansion of monocytic myeloid derived suppressor cells (Mo-MDSCs) and their distant metastatic potential is highly prescient. In recent years, a substantial body of evidence has further corroborated the close link between clonal hematopoiesis and solid tumors.[5-7] For example, a paper published in *Cell Reports Medicine* demonstrated that inflammatory reprogramming of the solid tumor microenvironment, driven by infiltration of leukocytes associated with clonal hematopoiesis, is significantly correlated with adverse prognosis.[8] In our LIP model of *Dnmt3a*^{R878H} mutant mice, we indeed observed systemic expansion of Mo-MDSCs in the bone marrow, peripheral blood, and gingival tissues. However, whether these mutations bearing Mo-MDSCs infiltrate other distant organs, such as the brain and lungs, has not yet been systematically assessed within our current experimental framework, and this important question will be a focus of our future investigations.

Thirdly, we are greatly inspired by their thoughtful evaluation of our findings through the lens of early clinical drug development. Both clonal hematopoiesis driven by *DNMT3A* mutation and periodontitis are highly prevalent in the elderly population. Their synergistic induction of systemic cytokine storms and aberrant myelopoiesis is likely to exert considerable effects on the toxicity and efficacy assessments of novel anticancer agents. Their recommendation to incorporate routine periodontal screening and targeted local anti-inflammatory interventions into the baseline assessment of high-risk CH mutation-bearing cancer patients is highly clinically actionable. We are currently designing relevant research protocols to systematically evaluate the impact of periodontal interventions (such as nonsurgical periodontal therapy and pharmacological interventions) on peripheral blood myeloid cell composition, serum cytokine profiles, and immunotherapy-related adverse events in CH mutation carriers.

Finally, we would like to thank Dr. Cheng and Dr. Wu again for their interest in our study and their insightful comments. The three key perspectives they have raised not only help us to more comprehensively examine the limitations and potential of our current findings, but also point toward promising avenues for future research and clinical translation.

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