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Bridging periodontitis and clonal hematopoiesis: implications for solid tumor metastasis, clinical trial design, and microbiome dynamics. Comment on: "Ligature-induced periodontitis promotes Dnmt3a^{R878H}-driven clonal hematopoiesis"

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Author Contributions

C.C. and X.W. participated in manuscript conception, data interpretation, and critical revision of the draft. All authors reviewed and approved the final submitted version.

Disclosure

The authors declare no conflict of interest.

To the Editor,

We read with great enthusiasm the recent article by Yuan et al. [1] published in Haematologica. The authors present a highly compelling and elegantly designed study demonstrating that ligature-induced periodontitis (LIP) actively promotes Dnmt3aR878H-driven clonal hematopoiesis (CH) through a systemic CCL17-mediated chemokine storm. By establishing a vicious cycle where mutated hematopoietic stem cells (HSCs) exacerbate local bone destruction while simultaneously gaining a proliferative advantage via systemic chemokine feedback, this work provides a crucial missing link between localized chronic inflammation and hematopoietic aging. Building upon these robust findings, we wish to highlight three critical perspectives regarding mechanistic triggers, distant metastasis, and translational oncology management that warrant further discussion.

First, regarding the upstream triggers of the observed chemokine storm, it is essential to distinguish between microbiota-driven dysbiosis and sterile mechanical injury. The authors hypothesize that dysbiosis and microbial metabolites might activate specific pathways in HSCs to promote clonal expansion. However, the LIP model inherently introduces severe initial mechanical trauma and foreign body responses. We respectfully ask the authors: could the initial surge in CCL17 from gingival myeloid cells be predominantly a sterile injury response rather than a purely pathobiont-driven phenomenon? Have the authors considered evaluating this CCL17 axis in germ-free mice or utilizing targeted antibiotic interventions? Decoupling mechanical trauma from maladaptive immune training [2] would elegantly clarify the primary origin of the signals driving this specific inflammatory feedback loop.

Second, the systemic expansion of monocytic myeloid-derived suppressor cells (Mo-MDSCs) observed in the Dnmt3aR878H cohorts subjected to LIP presents profound implications for systemic oncology. In our clinical practice, the systemic burden of Mo-MDSCs is a recognized hallmark of immune evasion, intimately linked to the establishment of pre-metastatic niches [3]. When managing highly aggressive malignancies such as lung cancer, we consistently observe that immunosuppressive myeloid cell expansion heavily correlates with devastating clinical complications, including leptomeningeal metastasis. We wonder if the systemic Mo-MDSC dissemination driven by the periodontitis-CH axis could inadvertently facilitate such distant solid

tumor metastases by pre-conditioning distant organ microenvironments. We would be highly interested to know if the authors observed altered infiltration of these mutation-bearing Mo-MDSCs in other distal organs (such as the brain or lungs) in their murine models.

Third, these findings hold significant translational value for clinical oncology management and the design of early-phase clinical trials. In drug development, particularly during Phase I dose-escalation studies utilizing 3+3, BOIN, or CRM designs, the accurate assessment of dose-limiting toxicities is paramount. Because both DNMT3A mutations and chronic periodontitis are highly prevalent in older adult populations [4], their synergistic capacity to induce systemic chemokine storms and aberrant myelopoiesis could selectively drive clonal expansion under inflammatory stress [5], which could severely confound toxicity evaluations or inadvertently blunt the efficacy of novel cancer therapies. We invite the authors to comment on the feasibility of integrating routine periodontal screening and targeted, localized anti-inflammatory interventions into the baseline assessments for oncology patients harboring high-risk CH mutations. Disrupting this localized inflammatory nexus could potentially stabilize systemic immune homeostasis and optimize therapeutic responses.

In conclusion, Yuan et al. have provided a transformative framework for understanding how localized periodontal inflammation shapes the hematopoietic landscape. Addressing the nuances of microbiome dynamics, the metastatic potential of expanded Mo-MDSCs, and the clinical management of these systemic feedback loops will undoubtedly accelerate the translation of these preclinical insights into precision oncology paradigms. We look forward to the authors' insights on these points.

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