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EDITORIAL

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Regulation of metabolism and inflammation: The host response

The second part of this special issue presents original work illustrating the complex and critical role of the host immune response and reveals intriguing insights into how the oral environment works in health and disease. The host response is wrapped up with regulation of metabolism, and these processes are integral to maintaining homeostasis and health and in chronic diseases such as periodontitis. In this issue, the authors have used a variety of mouse models, modified mouse strains and human cells to dissect novel pathways of host regulation.

Zhao et al illustrate the manipulation of liver X receptors (LXRs) to modify periodontal bone loss. LXRs, which regulate cholesterol, fatty acid and glucose metabolism, also modulate inflammation. Synthetic small molecule antagonists of LXRs proved protective against periodontal bone loss in a mouse ligature model of periodontitis through suppression of the abundance and osteoclastogenic potential of osteoclast precursor cells. Intriguingly, there was no change in the expression of IL-6 or TNF, commensurate with previous observations of context-dependent functions of LXRs (Zhao et al., 2023).

Guido et al explore lipid metabolism in epithelial cells. Periodontitis-associated bacteria generate and release immune modulatory lipids. Their data show that gingival fibroblasts can take up specific bacterial lipids and hydrolyse these into a variety of products – some of which are retained and may be incorporated into the fibroblasts, whilst other products are released. The extent to which host cells alter or incorporate bacteria-derived lipids will influence the host cell function and as such form part of the interplay between the host responses and the local bacteria (Guido et al., 2023).

The role of connective tissues in immune response regulation is well established, and Chen et al demonstrate that understanding this requires evaluating different subsets of cells involved. This work shows an essential role in wound healing for a fibroblast subset characterised by the expression of Prx1 (a marker of mesenchymal cells upregulated during limb development and wound regeneration). The studies used Cre-LoxP to generate mice without Prx1 fibroblasts and showed that these cells are essential for wound healing in both skin and oral mucosa. Intriguingly, in the absence of the Prx1 fibroblasts, there was an increased accumulation of CD45 leukocytes and Ly6G neutrophils and a greater accumulation of bacteria at wounds – but an absence of F4/80 macrophages. Therefore, the Prx1 fibroblast subset recruits macrophages that are key to regulation of wound healing (Chen et al., 2023).

Moving from soft tissue wound healing to bone healing, Feng et al show the signal transducer and activator of transcription 3 (Stat3) promotes bone healing in an inflammatory environment. Selective removal of Stat3 from mesenchymal progenitors has previously been shown to result in defects in bone development, resulting in functional bone defects, reduced bone mass and multiple fractures. The new data presented show the impact of Stat3 on bone in an inflammatory environment by employing the lipopolysaccharide-induced calvaria osteolytic model in mice. In this model, conditional knockout of Stat3 resulted in decreased bone healing (Feng et al., 2023). Bone remodelling physiology is further explored by Duarte et al., who show that local injection of a neutralising anti-IL-34 monoclonal antibody reduced alveolar bone loss in a murine model of ligature periodontitis. Regulation of bone turnover by cross-talk between macrophage colony stimulating factor (M-CSF) and receptor activator of the nuclear factor kappa-B ligand is well documented. IL-34 is a ligand for the colony-stimulating factor-1 receptor, which appears to out-compete the receptor's namesake ligand, M-CSF. IL-34 is, therefore, another part of the cellular conversations that regulate bone remodelling, and as IL-34 is elevated in periodontitis and the authors suggest this may be a therapeutic target (Duarte et al., 2023).

The novel work presented here demonstrates how a variety of technologies: RNAseq to characterise subsets of cells, gene manipulations to generate mice to investigate hypothesis and the use of recombinant proteins and small molecules to manipulate pathways – can inform how the oral cavity works in health and disease. The next challenge is to translate these into 'real-world' solutions to the immense challenges facing oral health.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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PEER REVIEW

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