

Knock, Knock, It's AM o'clock!

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Introduction

Circadian rhythms regulate physiological processes, including immune responses. In the lung, the most pronounced time-of-day-dependent changes were observed in the transcriptomic state of monocytes, endothelial cells, and alveolar macrophages (AMs).

Objectives

Considering the importance of AMs in shaping lung immunity, this study investigates how myeloid cell intrinsic- and extrinsic circadian rhythms influence lung immunity, focusing on AM effector functions and disease outcomes.

Methods

To investigate the AM clock specifically, AMs are isolated via bronchoalveolar lavage at four time points (ZT0, ZT6, ZT12, ZT18), and then challenged with bacterial and viral stimuli to assess cytokine production and phagocytic capacity. In parallel, we study how the myeloid cell intrinsic clock shapes the outcome of bacterial and viral pneumonia *in vivo*. So far, we have infected *Bmal1^{fl/fl}LysM^{Cre}* and control mice with SARS-CoV-2 at different times. Immune cell populations are quantified via flow cytometry, and inflammatory responses are assessed using qPCR and cytokine analysis.

Results

In vitro, inflammatory cytokine mRNA expression (e.g., *Il6*, *Il1b*, *Tnfa*) in AMs exhibited circadian rhythmicity upon LPS, R848, and HKSP stimulation and this was dependent on the AM-intrinsic clock. *In vivo*, lung immune cell composition oscillated with circadian time under healthy conditions, while SARS-CoV-2 infection altered these patterns. Loss of the myeloid clock in the bone marrow reduced oscillation across all leukocyte types. Interestingly, in the lung, myeloid clock disruption amplified the oscillation of myeloid leukocytes but not lymphocytes.

Conclusion

AM immune responses are regulated by circadian rhythms, with additional contributions from non-myeloid cells. Understanding circadian lung immunology could optimise therapeutic strategies for respiratory infections and inform vaccinology.