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EDITORIAL

REVIEW SERIES: CIRCADIAN RHYTHMS FOR IMMUNOLOGISTS
Series Editor: Rachel Edgar

It's time to think about circadian rhythms

OTHER ARTICLES PUBLISHED IN THIS REVIEW SERIES
Circadian rhythms in innate immunity and stress responses. Immunology 2020, 161: 261-267.
Circadian rhythms in adaptive immunity. Immunology 2020, 161: 268-277.
Crosstalk between circadian rhythms and the microbiota. Immunology 2020, 161: 278-290.

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Summary

We here introduce a Review Series focussing on the important influences circadian rhythms have on immune responses. The three reviews in this series, expertly curated by Rachel Edgar, discuss how the cyclic oscillations in our cellular clock affect the innate and adaptive immune response, and how interactions with the intestinal microbiota, themselves subject to daily oscillations, also influence immune responses. As we understand more about these mechanisms, by which chronobiology contributes to immunology, it is becoming increasingly clear that they have important functions in maintaining health, influence autoimmunity and may contribute to the effectiveness of vaccinations.

Time changes everything, not least the immune system. This is true not only over the life course, but also during each passing day. The fact that the immune system experiences rhythmic changes that occur over hourly, daily and longer periods has apparently been recognized for over a hundred years.[1] These rhythmic changes are associated with well-co-ordinated metabolic changes that affect many mammalian anatomical systems, influencing, for instance, pregnancy,[2] immune cell functions,[3] growth and responses to external stimuli. The daily, or circadian, rhythms are strongly influenced by exposure to a light/-dark cycle.[4] As a society, we are becoming increasingly concerned that disturbances to these rhythms, induced for example by night-time exposure to screens or by fluorescent lighting, may have a negative influence on our health.[5,6] Here, we present three reviews, commissioned by Rachel Edgar, focussing on the mechanisms by which circadian rhythms affect different aspects of the immune response. The first two articles address the influence of the circadian clock on innate immunity[7] and on the adaptive immune response.[8] The third addresses the complex interactions between mammalian circadian rhythms and the rhythms of the commensal intestinal microbiota.[9] Together, these reviews provide an important update and bring together some of the most important research in this field.

In the first of out reviews,[7] the authors describe the highly conserved molecular features that underpin the functioning of mammalian circadian clocks. They discuss how the circadian timing mechanisms in most cells are synchronized by a central pacemaker in the hypothalamus, and how clocks in individual tissues can also be influenced by local hormonal or metabolic signals. Importantly, because of the central role played by the clock in regulating cells' energy requirements, it modulates energy-dependent pathways as energetic requirements fluctuate through the day. These mechanisms regulate the highly energy-dependent inflammatory response, for instance, by tuning macrophages[10] and neutrophils to make optimal responses to pathogenic bacteria at specific times of day. This tuning of the inflammatory response is controlled, at least in part, through regulating the functions of glucocorticoid receptors. The authors argue therefore that an understanding of circadian rhythms is important for effective therapeutic modulation of inflammation.

Our second review focusses on the influences of the circadian clock on adaptive immune responses.[8] Here, the authors focus on how the intrinsic circadian machinery expressed in B cells and T cells can be directed by extrinsic rhythmic signals. They describe, for instance, how both human and mouse T cells extravasate from the circulation into tissues at specific times of day. They also describe how, in humanized mice carrying both human and murine T cells, the human and mouse cells display opposite rhythms, consistent with the contrasting nocturnal and diurnal habits of mice and humans. The discussion is extended to consider how the clock may influence B-cell- and T-cell-mediated pathologies and responses to pathogens, and how it may even affect the optimal timing

for delivery vaccinations. Here, it appears that vaccination of mice or humans during their more active phase, in the morning for most humans, might result in stronger vaccine responses. Again, they draw the clear conclusion that a better understanding of the effects of circadian rhythms may bring important clinical benefits. Simply put, immune modulatory treatments given at the optimal time of day are potentially more effective.

The third review in the series[9] examines the intriguing concept that, while light is the most important inducer of circadian rhythms, the intestinal microbiota may also contribute important influences. It is clear, for instance, that circadian oscillations occur in the interdependent intestinal microbial communities and that these have direct impacts on host metabolism and on the host immune system. It is also clear that there are two-way interactions between oscillations in microbial composition and the circadian rhythms of the host, with each influencing the other. In this review, the authors examine the potential mechanisms connecting these host and microbial interactions and suggest how they may be exploited therapeutically.

Together, these reviews examine how the fundamental cell biological mechanisms that have evolved to optimize energy expenditure through the day have been co-opted by the innate and adaptive immune systems to maximize our ability to provide protection from pathogens. The mechanisms controlling these circadian immune responses include bidirectional interactions with the intestinal microbiota and influence almost all aspects of protective and pathogenic immunity. As immunologists, we ignore the importance of circadian rhythms at our peril!

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