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INTRODUCTION

Chronoimmunology: from preclinical assessments to clinical applications

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The circadian clock is an endogenous timing program that structures physiology and behaviour to meet the predictable diurnal changes in environmental demands brought about by the Earth's rotation around its axis. Over the past three decades, the molecular mechanisms of circadian timekeeping have been discovered. A set of so-called core circadian clock genes and variants thereof have been identified in various model organisms and humans and the mechanistic principles of their interaction described. Synchronization between endogenous circadian rhythms and exogenous environmental cycles is increasingly recognized as a critical factor for health and well-being. Vice versa, circadian rhythm disruption has been associated with various diseases including psychiatric and neurodegenerative disorders, metabolic and cardiovascular disorders, and, importantly, immune system dysfunctions.

With this increasing knowledge on the biological mechanisms of circadian clocks and rhythms, a new field—circadian (or chrono-) medicine—is emerging that aims at uncovering the mechanisms linking circadian clock function and health [1]. Its final goal is the application of knowledge on clock function towards improving diagnosis, treatment, and prevention of diseases. More than 50 years ago, it was first reported that circulating lymphocyte counts oscillate in healthy humans in a time-of-day dependent manner and that endotoxin susceptibility of mice depends on the time of exposure [2, 3]. Since then, evidence from, both, observational and experimental studies is steadily accumulating on the vast impact of circadian clocks on all levels of immunity—from immune cell maturation and migration to cytokine secretion—and on the various ways in which immune parameters can feedback on clock function (reviewed [4]).

In this special issue of Seminars in Immunopathology, we have assembled contributions of leading researchers in the field of chronoimmunology. Not all details of clock-immune interaction could be covered; these would fill a book. However, here prioritize at reflecting the vast breadth of the field with this selection—from biological aspects of circadian immune regulation (e.g. Olejniczak et al. [5]) to their implications for everyday life (Walker et al. [6]) and clinical relevance (Zhuang et al. [7]).

Poole and Kitchen [8] summarize the evidence on circadian clock impact on innate immune cells which drive rhythmic immune functions—from the magnitude of inflammatory responses to the circulation of immune cells throughout the day.

Cermakian et al. [9] focus on the circadian regulation of the adaptive immune system and the responses of T cells to antigen presentation by dendritic cells, due to T cell-intrinsic mechanisms as well as cues from other tissues. In a complementary paper, Gray and Gibbs [10] describe how circadian clocks affect homeostatic aspects of adaptive immunity (such as lymphocyte trafficking and development of T lymphocyte subsets) as well as adaptive responses to acute challenges, again considering the interaction of the cellular clockwork machinery and extrinsic rhythmic signals. Here, it is particularly noteworthy that disruption of clock-adaptive immune interaction promotes the development of

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autoimmune diseases such as rheumatoid arthritis, ulcerative colitis and multiple sclerosis.

Zhuang et al. [7] summarize experimental and clinical evidence on the interplay between different viral pathogens and biological clocks. They outline how important circadian regulation of pharmacogenetics and dynamics is in this context and emphasise the continuous need for research in this area against the background of current pandemics.

Cox et al. [11] describe how circadian clocks link two major aspects of human physiology, energy metabolism and immune function. They outline how the circadian-metabolic axis may be a key factor in driving rhythms in immune function and how circadian disruption is associated with a range of chronic inflammatory diseases—from atherosclerosis to diabetes. Within the immune system, individual cell types carry out unique roles and, consequently, circadian immunometabolism effects are highly specific to each innate immune cell.

Lange et al. [12] emphasize the important role of sleep—as a major output of the circadian system—and sleep-associated parameters in the neuroendocrine regulation of rhythmic immune cell trafficking with a focus on human leukocyte subsets. Sleep has overall immune-supportive effects while integrin de-activation and redistribution of certain leukocytes to the bone marrow during daytime activity may critically adjust immune homeostasis.

Walker et al. [6] describe the effect of one of the most prevalent circadian disruptors, nocturnal light pollution (or artificial light at night— ALAN), on different aspects of immune function. ALAN alters clock gene expression and suppresses nocturnal secretion of melatonin by the pineal gland. This consequently affects inflammatory processes via the innate and adaptive immune systems in humans and various other species.

Finally, Olejniczak et al. [5] highlight the interaction of immunity with one major endocrine output of the circadian system, adrenal glucocorticoid (GC) hormones. GCs and their daily concentration rhythms prepare the immune system to face anticipated environmental threats. GC rhythm targets include immune cell migration through rhythmic expression of chemo-attractants and their receptors. On the other hand, chronotherapeutic approaches may exploit the circadian immunomodulation by GCs and their widespread role in other physiological functions such as metabolism.

Conclusions

Basic chronobiological research has firmly demonstrated the important role the circadian clock plays in immunology. On the other hand, circadian disruption may affect immune disorders, and, in turn, diseases lead to circadian disruption. Still, chrono-immunological knowledge is far from being integrated into routine medical practice [13]. The main reason for this may be that the mechanisms of circadian disruption and the mode of action of their therapies have not been sufficiently studied and validated. In particular, there is still a lack of knowledge about the overarching principles of circadian immune disruption, its diagnosis and prevention/therapy. Moreover—as is exemplified in the paper by Cox et al. in this issue—chronoimmunology is intimately linked to other targets of circadian regulation such as energy metabolism or endocrine function [11]. Thus, inter-disciplinary studies are needed to comprehensively understand the role of circadian clocks and rhythms in physiological homeostasis and to seize the full clinical potential of chronoimmunology and we envision that the present special issue will spark such studies.

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