Diurnal control of adaptive immune responses by adrenergic nerves

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A group of researchers led by **Kazuhiro Suzuki** (Associate Professor, WPI Immunology Frontier Research Center [IFReC], Osaka University) has revealed that neural inputs to β_2-adrenergic receptors (β_2ARs) expressed on lymphocytes generate the diurnal variation in the frequency of lymphocyte egress from lymph nodes, which is reflected in the magnitude of the adaptive immune response.

It has long been proposed that various aspects of immune responses are influenced by nervous system activity. However, the cellular and molecular basis for neural regulation of immunity are largely unclear. Adrenergic nerves constitute the efferent arc of the sympathetic nervous system and play important roles in coordinating organ functions through the release of a neurotransmitter, noradrenaline. Like other vital organs, lymphoid organs, including the bone marrow, thymus, spleen and lymph nodes (LNs), receive a rich supply of adrenergic nerves. We recently reported that inputs from adrenergic nerves control lymphocyte egress from LNs through β_2ARs. Activation of lymphocyte β_2ARs enhances the responsiveness of chemokine receptors that promote LN retention of lymphocytes, and consequently inhibits their LN egress (Nakai et al., *J. Exp. Med.* 2014). However, the physiological role of this mechanism in adaptive immune responses has been unclear.

The activity of adrenergic nerves displays a circadian rhythm that is synchronized with the rest-activity cycle of the species. The noradrenaline release from adrenergic nerves increases during the daytime in humans, whereas it reaches a peak at night in rodents. Indeed, we found that the noradrenaline content in LNs was elevated toward the night time in mice. Given this observation, we interrogated the physiological relevance of the β_2AR-mediated control of lymphocyte trafficking in relation to the circadian oscillation of adrenergic nerve activity. The night time surge of adrenergic nerve activity in LNs was accompanied by an increase of lymphocyte numbers in LNs and their reciprocal decrease in lymph and blood. Consistent with these observations, we found that lymphocyte egress from LNs was restricted during the night time in mice. The diurnal

variation of LN egress was dependent on neural inputs to lymphocyte β_2ARs.

Lymphocytes specific for a given antigen are very rare (estimated to be less than 10 cells per LN) and the population size dictates the magnitude of responses. Therefore, we hypothesized that the accumulation of lymphocytes in LNs during the period of high adrenergic nerve activity may increase the chance of antigen encounter and potentiate adaptive immune responses. We found in mice that immunization in the night time, when lymphocyte numbers in LNs were high, induced more robust humoral immune responses than immunization in the daytime. The diurnal variation of humoral immune responses was dependent on β_2AR-mediated neural signals and diminished by stopping lymphocyte circulation through LNs. These findings suggest that the β_2AR-mediated control of lymphocyte trafficking contributes to the daily fluctuation of adaptive immune responses (Figure).

Previous studies from other groups showed that the innate immune system is prepared to sense pathogens more efficiently during periods of activity. Our present study has demonstrated that the adaptive immune system is also poised to mount higher responses in LNs during the active phase. The synchronization of both arms of the immune system may have evolved to maximize the efficiency of host defense when encounters with pathogens are more likely to occur. The time-dependent differences in immune responses can be exploited in clinical settings, such that vaccination during the immunologically active phase might ensure potent protection against infectious diseases.

Abstract

Various aspects of the immune system display circadian rhythms. Although lymphocyte trafficking has been suggested to show diurnal variations, the mechanisms and influences on immune responses are unclear. Here, we show in mice that inputs from adrenergic nerves contribute to the diurnal variation of lymphocyte recirculation through lymph nodes (LNs), which is reflected in the magnitude of the adaptive immune response. Neural inputs to β_2-adrenergic receptors (β_2ARs) expressed on lymphocytes reduced the frequency of lymphocyte egress from LNs at night, which was accompanied by an increase of lymphocyte numbers in LNs. Immunization during the period of lymphocyte accumulation in LNs enhanced antibody

responses. The diurnal variation of the humoral immune response was dependent on β_2AR-mediated neural signals and diminished by stopping lymphocyte recirculation through LNs. This study reveals the physiological role of adrenergic control of lymphocyte trafficking in adaptive immunity and establishes a novel mechanism that generates diurnal rhythmicity in the immune system.

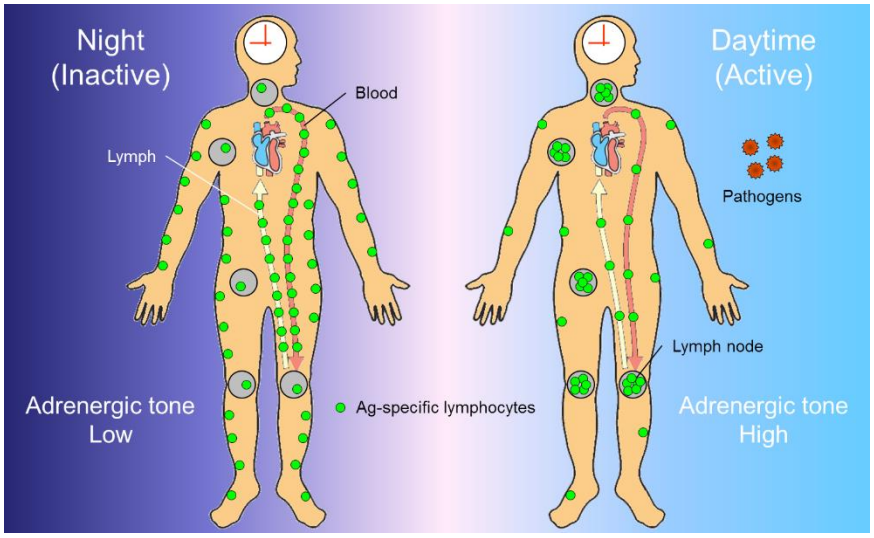

Figure. Adrenergic control of adaptive immunity by diurnal lymphocyte trafficking. During the period of high adrenergic nerve activity, lymphocyte egress from LNs is restricted, which leads to an increase of lymphocyte numbers in LNs. Immunization during the period of lymphocyte accumulation in LNs promote adaptive immune responses. This diurnal variation of lymphocyte trafficking may have evolved to maximize the efficiency of host defense against pathogens.