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It's all about rhythm: how the circadian cycle modulates long-term immunity

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Circadian rhythms can influence adaptive immune responses and vaccine efficacy, but mechanistic details are sparse. A new paper in *Nature Communications* shows that an immune challenge given during the daytime enhances immune responses compared to a night-time challenge because of rhythmic interactions of immune cells at various stages of the adaptive response.

The authors first investigated how circadian rhythm affects the initial stage (12-48hr) of the adaptive immune response. In mice, a daytime immune stimulus caused more dendritic cells to migrate from the skin to the lymph node than a night-time stimulus, and dendritic cells migrated faster during the day. In addition, the number of T cells in lymph nodes was higher during the day, and T-cell movement from blood to lymph nodes was controlled by the circadian expression of the homing molecule ICAM-1.

Mathematical modelling revealed that the presence of dendritic cells and T cells in the lymph node during the day increased the probability of immune interactions between antigen-presenting dendritic cells and antigen-recognizing T cells.

The circadian rhythm also affected the proliferation of T cells in the lymph nodes at a later stage of the adaptive immune response. One week after an immune stimulus, T cells proliferated more during the day than at night, and proliferating cells had higher expression of proteins involved in immune regulation. The temporal differences in T-cell proliferation and protein expression were not seen in mice lacking the circadian transcription factor *Bmal1* in T cells.

Notably, the timing of when the immune challenge was given also affected the later stages of the adaptive response. Mice vaccinated against hepatitis A virus during the day had more antibody-producing B cells at 14 days and more virus-specific antibodies at 28 days than mice vaccinated at night. Day-vaccinated mice also had a stronger virus-specific T-cell response at 28 days; this effect was not seen in mice lacking *Bmal1* in T cells.

Finally, by combining their experimental results with mathematical modelling, the researchers showed that, overall, the oscillating nature of one stage of the immune response (such as T-cell movement) feeds into and is necessary for the next stage (such as T-cell proliferation), which is also rhythmic. This mechanism enables the immune response to remain rhythmic for several weeks after an initial challenge. The authors note that their study provides "a strategy for using time-of-day to optimize vaccination regimes".

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