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Macrophage Circadian Rhythms are Differentially Affected Based on Stimuli

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Macrophages are white blood cells that play disparate roles in homeostasis and immune responses. They can reprogram their phenotypes to pro-inflammatory (M1) or anti-inflammatory (M2) states in response to their environment. About 8–15% of the macrophage transcriptome has circadian oscillations, including genes related to their functioning. As circadian rhythms are associated with cellular phenotypes, we hypothesized that polarization of macrophages to opposing subtypes might differently affect their circadian rhythms. We tracked circadian rhythms in RAW 264.7 macrophages using luminescent reporters. Cells were stably transfected with Bmal1:luc and Per2:luc reporters, representing positive and negative components of the molecular clock. Strength of rhythmicity, periods and amplitudes of time series were assessed using multiple approaches. M1 polarization decreased amplitudes and rhythmicities of Bmal1:luc and Per2:luc, but did not significantly affect periods, while M2 polarization increased periods but caused no substantial alterations to amplitudes or rhythmicity. As macrophage phenotypes are also altered in the presence of cancer cells, we tested circadian effects of conditioned media from mouse breast cancer cells. Media from highly aggressive 4T1 cells caused loss of rhythmicity, while media from less aggressive EMT6 cells yielded no changes. As macrophages play roles in tumors, and oncogenic features are associated with circadian rhythms, we tested whether conditioned media from macrophages could alter circadian rhythms of cancer cells. Conditioned media from RAW 264.7 cells resulted in lower rhythmicities and periods, but higher amplitudes in human osteosarcoma, U2OS-Per2:luc cells. Phenotypic changes in macrophages result in altered circadian characteristics and suggest that there is an association between circadian rhythms and macrophage polarization state. Additionally, our data demonstrate that macrophages treated with breast cancer-conditioned media have circadian phenotypes similar to those of the M1 subtype, and cancer cells treated with macrophage-conditioned media have circadian alterations, providing insight to another level of cross-talk between macrophages and cancer.

Biography

Michelle Farkas is interested in the generation and application of new tools and platforms for the study, imaging, and treatment of disease. Her research is focused on dynamic biological systems, including understanding the molecular clock and contributions of altered circadian rhythms to disease, and macrophage phenotypic interconversion. Prof. Farkas received her PhD from the California Institute of Technology (USA) in 2010, followed by postdoctoral training at the University of California, Berkeley (USA). In 2013, she began her independent career at University of Massachusetts Amherst. She has received multiple honors including most recently, a Maximizing Investigators' Research Award (MIRA) from the National Institutes of Health (2021), and was named a Scilog Fellow by the Research Corporation for Science Advancement (2020).