BREAST CANCER

More of a nightmare: metastasis accelerates during sleep

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Metastasis, the spread of cancer to secondary locations, is achieved via dissemination of circulating tumor cells (CTCs). However, the mechanisms dictating the generation of CTCs in breast cancer metastasis remain largely unknown. In a new study published in *Nature*, Diamantopoulou et al. show that breast cancer metastasis increases during sleep.

During a 24-hour period, multiple physiological changes take place in the body that follow circadian rhythms, including a sleep-wake cycle. Here, Diamantopoulou et al. analyzed blood samples from women with breast cancer at "rest" (night) and "active" (day) phases to compare CTC abundance and composition at different phases of the circadian rhythm, which revealed higher CTC release from the primary tumor at rest phase. By using mouse tumor cells transplantation in wild-type and in arrhythmic knockout mice, or xenografts, the researchers confirmed a peak of CTC release during the rest phase in mice.

Next, the researchers perturbed the circadian rhythms in mice by reversing the light/dark cycle to induce jet-lag and/or using melatonin, and analyzed the effects of these perturbations on the pattern of CTC release. They showed that jet-lag induction decreased circulating CTCs at rest phase, while melatonin had the opposite effect, further suggesting CTC production occurs mainly during sleep.

However, an increased CTCs number is not necessarily associated with increased metastasis ability. The investigators injected rest- and active-phase CTCs from different mouse models of breast cancer with different fluorescent tags in healthy mice at multiple phases of their circadian cycles. They revealed that injection of CTCs from the rest phase induced a higher metastatic burden than CTCs from the active phase, in particular after injection during rest phase.

Next, the investigators used single-cell RNA sequencing to compare gene expression between rest and active phase CTCs. Results showed an increased expression of genes associated with cell proliferation in rest-phase CTCs, while protein-synthesis genes were upregulated in active-phase CTCs. Finally, the investigators treated mice with circadian rhythm-related hormones, which affected the release of CTCs, suggesting that breast cancer cells are governed by oscillations in such hormones affecting metastasis dynamics.

Although future research is needed to evaluate whether such results could be obtained in other types of metastatic cancer, this work opens new avenues for cancer research, including the development of therapeutics that are more effective during sleep.

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