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The clock as a frenemy: the importance of the biological rhythms in cancer prognosis

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All body functions exhibit rhythmic behavior synchronized to the daily light-dark cycle. Disruption of our internal circadian clock can result in cancer. We show that disrupting the circadian rhythm increases tumor growth, interferes with the immune system and cell multiplication mechanisms.

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Have you ever wondered why we wake up in the morning? Or why we get hungry at noon? Most physiological processes oscillate with a period close to 24 hours, called circadian rhythms. These rhythms are controlled by a central clock in our brain, which acts as a pacemaker coordinating the circadian oscillations of peripheral clocks present throughout the body (for example in liver or spleen). Under normal conditions, central and peripheral clocks are well synchronized thanks to environmental daily light-dark cycle, which facilitate the proper functioning of our body.

What happens when our daily activities are not correctly coupled with the light-dark cycle? Shifting the activity period to an atypical time of the day causes a temporal misalignment that, over time, may result in an increased risk of diseases such as cardiometabolic syndrome, obesity and cancer. These is sometimes observed in people who work in nocturnal shifts or who travel frequently through different time zones (and thus suffer from jet-lag). The World Health Organization recognizes shift-work as a risk factor for cancer, making it clear that it is essential we understand how our internal clock and cancer are linked.

We investigated the effects of disrupting the circadian rhythm in mice, focusing on a type of cancer called murine melanoma. Considering that a normal light-dark schedule consists of 12 hours of light followed by 12 hours of darkness, we applied a disrupting schedule simulating chronic jet-lag by advancing the light-dark cycle by 6 hours every two

days. After three weeks of chronic jet-lag, we injected mice with tumor cells, and measured tumor size over time. We found that tumors were detectable earlier and grew faster in animals exposed to chronic jet-lag. These findings made us wonder who's the bad guy in this story. Well, let's introduce our main suspects.

First of all, we focused on the immune system, asking whether chronic jet-lag results in immune changes, facilitating tumor growth. We turned our attention to macrophages, important cells of the immune system. There are two types of macrophages: the M1 macrophages help our body to eliminate the tumor cells, whereas the M2 allow the tumor to avoid the immune system. Thus, the balance between M1 and M2 cells is certainly relevant for cancer prognosis. In a typical movie by Martin Scorsese, M1 macrophages would be the good cops, while the M2 would be the crooked ones doing an inside work for the mob, played by the tumor cells.

We found that under normal light-dark conditions, there is a daily pattern in M1 and M2 levels infiltrating the tumor tissue. M1 were predominant during the night, while M2 levels increased during the day. Since these cells have opposite functions and can inhibit one another, the M1/M2 ratio affects tumor growth. In general, tumors were more suppressed during the night, and more likely to grow during the day. Similar results were observed in spleen, an immune-related tissue. Interestingly, the chronic jet-lag schedule disrupted the daily balance between M1 and M2 macrophages, resulting in a tumor-prone phenotype for the whole day.

But there's even more! Disrupting the circadian rhythm also deregulates the cell division mechanisms both in the tumor and in the liver contributing to a faster tumor growth. Additionally, during chronic jet-lag normal rhythms were lost in the liver. Going back to the Scorsese example, it seems that disrupting the circadian rhythm has two crucial effects: it leads to more crooked cops (M2) being present at the crime scene, hindering the case and facilitating the tumor's escape, and it deregulates the cell division mechanism helping tumors to grow even faster.

Do we have a happy ending? Not yet, but understanding how this criminal organization works gives us more tools to stop them. These results support the relevance of studying the role of circadian rhythm in the development of cancer. We showed that circadian deregulation facilitates cancer progression. Moreover, since healthy mice also exhibited the same changes induced by chronic jet-lag , it may be linked with the generation of new tumors. In addition, immunotherapies are today an important tool to treat cancer, applying them at specific times of day in order could improve available therapeutic strategies.