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Nocturnal circulating tumor cells: The ultimate selective filter in cancer progression?

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The survival duration of circulating tumor cells (CTCs) in the vasculature is a critical parameter in the establishment of the metastatic cascade. Diamantopoulou and colleagues demonstrate that the metastatic capacity of CTCs is strongly influenced by circadian rhythms, suggesting a rationale for the time-controlled interrogation and treatment of metastatic cancers.

Cancer growth is initiated by genetic and epigenetic alterations that lead to local uncontrolled expansion of cells that thrive in specific microenvironments (e.g., chronic inflammation). Once the malignant cells spread through the body, i.e., the metastatic cascade, cancer progressively becomes a systemic and ultimately lethal disease. Metastasis formation is the main cause of cancer-related death in patients with solid tumors. At the beginning of this process, cancer cells escape from the primary tumor to the vascular system, where they become circulating tumor cells (CTCs). Only a small subgroup of CTCs will survive during the harsh journey in the blood and colonize distant sites.¹ The most critical parameter governing the formation of clinical metastases (i.e., the key step of the metastatic cascade) is the survival duration of CTCs,² and thus therapies reducing the survival of CTCs in the vascular system could significantly reduce the risk of metastasis.

Using evolutionary ecology reasoning, Cortés-Hernández et al. predicted that malignant cells, including CTCs, should behave differently between day and night.³ Following the recent work of Diamantopoulou et al.,⁴ this is now a proven fact for CTCs, and this discovery

will undoubtedly have major medical implications. Would this suggest that we have so far missed a major adaptive feature of the metastatic process?

The main findings by Diamantopoulou et al.⁴ include the following: (1) a correlation between the circadian rhythm and CTC intravasation. Diamantopoulou and colleagues identified a striking and unexpected pattern of CTC-generation dynamics in both patients with breast cancer ($n = 30$; 21 patients were diagnosed with early breast cancer—no metastasis—and 9 were diagnosed with stage IV metastatic disease) as well as in four different mouse models. Their results showed that CTCs are not shed continuously during tumor progression, but the greatest release and intravasation of single and clustered CTCs occurs during sleep (4:00 a.m.). Diamantopoulou et al. also discovered (2) a metastatic ability of CTCs during sleep. CTCs isolated during the rest phase (4:00 a.m.) are highly prone to metastasize, whereas CTCs generated during the active phase are devoid of metastatic ability. Indeed, when isolated during the night and compared with those isolated during the day, CTC clusters and CTC–white blood cell clusters seem to have greater metastasis-forming properties than those of single CTCs. This observation suggests that most of the

rest-phase-dependent metastatic spread of breast cancer could be ascribed to both homotypic and heterotypic CTC clusters. Another discovery is (3) a time-dependent gene expression in CTCs. A marked upregulation of mitotic genes exclusively during the rest phase (4:00 a.m.) in both patients and mouse models seems to enable metastasis proficiency. Molecular gene expression analysis of CTCs from patients and mouse models isolated during the rest and active phases highlights very distinct gene-expression patterns. During sleep (4:00 a.m.), gene expression is dominated by cell division and mitosis, whereas during the active phase (10:00 a.m.), there is high ribosome-biogenesis activity. This oscillatory proliferation timing is observed not only in CTCs, but also in the primary tumor, suggesting this as a general phenomenon occurring in breast cancer cells during disease progression. Lastly, Diamantopoulou et al. found (4) regulators of CTC intravasation. Proliferation and intravasation of breast cancer cells seem to be dictated by daily oscillations in key circadian-rhythm-regulated hormones, such as melatonin, testosterone, and glucocorticoids, whose action influences breast cancer metastasis dynamics.

The authors concluded that the spontaneous generation of CTCs with high metastatic capacity does not occur continuously but rather is concentrated during the night, providing a new rationale for time-controlled interrogation and treatment of metastatic cancers. The CTC dynamic between day and night may

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change how clinicians will treat cancer patients in the future. However, the study by Diamantopoulou et al. used *in vivo* models and a relatively low number ($n = 30$) of breast cancer patients. Thus, further analyses and validations in a larger cohort of patients with breast cancer will be required prior to the introduction of nocturnal liquid biopsy in clinical practice. It will be of utmost interest to assess whether nocturnal CTCs also play a key role in other solid cancers (e.g., colon, prostate, and lung cancers as well as melanoma) to confirm whether the observed patterns are specific to breast cancer or a common hallmark of solid cancers. In this aspect, the European Liquid Biopsy Society (ELBS, www.elbs.eu) will help to answer these important questions for the future of liquid biopsy and precision medicine for cancer patients.⁵

Here, we also argue that the complex links evidenced by Diamantopoulou et al. between malignant cells and circadian rhythm provide an additional reason to adopt a Darwinian approach in cancer research. The biology of most, if not all, living things is regulated by biological rhythms, in particular the circadian rhythm, from whole organisms to their constituent cells, their microbiota, and parasites. Given their parasitic lifestyle, malignant cells are also influenced by the circadian rhythm for many reasons.³ However, an important difference between parasitic organisms *sensu lato* and cancer cells is that, in the majority of cases, the latter are not transmitted between hosts. Even if cancer is an ancient disease that appeared at the dawn of multicellularity a billion years ago, each cancer must "reinvent the wheel" because the evolved adaptations selected during tumorigenesis disappear when their host dies. Thus, malignant cells are only under selective pressure for a few years at most, and sophisticated adaptive responses, as seen in organisms exposed to natural selection over evolutionary times, are unlikely to exist. Neverthe-

less, due to the extreme diversity of cells typically observed in tumors, natural selection acting on cells and/or groups of cells⁶ may also promote the emergence of clones that exhibit, for each stage of tumorigenesis, the best characteristics for a malignant lifestyle given the tissue in which they proliferate, thus allowing the tumor to continue its progression to the metastatic stage.⁷

The above evolutionary considerations suggest that, of the likely wide variety of tumors capable of releasing CTCs, only those with the characteristics found by Diamantopoulou et al. will be able to metastasize efficiently. Only in these "successful" tumors can adaptations related to the host circadian rhythm be detected. In other words, many CTC-producing neoplasms in the bodies of multicellular organisms lack the conditions required to produce metastasis. Diamantopoulou et al. have identified a novel selective filter in tumorigenesis, maybe the last one, and this is undoubtedly a major discovery.

These findings open the door to explore different research directions, as it is crucial to determine if, when, and how malignant cells acquire adaptive features that allow metastasis. Because many non-genetic variables are involved during tumorigenesis, it seems crucial to determine whether the exploitation of circadian rhythms in malignant cells is due to phenotypic plasticity or the result of genetic adaptation. Another promising direction arising from the work of Diamantopoulou et al. is the hypothesis that some tumors, instead of releasing CTCs primarily at night, are selected to manipulate the circadian rhythms of their hosts, as parasitic organisms sometimes do.³ Sleep disturbances are common in people affected by cancer, and for reasons that are so far unclear, many cancer patients often exhibit reduced distinction between daytime and nighttime activities.^{8,9} Sleep disturbances have a variety of causes, but clearly one that has so far been little explored is a direct tumor

effect on sleep cycles; for instance, through the secretion of cytokines that modulate the sleep/wake cycle. Because sleep alterations are nonspecific symptoms, however, it must be rigorously determined whether cancer cells are directly promoted by selection to disrupt sleep and/or whether this is simply a pathological side effect with incidental positive consequences for carcinogenesis. We believe that exploring the proximal mechanisms used by parasitic organisms that manipulate their host's circadian rhythm is promising, as cancer cell strategies may rely on similar biochemical precursors. In this context, it would be promising to test whether therapies that target manipulative activities in parasites could be equally effective in preventing tumors from metastasizing. Finally, given the wide diversity of mammalian species that develop metastatic cancers, which are monitored by veterinarians in zoos,¹⁰ an original direction would be to explore the behavior and activity of CTCs in nocturnal species, predicting that an opposite pattern should be observed compared to diurnal species. Similarly, knowing that large, long-lived animals nonintuitively do not have more cancers than other species (a phenomenon called Peto's paradox¹⁰), the results of Diamantopoulou et al. are an invitation to explore nocturnal anti-cancer defense in these species.

In conclusion, the fascinating discovery by Diamantopoulou et al. opened the door for further research including interdisciplinary approaches that consider different types of cancer not only in humans, but also in other species with varied cancer susceptibility. Such approaches would be needed to identify the typical time when organisms are most at risk of invasive cancer cells to emerge. Once these general patterns are identified, new preventive strategies can be developed.

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DECLARATION OF INTERESTS

C.A.-P. has received honoraria from Menarini and patent applications related to CTC technologies.

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