Tumour biology

Time of day shapes success of a cancer treatment

Christian H. Gabriel & Achim Kramer

Daily rhythms affect many aspects of mammalian biology. A discovery in mice that the activity of a key type of immune cell is shaped by such rhythms might have implications for clinical efforts to tackle cancer. See p.136

When is the best time of day to fight cancer? Cancer cells can arise in our bodies at any time, but, fortunately, they are almost always recognized and eliminated by the immune system[1]. Therefore, engaging these defences is an important strategy in many promising new cancer immunotherapy approaches. Wang *et al.*[2] show on page 136 that the ability of immune cells to recognize cancer cells and promote their removal is dependent on the body's internal clock, a finding that might be exploited to improve the effectiveness of cancer treatments.

Most of our body's cells track the time of day by means of a molecular clock, to prepare them for the challenges that recur every 24 hours. Liver cells, for example, routinely produce digestive enzymes before you make your breakfast, so that these enzymes are available exactly when needed[3]. These daily (circadian) clocks produce 24-hour rhythms that underpin countless physiological processes, including blood pressure, body temperature, hormone levels and gene activity.

The immune system also exhibits daily rhythms, for example in the distribution of immune cells between the bloodstream and the lymph nodes — the sites where these cells are primed to combat disease-causing agents or cancer[4]. Evidence is accumulating that, as a result of these rhythms, the time of day of an immune treatment can influence the therapeutic outcome[5]. However, this factor is rarely taken into account in animal or clinical studies.

Wang and colleagues show that overlooking this could be a missed opportunity. When the authors injected cancer cells into healthy mice, the tumours grew faster when injected during the animals' active phase than during their rest phase. However, this timing-dependent difference was not seen in immunocompromised mice, prompting the authors to investigate the contribution of immune cells in more detail. They found that the slower-growing tumours harboured more of a type of immune cell called a cytotoxic T cell, which can kill cells identified as foreign or malignant, than did the faster-growing tumours.

How does the time of day of cancer-cell injection affect the number of cytotoxic T cells present a few days later? The authors took a closer look at another type of immune cell, dendritic cells (DCs), which are crucial for the initiation of a response by T cells. DCs ingest components of disease-causing agents or cancer cells and present protein fragments of these components, called antigens, to T cells at specially equipped sites in the body's lymph nodes. When a cytotoxic T cell recognizes antigens there, it can become activated and gains the ability to destroy any cell that carries a matching antigen on its surface.

The authors report that, compared with when injections were given during the active phase, when tumour cells were injected during the animals' rest phase, not only were there more DCs at the injection site shortly afterwards, but also these extra DCs were more 'alert'; that is, they expressed more of the protein CD80, a surface molecule needed for efficient activation of T cells. This time-of-day variation in the readiness of DCs to produce CD80 and initiate anticancer activity is regulated by the circadian clock. In mice in which the molecular clock was disrupted specifically in DCs, tumour growth was no longer influenced by injection time.

It therefore seems that the circadian clock of immune cells makes these cells more likely to respond to cancer cells if they first encounter them in the rest phase than in the active phase. This led the authors to speculate that the effectiveness of antitumour vaccines could also be increased by an application adapted to the time of day. Unlike conventional vaccines, which contain particular viral or bacterial antigens that are not tailored to the individual recipient to elicit an immune response, tumour vaccines usually contain components specific to the individual's cancer cells and are designed to stimulate immune cells to attack the malignant tissue. Indeed, when the authors treated mice with a tumour-specific vaccine several days after tumour injection, the tumours grew more slowly if the mice were vaccinated during

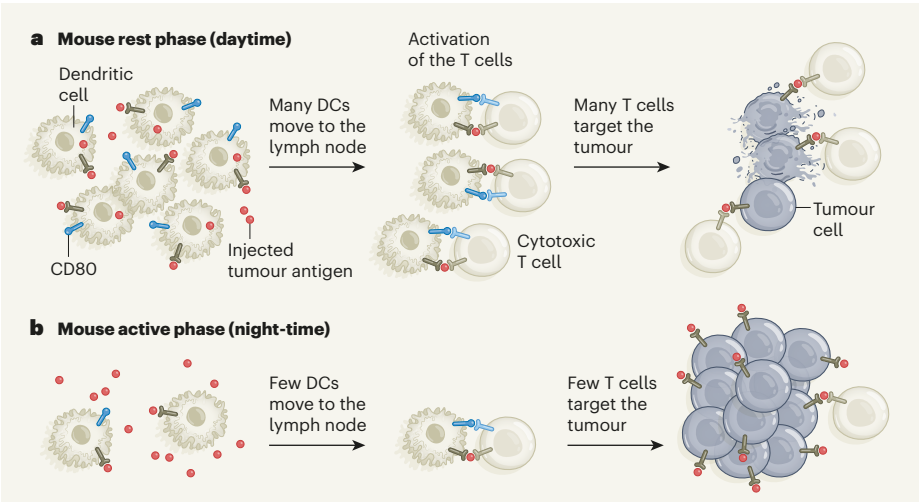

Figure 1 | Effect of treatment timing on anticancer vaccination. Wang *et al.*[2] studied mice that had been injected with tumour cells and subsequently received an injection of a protein component, called an antigen, specific to the tumour cells. The antigens can help to activate immune cells that target the cancer through an interaction mediated by antigen-presenting molecules (dark brown) and a receptor (light brown) on the immune cell. **a**, Treatment was most successful when vaccination was given during the daytime, the animals' rest phase. In this context, high numbers of immune cells called dendritic cells (DCs) were at the injection site to take up the antigen. These DCs expressed the protein CD80, which can bind to a receptor (light blue) that activates other immune cells. High numbers of DCs moved to the lymph node, where they could activate immune cells called cytotoxic T cells that then recognized and destroyed tumour cells. **b**, By contrast, vaccination during the animals' active phase (night-time) was associated with fewer DCs and less CD80 production, resulting in less activation of T cells and poorer limitation of tumour growth. Mice are nocturnal animals and humans rest at night, so the best time for antitumour vaccination in humans remains to be explored.

From the archive

Support from America for natural selection, and the search for a suitable standard.

100 years ago

I note with interest, perhaps I might say amusement, the statement by Mr. Cunningham that Natural Selection is "as extinct as the dodo." It may be in the land of its birth, but it is still very much in evidence in America. Nearly every systematic zoologist whom I know personally believes in it as a factor in evolution ... Prof. E. G. Conklin of Princeton, certainly one of our foremost zoological thinkers, has just completed a course of Lowell Institute lectures in Boston on "The Revolt against Darwinism," in which he has most clearly and emphatically stated his strong conviction, not only that such revolt is unjustifiable, but that Natural Selection is the most important theory that has yet been proposed for helping us to understand adaptation. It surely seems a little rash to call Natural Selection, or anything else, "extinct" because it has disappeared from one's own horizon. Horizons contract with increasing near-sightedness.

From *Nature* 3 February 1923

150 years ago

The material for constructing ... new Standards, for which an alloy of pure platinum with 10 per cent. of iridium has been selected, is obviously a matter of primary importance. Before determining upon this metallic alloy, a series of experiments was made ... A material was needed ... that should as far as possible be unalterable in its composition and molecular structure, in its form and dimensions, from the ordinary action of air, water, fire, or other chemical agents, or from mechanical forces to which it might be subject; that would in fact possess physical properties rendering it invariable with time ... [P]latinum, which was the best pure metal for the purpose, has the disadvantage of being too soft and too weak for a measuring bar. Combined, however, with a proper proportion of iridium, platinum satisfied all the conditions required either for a Standard metre or kilogramme.

From *Nature* 30 January 1873

their rest phase than during their active phase (Fig. 1).

Does this principle apply to humans? Perhaps. The authors observed that human DCs, like their mouse counterparts, display time-of-day-dependent properties, both in CD80 production and in their activation of tumour-specific cytotoxic T cells. However, one difference between humans and mice is that humans are active during the day, whereas mice are active at night.

This raises the question of when might be the right time to vaccinate humans — during our rest phase at night or during our active phase, when mice are normally resting? The authors retrospectively analysed data from a clinical anticancer vaccination trial of ten people with a skin cancer called melanoma, and found an advantage of morning over afternoon vaccination (vaccination at night was not performed in that trial).

Anticancer vaccines in humans are designed to stimulate the immune system to attack tumours that have been developing for months or years. Such tumours are usually not new threats to the body's defences, and have often acquired mechanisms to escape targeting by the immune system[1,6]. Therefore, it will be important to assess whether a favourable time-of-day-dependent effect of vaccination obtained against newly injected tumour cells would also apply to a vaccination aimed at mature and immune-experienced tumours.

Nevertheless, the authors' study adds to a growing body of evidence indicating that the timing of treatment can influence the outcome of therapeutic approaches, as has been suggested for conventional vaccination[7] and cancer immunotherapy using drugs called checkpoint inhibitors[5]. Including treatment timing as a variable in future clinical trials of cancer vaccines might therefore have the potential to improve patient outcomes. In addition, there is a plethora of other circadian-controlled processes waiting to be exploited in the realm of circadian medicine[8]. Clever timing of interventions, such as administering a treatment when it has the strongest effect and the fewest side effects, might improve the effectiveness and safety of already available therapies for a variety of diseases. We should not miss this opportunity.

Christian H. Gabriel and **Achim Kramer** are at Charité – Universitätsmedizin Berlin, Institute of Medical Immunology, 10117 Berlin, Germany.
e-mails: christian.gabriel@charite.de; achim.kramer@charite.de

1. Shankaran, V. et al. *Nature* **410**, 1107–1111 (2001).
2. Wang, C. *et al. Nature* **614**, 136–143 (2023).
3. Robles, M. S., Cox, J. & Mann, M. *PLoS Genet.* **10**, e1004047 (2014).
4. Pick, R., He, W., Chen, C.-S. & Scheiermann, C. *Trends Immunol.* **40**, 524–537 (2019).
5. Qian, D. C. *et al. Lancet Oncol.* **22**, 1777–1786 (2021).
6. Beatty, G. L. & Gladney, W. L. *Clin. Cancer Res.* **21**, 687–692 (2015).
7. Long, J. E. *et al. Vaccine* **34**, 2679–2685 (2016).
8. Kramer, A. *et al. PLoS Biol.* **20**, e3001567 (2022).

The authors declare no competing interests.
This article was published online on 17 January 2023.

Metabolism

Lack of serine causes complications in diabetes

Thorsten Hornemann

Impaired sensory-nerve function is a common complication of diabetes. Evidence in mice indicates that deficiency of the amino acid serine causes these complications — and suggests that supplements could help to treat them. **See p.118**

One of the most common complications of type 2 diabetes is diabetic polyneuropathy (DPN), in which impaired nerve function causes a range of symptoms, including pain and numbness. DPN can lead to skin ulcers and difficulties in wound healing[1] and is a leading cause of limb amputations[2]. There is currently no way to treat the underlying causes of DPN — a mechanism-based therapy is therefore in high demand. On page 118, Handzlik *et al.*[3] demonstrate that changes in the levels of the amino acid serine can impair nerve function, and suggest that the pathway altered could be targeted therapeutically.

DPN is associated with changes in how neurons and neuron-insulating Schwann cells generate energy from glucose and fatty acids. Diabetes causes increases in the levels of these two substrates, which have been proposed to affect neurons detrimentally in several ways. First, high levels of the substrates saturate the pathway that metabolizes fatty acids, leading