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TUMORS MIGHT GROW FASTER AT NIGHT

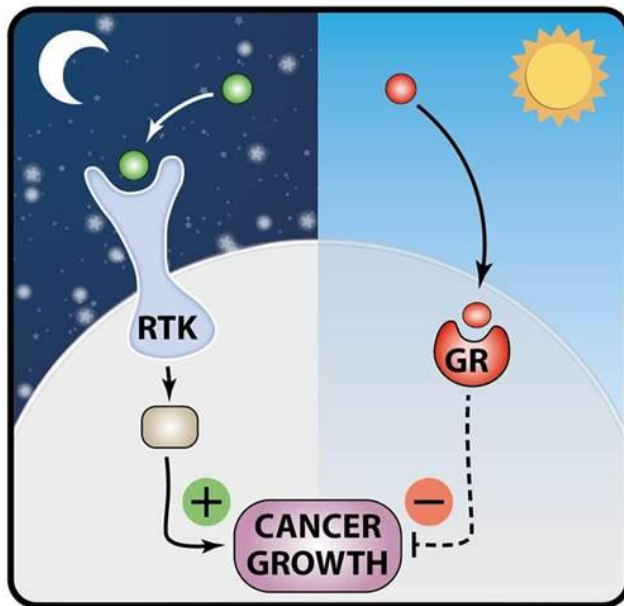
Weizmann Institute scientists reveal that a hormone that keeps us alert also suppresses the spread of cancer

REHOVOT, ISRAEL—October 6, 2014—They emerge at night, while we sleep unaware, growing and spreading out as quickly as they can. And they are deadly. In a surprise finding that was recently published in *Nature Communications*, Weizmann Institute of Science researchers showed that nighttime is the right time for cancer to grow and spread in the body. Their findings suggest that administering certain treatments in time with the body's day-night cycle could boost their efficiency.

This finding arose out of an investigation into the relationships between different receptors in the cell – a complex network that we still do not completely understand. The receptors – protein molecules on the cell's surface or within cells – take in biochemical messages secreted by other cells and pass them on into the cell's interior. The scientists, led by Dr. Mattia Lauriola, a postdoctoral fellow in the research group of Prof. Yosef Yarden of Weizmann's Department of Biological Regulation, working with Prof. Eytan Domany of the Department of Physics of Complex Systems, focused on two particular receptors. The first, the epidermal growth factor receptor (EGFR), promotes the growth and migration of cells, including cancer cells. The second binds to a steroid hormone called a glucocorticoid (GC). The GC plays a role in maintaining the body's energy levels during the day, as well as the metabolic exchange of materials. It is often called the stress hormone because its levels rise in stressful situations, rapidly bringing the body to a state of full alert.

With its multiple receptors, the cell receives all sorts of messages at once, and some of these messages can take precedence over others. Dr. Lauriola and Prof. Yarden found that cell migration – the activity promoted by the EGFR – is suppressed when the GC receptor is bound to its steroid messenger.

Since the steroid levels peak during waking hours and drop off during sleep, the scientists asked how this might affect EGFR. Checking the levels of this activity in mice, they found that there was a significant difference: This receptor is much more active during sleep and quiescent during waking hours.



How relevant are these findings for cancers, particularly those which use EGFRs to grow and spread? To find out, the scientists gave Lapatinib – one of the new generation of cancer drugs – to mouse models of cancer. This drug, used to treat breast cancer, is designed to inhibit EGFR, and thus to prevent the growth and migration of the cancer cells. In the experiment, they gave the mice the drug at

different times of day. The results revealed significant differences between the sizes of tumors in the groups of mice, depending on whether they had been given the drug during sleep or waking hours. The experimental findings suggest that it is indeed the rise and fall in the levels of the GC steroids over the course of 24 hours that hinder or enable the growth of the cancer.

The conclusion, say the scientists, is that it could be more efficient to administer certain anticancer drugs at night.

“It seems to be an issue of timing,” says Prof. Yarden. “Cancer treatments are often administered in the daytime, just when the patient’s body is suppressing the spread of the cancer on its own. What we propose is not a new treatment, but rather a new treatment schedule for some of the current drugs.”

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Prof. Eytan Domany's research is supported by the Leir Charitable Foundations; Mordechai Segal, Israel; and the Louis and Fannie Tolz Collaborative Research Project. Prof. Domany is the incumbent of the Henry J. Leir Professorial Chair.

Prof. Yosef Yarden's research is supported by the Dr. Miriam and Sheldon G. Adelson Medical Research Foundation; the Maurice and Vivienne Wohl Biology Endowment; the Louis and Fannie Tolz Collaborative Research Project; the European Research Council; and the Marvin Tanner Laboratory for Research on Cancer. Prof. Yarden is the incumbent of the Harold and Zelda Goldenberg Professorial Chair in Molecular Cell Biology.

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