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8 hours of resistance: Why do cancer cells easily give in to the temptation to divide?

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Temptations to exceed the speed limit are always plentiful, but only reckless drivers give in to such impulses. Likewise, numerous growth factors always abound in our bodies, but only cancerous cells are quickly "tempted" by these chemicals to divide again and again. Healthy cells, in contrast, divide only after being exposed to growth factors for eight continuous hours. What happens during these eight hours in a healthy cell that resists the call to divide? And even more important, what fails to work properly in the cancerous cell during these same hours? Why do cancerous cells give in so easily to the influence of growth factors, dividing so readily?

Answers to these questions have emerged from a study by a multidisciplinary team of Weizmann Institute researchers published recently in *Molecular Cell*. The scientists found that when a cell first receives a signal from a growth factor, ten groups of genes, about 8,000 in total, become activated. Of these, one group, consisting of about ten genes governed by the tumor suppressor p53, is the most crucial: These genes prevent the cell from dividing. Only if the growth factor continues to affect the cell for eight hours does p53 release its grip on the cell's DNA, allowing it to divide. Like a careful driver who puts the brakes on before proceeding, the activation of p53 at the time the cell receives a growth factor signal serves as a "brake," preventing instant division. In this manner, the healthy cell ensures that it will not divide as a result of accidental, mistaken or otherwise superfluous growth signals, but only if the signal is continuous and necessary. In cancerous cells, this mechanism malfunctions because in most of them, p53 is defective or

missing altogether, so that even a fleeting growth signal can cause them to divide, leading to cancerous growth.

This interdisciplinary study has resulted from a collaboration between three research teams at the Weizmann Institute, headed by Prof. Yosef Yarden of the Biological Regulation Department, Prof. Eytan Domany of the Physics of Complex Systems Department and Prof. Moshe Oren of the Molecular Cell Biology Department. The study was coordinated by former graduate student Dr. Yaara Zwang; taking part were Aldema Sas-Chen, Yotam Drier, Dr. Tal Shay, Roi Avraham, Dr. Mattia Lauriola, Efrat Shema and Efrat Lidor-Nili. Also taking part were clinical researchers: Dr. Jasmine Jacob-Hirsch, Dr. Ninette Amariglio and Prof. Gideon Rechavi of the Chaim Sheba Medical Center and Drs. Yiilng Lu and Gordon B. Mills of the M.D. Anderson Cancer Center at the University of Texas.

This research sheds new light on the differences between healthy and cancerous cells. It might help develop new effective approaches to chemotherapy. Cancerous tumors sometimes develop resistance to the therapy, among other reasons because it stresses the body. The stress, in turn, leads to the production of growth factors that cause cells to divide, so that the treatment ultimately defeats itself. A better understanding of how growth factors work can help identify intervals for chemotherapy that will prevent the increased division of cancerous cells.

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