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**CONTACT:** Yivsam Azgad, Tel: 972-8-934-3856/2  
**EMAIL:** [Yivsam.azgad@weizmann.ac.il](mailto:Yivsam.azgad@weizmann.ac.il) / [news@weizmann.ac.il](mailto:news@weizmann.ac.il)

## **WEIZMANN INSTITUTE SCIENTISTS DISCOVER:**

### **A CONTROL MECHANISM FOR METASTASIS**

Metastasis – when cancer cells dissociate from the original tumor and migrate via the blood stream to colonize distant organs – is the main cause of cancer death. A team of scientists at the Weizmann Institute of Science has now revealed new details about the mechanisms controlling metastasis of breast cancer cells. Their findings, published recently online in *Nature Cell Biology*, add significantly to the understanding of metastasis and may aid, in the future, in the development of anti-cancer drugs.

For a cell such as a cancer cell to migrate, it first must detach itself from neighboring cells and the intercellular material to which it is anchored. Before it can do this, it receives an order from outside the cell saying: “prepare to move.” This signal takes the form of a substance called a growth factor, which, in addition to controlling movement, can activate a number of processes in the cell including division and differentiation. The growth factor attaches to a receptor on the cell wall, initiating a sequence of changes in the cellular structure. The cell’s internal skeleton – an assembly of densely-packed protein fibers – comes apart and the protein fibers then form thin threads on the outside of the cell membrane that push the cell away from its neighbors. In addition, a number of protein levels change: some get produced in higher quantities and some in less.

To understand which proteins are modulated by the growth factor and the nature of the genetic mechanisms involved in cancer cell migration, a team of researchers pooled their knowledge and resources. This team, headed by Prof. Yosef Yarden of the Weizmann Institute’s Biological Regulation Department and his research group, including Drs. Menachem Katz, Ido Amit and Ami Citri; Tal Shay, a student in the group of Prof. Eytan Domany of the Physics of Complex Systems Department; and Prof. Gideon Rechavi of the Chaim Sheba Medial Center at Tel Hashomer.

To begin with, the team mapped all of the genetic changes that take place in the cell after the growth factor signal is received. As they sifted through the enormous amount of data they received, including details on every protein level that went up or down, one family of proteins stood out. Tensins, as they’re called, are proteins that stabilize the cell structure. But to the scientists’ surprise, the amounts of one family member rose dramatically while, at the same time, the levels of another dropped.

Despite the familial similarity, the team found a significant difference between them. The protein that drops off has two arms: One arm attaches to the protein fibers forming the skeleton, and the other anchors itself to the cell membrane. This action is what stabilizes the cell’s structure. The protein that increases, on the other hand, is made up of one short arm that only attaches to the anchor point on

the cell membrane. Rather than structural support, this protein acts as a kind of plug, blocking the anchor point, and allowing the skeletal protein fibers to unravel into the threads that push the cells apart. The cell is then free to move, and, if it's a cancer cell, to metastasize to a new site in the body.

In experiments with genetically engineered cells, the scientists showed that the growth factor directly influences levels of both proteins, and that these, in turn, control the cells' ability to migrate. Blocking production of the short tensin protein kept cells in their place, while overproduction of this protein plug increased their migration.

Next, the scientists carried out tests on tumor samples taken from around 300 patients with inflammatory breast cancer, a rare but swift and deadly form of the disease, which is associated with elevated growth factor levels. The scientists found a strong correlation between high growth factor activity and levels of the "plug" protein. High levels of this protein, in turn, were associated with cancer metastasis to the lymph nodes – the first station of migrating cancer cells as they spread to other parts of the body.

In another experiment, the scientists examined the effects of drugs that block the growth factor receptors on the cell walls. In patients who received these drugs, the harmful "plug" proteins had disappeared from the cancer cells. Prof. Yarden: "The mechanism we identified is clinically important. It can predict the development of metastasis and possibly how the cancer will respond to treatment." This discovery may, in the future, aid in the development of drugs to prevent or reduce the production of the unwanted protein, and thus prevent metastasis in breast or other cancers.

*Also participating in this research were Sara Lavi, Nir Ben-Chetrit, Gabi Tarcic, Dr. Moshit Lindzen, and Roi Avraham from Yarden's group; Tal Sahy from Domany's group, Dr. Ninette Amariglio and Dr. Jasmine Jacob-Hirsch from Rechavi's group at Sheba Medical Center, a research team from the Institute of Molecular Pathology and Immunology and the Medical Faculty at Porto University, Portugal; and researchers from the University of California at Davis, Boston University and GlaxoSmithKline, North Carolina.*

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The Weizmann Institute of Science in Rehovot, Israel, is one of the world's top-ranking multidisciplinary research institutions. Noted for its wide-ranging exploration of the natural and exact sciences, the Institute is home to 2,600 scientists, students, technicians and supporting staff. Institute research efforts include the search for new ways of fighting disease and hunger, examining leading questions in mathematics and computer science, probing the physics of matter and the universe, creating novel materials and developing new strategies for protecting the environment.

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