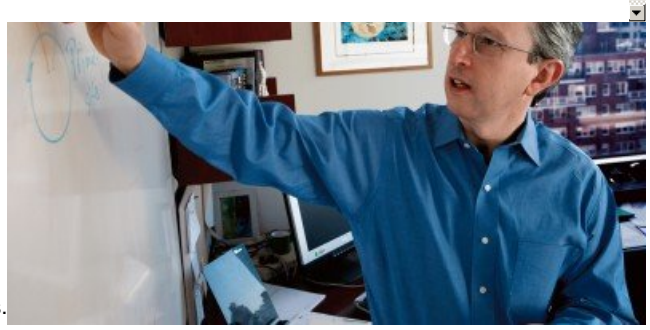
changes inside breast cancer cells.



Joan Massagué, Chair of the Cancer Biology and Genetics Program

Doctors who treat patients with breast cancer have known that tumors that develop resistance to chemotherapy are also more likely to grow larger and to spread, or metastasize, to other parts of the body.

Now a team of investigators from Memorial Sloan Kettering has shown for the first time that these three phenomena — tumor growth, metastasis, and chemotherapy resistance — are connected to the same molecular changes inside breast cancer cells.

"The common link is a hormone that makes it easier for cancer cells to survive stress, whether it is the stress of chemotherapy or the stress of leaving their tumor of origin and trying to grow or establish themselves in another part of the body," explains Joan Massagué, Chair of the Cancer Biology and Genetics Program in the Sloan Kettering Institute and the senior author of the study, which was published July 6 in *Cell*. The study's coauthors included Edi Brogi, Director of Breast Pathology, and Larry Norton, Deputy Physician-in-Chief for Breast Cancer Programs.

The findings also suggest that a new approach for developing treatments could make chemotherapy more effective, while at the same time preventing tumor growth and metastasis.

Studying Metastasis

Dr. Massagué's laboratory has spent several years studying the genetic changes that allow breast cancer cells to survive and colonize in other parts of the body — such as the lungs, brain, and bones. In the current study, his team uncovered a mechanism that makes some breast cancer cells more resilient.

As they were analyzing the genes involved in metastasis, the researchers learned that two of them are genes called *CXCL1* and *CXCL2*, which were already known to participate in inflammation, a natural response by which cells protect themselves from infection or injury.

"As the cancer cells spread and establish themselves in other parts of the body, they use the products from these genes to send out a signal that fools immune cells into protecting them and helping them survive," Dr. Massagué explains. "And even more of this signal is sent out when cancer cells are exposed to chemotherapy."

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Finding Drugs to Target the Signal

“This research is important because it establishes a particular inflammation hormone as an important factor in the survival of cancer cells,” Dr. Massagué says. Because inflammation is a common problem in many different medical conditions, several classes of drugs already have been developed to address it.

In the paper, the investigators report that drugs designed to block the action of CXCL, which are currently in clinical trials for chronic inflammatory diseases, potentially could be useful as cancer therapies. The drugs were shown to shrink tumors and reduce metastasis to the lung in mouse models of breast cancer when used in combination with chemotherapy. These drugs made chemotherapy more effective at eliminating residual cancer cells in mice.

The researchers predict that, for patients, the greatest benefit of these drugs would likely be as a supplement to chemotherapy that is given as an additional treatment after surgery. “Eventually there may be other drugs that prove to be more effective,” Dr. Massagué concludes. “But this research establishes the principle that the genetic changes that make cancer cells aggressive have more consequences than we previously knew.”

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