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PRIMARY TUMORS CAN CHOSE AMONG (AT LEAST) THREE DIFFERENT STRATEGIES TO SPREAD AND FORM METASTASES

Depending on the mode of invasion – as single cells or cell clusters – tumors develop several alternative ways to detach from the primary site and disseminate throughout the organism. This provocative idea re-writes the concept of metastasis and the clinical approaches needed to halt cancer cells.

The finding was presented today in the final session of the SEMM Workshop on Cell Migration (IFOM-IEO Campus, Milan, May 12th-14th)

Primary tumors can spread towards distant organs as single cells, when they lose a protein called *E-cadherin*. But they can also move as a cell cluster, if they sense the activity of a protein called *podoplanin*. Or, in a third scenario, they can sprout lymphatic vessels that facilitate their dissemination when they perceive the presence of two molecules called *VEGF-C* and *VEGF-D*. The existence of several different kinds of metastatic mechanisms was advanced today by Gerhard Christofori, head of the Tumor Biology group at the Center of Biomedicine of the University of Basel, during the closing keynote of the **Workshop on Cell Migration: From Molecules to Organisms and Diseases** promoted by the **European School of Molecular Medicine (SEMM)** and the **University of Milan**, in collaboration with **IFOM – The FIRC Institute for Molecular Oncology of the Italian Foundation for Cancer Research**, and **IEO – European Institute of Oncology**. The Workshop was held at the **IFOM-IEO Campus** (via Adamello, 16, Milan) that was recently opened and represents the biggest area dedicated to the oncological research in Europe.

Until recently, cancer scientists thought that tumors followed a unique pattern of dissemination within the body, being the first step triggered by the detachment of single “riot” cells that were freed from the original tissue and became insensitive towards the surroundings. Now, this scenario has completely changed, as deeper investigations have revealed the existence of at least three distinct mechanisms of spreading, each of them relying on diverse signaling molecules. “When single cells detach from the “mother tissue” – explains Christofori – we can observe the inhibition of a protein called *E-cadherin*. Its absence represents a molecular switch able to trigger a cascade of events leading to single cell migration”.

This mechanism, however, is not the only one. As Christofori proved, the invasion of surrounding tissues by clusters of malignant cells is promoted by a protein called *podoplanin*. “We were able to show that podoplanin induces the formation of so-called filopoda, long protrusions stemming from the front line of the tumor that sense the environment and help the cells to make decisions as where to go.”

The third process identified by Christofori and colleagues involves the two lymphoangiogenic (i.e. involved in the development of novel lymphatic vessels) growth factors *VEGF-C* and *VEGF-D*. Due to upregulated expression of these two molecules, the tumor induces an increase of lymphatic vessel

density in its surroundings, which in turns facilitates the dissemination of tumor cells (through the lymphatic system) and the formation of lymph node metastases.

“These results altogether – comments Ugo Cavallaro, IFOM scientist and member of the Workshop Scientific Committee – could change the way scientists have so far thought about metastases formation, since the three processes do not exclude one another in an individual patient.” These findings open then new possibilities for clinical approach, which should be diversified depending on what mechanism(s) is observed in each patient.

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