PRESS RELEASE

LIKE FLOCKS OF BIRDS: THAT IS HOW CANCER CELLS DEVELOP METASTASES

Metastases are the major cause of death from cancer. An interdisciplinary study conducted at IFOM and the University of Milan reveals that the ability of tumor cells to metastasize is facilitated when cells migrate in a "flock", rather than as individual cells. Researchers using advanced imaging, bioinformatics and applied mathematics have discovered that malignant immune cells tend to form aggregates that move in a manner similar to flocks of birds or schools of fish.
Objective for the future: identify molecules that interfere with the ability of cancer cells to aggregate, thereby breaking the compactness of collective migration. This research, conducted in collaboration with the Weizmann Institute of Science in Israel, the University of Toulouse, the National University of Singapore, and A*STAR of Singapore, was published in the international journal *Current Biology*.

Milan, February 2015 – They migrate in groups of at least 23 members, moving in an autonomous and seemingly random, but perfectly coordinated and compact way. A group leader indicates the movement strategies and migration route. To ensure the effectiveness of migration, the role of leader, more exposed to environmental factors, is constantly rotated among group members, allowing them to rest. Only in this way are they able to reach their destination and proliferate.

This is not a description of the behavior of a flock of birds or a school of sardines, but of cancerous B-cells, a typical example of “liquid tumors” such as lymphomas. Using a combination of cutting-edge technologies, a team of researchers at IFOM (FIRC Institute of Molecular Oncology) and the University of Milan led by Professor Giorgio Scita has managed for the first time to "sketch" their behavior, showing how aggregated cancer cells are more sensitive to migratory stimuli from chemokines, their molecular "fuel", and thus acquire the ability to invade tissues more effectively, to resist cell death and, in the end, to reach lymph nodes and colonize distant organs, causing metastasis. Cell aggregation is observed in lymphomas and chronic leukemias, but is also typical of solid tumors such as breast cancer, colon cancer and melanoma. Understanding why and how they aggregate and identifying potential disruptive factors could contribute significantly to the identification of targeted therapies.

As recently quantified in a study from Harvard Medical School (see Cell), the collective motility that allows cancer cells to aggregate and circulate in the blood is a minor phenomenon, accounting for 3% of circulating tumor cell; but it is precisely these cancer cells that have a 50% higher potential for metastatic invasion compared to single cells. "Next - explains Giorgio Scita, director of the *Mechanisms of Tumor Cell Migration* research unit at IFOM and professor at the University of Milan - we worked to identify the molecular mechanisms and biological processes that increase the migration potential and resistance in collective aggregations compared to solitary cancer cells." Using a combination of real-time microscopy, in vitro chemotaxis assays and advanced imaging techniques, it was possible to monitor the phenomenon ~~ni~~ in real time. "At low chemokine concentrations - continues Gema Malet-Engra, first author of the study - a solitary malignant B-cell does not migrate, whereas an aggregate of cells shows increased migratory capacity. If the chemotactic stimulus is intensified, the single cell undergoes a reverted migration: the excess "fuel" drives it, but once the lymph node is reached it turns back. In contrast, the aggregated cells continue to move forward."

Analyzing these migrating cells using physical parameters similar to those used in the field of ethology, the researchers found that the cancer cells have behavioral and relational dynamics identical to those typical of

migratory birds or sardines, which tend to move in groups to confuse an attacker." We observed - continues Scita – that, whereas the individual components appear move in a random fashion, in reality they maintain perfect coordination in the way they migrate. There are lead cells that drive the movement. These would be subject to a progressive decrease in efficiency and motility due to frictional forces encountered during migration, like a single cell. But within the group there is constant substitution of the leader cells with follower cells. This continuous rotation (every 8-15 minutes) moves fresh cells that have not been weakened to the outside. A mathematical model developed with colleagues from the Weizmann Institute and analysis software developed with colleagues from Singapore have identified for the first time the vectors representing motility, speed and direction of each individual cell and those that identify their 'flight strategy': rotation among leaders and followers in response to chemotactic stimuli." The parameters used also describe the alternation of phases that characterize the migration process, which are closely interconnected with the concentration of chemokine in the environment that they cross: movement is compact and directional when the concentration is high. Group of cells, however, alternate this running state with pauses during which cells within the group move in a rotational or random fashion when the chemokine is scarce, This pausing allows the group to sample the environment and locate higher concentrations and change course.

"It emerges - concludes Scita – that there is a flawless cell-cell communication mechanism behind this ability to aggregate and migrate efficiently. Prospectively, the clinical objective will be to identify an inhibitor that interferes with this intercellular communication mechanism, disrupting the group and eliminating or reducing migration and chemotaxis".

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