



PRESS RELEASE

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Scientists discover the origins of metastasis

Researchers at UNIGE show that the experience of impending cell death within a primary tumour can lead to the development of «pro-metastatic» cells.

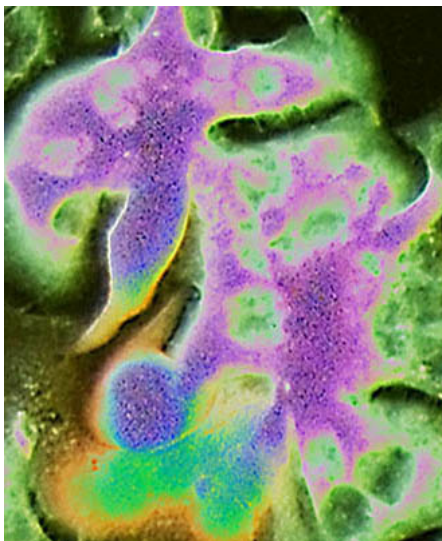
Metastatic cells form in a primary tumour and then break away from it, migrate to other organs, attach to them and form new tumours. This spread reduces patients' chances of recovery. Scientists at the University of Geneva (UNIGE) have discovered some of the mechanisms by which these cells arise. This is due to cells that have narrowly escaped cell death (apoptosis) following a chemotherapeutic treatment. Those cells reprogram themselves to acquire metastatic skills. Thanks to this study, these cells - called PAME by the researchers - now appear as new therapeutic targets. These results can be read in the journal *Cell Reports*.

Metastatic cells occur in many forms of cancer. They originate in primary tumours and then break away and migrate. They travel through the tissues surrounding them, through blood vessels or lymphatic channels. Along the way, they may attach to one or more organs - such as the lungs, brain, bones or liver - and form new tumours also called metastases. This spread of the disease can negatively affect a patient's chances of recovery.

Previous studies have identified metastatic cells during migration. It is also known that certain treatments can induce them. However, the precise mechanisms of their development remain a mystery. "We don't know why, at a given moment, certain cells separate from the primary tumour," explains Ariel Ruiz i Altaba, a Full Professor in the Department of Genetic Medicine and Development at the UNIGE Faculty of Medicine. "The phenomenon is difficult to analyze because, before they migrate, there is nothing to distinguish future metastatic cells, or pro-metastatic cells, from other cells within the tumour".

Cells that should have died

Professor Ruiz i Altaba's team composed of two postdocs for this study, Arwen Conod (first author) and Marianna Silvano, has now provided some answers. Thanks to a recent research, these UNIGE scientists have discovered that the experience of imminent death within the primary tumour pushes certain cells to acquire pro-metastatic states. This near-death experience occurs in particular in the context of certain treatments aimed at depriving cancer cells of energy or oxygen. The team observed that these cells, which should have died, reprogram themselves and then present a high metastatic risk. These cells are called PAME for "post-apoptotic pro-metastatic cells".



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Photomicrograph of a cell co-culture of pro-metastatic primary colon cancer PAME (purple) mixed with induced migratory PIM (green).

A storm of cytokines

To reach these conclusions, the UNIGE team used tumour samples taken from two colon cancer patients. Tumour cells from these samples were then transplanted into mice, where they grew and formed new tumours. These cells were subjected to an imminent death experience causing endoplasmic reticulum stress similar to that caused by certain chemotherapeutic drugs. This allowed the development of PAME cells.

The scientists also discovered that PAMEs trigger a storm of cytokines - proteins and other factors that ensure cell-to-cell communication - inducing adjacent cells to become PIMs, for PAME-induced migratory cells. These PIMs then associate with PAMEs and help them migrate to form metastases.

The present results open up promising new prospects for therapeutic management, including the prevention of the development of pro-metastatic fields generated by certain treatments. “Currently, one of the main criteria when defining a treatment is tumor shrinkage. Thanks to our study, PAME cells now appear as potential therapeutic and metastasis prevention targets to be taken into account”, concludes Professor Ruiz i Altaba.

contact

Ariel Ruiz i Altaba

Full Professor
Department of Genetic Medicine
and Development

Faculty of Medicine

+41 22 379 56 46
Ariel.RuizAltaba@unige.ch

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UNIVERSITÉ DE GENÈVE
Communication Department

24 rue du Général-Dufour
CH-1211 Geneva 4

Tel. +41 22 379 77 17

media@unige.ch

www.unige.ch