



Revealing the colors of lung cancer mosaics

Tumors sometimes develop a surprising, even graphic, architecture. This is the case of lung cancer, where cellular architecture can be appreciated under the microscope and is used by pathologists to classify the disease into distinct subtypes. The study of the morphology and genomics of cancer cells is at the core of the research work of Prof. Giovanni Ciriello of the Department of Computational Biology of UNIL, which was published on February 9th, 2021 in "Cancer Discovery".



At the center is a tissue slide taken from a lung tumor (haematoxylin and eosin stain). Tumor cells are delimited by colored lines, each color identifying different patterns (the gray line delimit an area of normal lung tissue). Zoom-ins for each pattern are shown on the left and right sides. The least aggressive pattern (top left) is delimited in blue and resembles the normal lung tissue. The most aggressive pattern (bottom right) is delimited in red and has completely lost any resemblance with the tissue of origin. © Département de biologie computationnelle - UNIL

Lung cancer is the first cause of cancer-related mortality worldwide, with about 2 million deaths per year. In the clinic, pathologists categorize these tumors in subtypes based on how they look under the microscope. Indeed, tumor cells can grow in different shapes and patterns, sometimes following the structure of the lung region where they originated, other times making that original architecture unrecognizable.

Four major patterns of lung adenocarcinoma

In lung adenocarcinoma, the most frequent type of lung cancer, about 4-to-5 patterns are most frequently observed. Typically, each single tumor is composed by multiple patterns, similar to a mosaic made with tiles of different shapes. Although these patterns are routinely used in the clinic to classify patients' tumors, scientists and physicians don't know their origin and whether cells in distinct patterns are actually different: "It is like looking at a painting in black-and-white: you can see what's in it, but you cannot really tell what it looks like!" says Giovanni Ciriello, associate





professor of the Department of Computational Biology of the Faculty of Biology and Medicine of UNIL and a member of the Swiss Cancer Center Leman in Lausanne.

Now, Prof. Ciriello took up this challenge in a study that he co-led with Dr. Igor Letovanec, pathologist of the CHUV and head of department at the Hôpital du Valais. The results have been published in Cancer Discovery, one of the leading journals in the field, and a journal of the American Association for Cancer Research (AACR).

Disassembling the mosaic

Using a wide variety of technologies and innovative approaches, the interdisciplinary team isolated individual patterns from multiple tumors and spatially analyzed the characteristics of each of them. "In simpler terms, we took apart the mosaic, to reveal the color of each tile" clarifies Giovanni Ciriello. The authors discovered that tumor cells from distinct patterns activated very different genes and proteins: "As cancer cells form new patterns, they modify their identity and behavior, often increasing the tumor aggressiveness" says Daniele Tavernari, Ph.D. student in Ciriello's lab and first author of the study. By analyzing this data with advanced computational approaches, the researchers could determine the identity of the most aggressive cells in more than 2,000 patients! "These results could now serve the design of tools to predict patients' prognosis and personalize their treatments. In particular, this will be important for early-stage tumors detected by recently deployed screening programs" continues the young scientist.

An immune system kept at bay

Interestingly, the team led by Ciriello and Letovanec discovered that tumor cells in different patterns were surrounded by different types of normal cells of the immune system, which is supposed to attack the tumor. "In the least aggressive patterns, immune cells were nowhere in the vicinity, as if they had not yet been alerted. In others, they were in "full attack mode" and infiltrated the tumor region. Lastly, in the most aggressive patterns, most immune cells were kept at bay and the few inside the tumor were unable to fight the disease" describes Giovanni Ciriello. All of these scenarios were sometime concurrently observed in the same tumor and could provide important information for the adoption of most recent therapies designed to stimulate the immune system of the patient against the tumor.

"This study highlights the value of combining computational, experimental and clinical approaches" concludes Dr. Letovanec "The combination of diverse data and expertise will be essential to provide a complete picture of the disease and translate scientific discoveries into clinically actionable approaches".