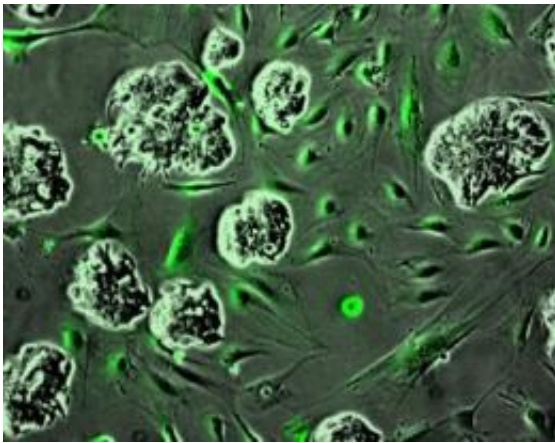


Scientists discover key process that allows colon cancer to metastasize

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These are microscopy images of growing colon cancer cells surrounded by stroma cells, mainly fibroblasts (in green). Credit: © E. Batlle lab, IRB Barcelona. Autor: Alexandre Calon

A team of 17 researchers, led by scientists Eduard Batlle and Elena Sancho in the Colorectal Cancer Laboratory at the Institute for Research in Biomedicine (IRB Barcelona), have determined that the ability of colon cancer to metastasize lies in the healthy cells, called stroma, that surround the tumour. Although the stroma has long been hypothesized to be complicit in this process, this study marks the first time that healthy cells in the microenvironment have been observed to play a fundamental role in allowing metastasis to occur in a specific tumour type.

The discovery, which will be tomorrow's *Cancer Cell* cover story, could

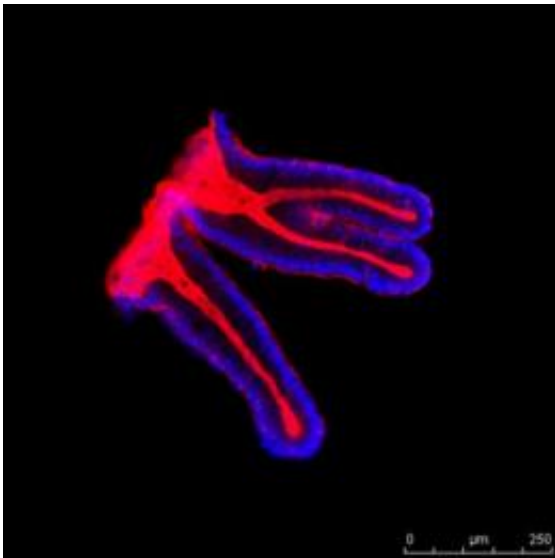
translate into direct benefits for patients given that in a little more than five years, tests could be available to predict relapse allowing doctors to target treatment according to prognosis. IRB Barcelona Group Leader Eduard Batlle, ICREA researcher and recipient of an ERC Starting Grant and the Banco Sabadell Biomedical Research Prize, and Associate Researcher Elena Sancho, presented their results at a press conference held during the Barcelona BioMed Conference on "[Normal and Tumour Stem Cells](#)", organized by IRB Barcelona and the BBVA Foundation at the Institute d'Estudis Catalans.

Tumour stem cells corrupt healthy cells in tumour microenvironment

By studying 345 cases of [colon cancer](#), using information in public databases and samples of patients provided by three hospitals in Barcelona, the team was able to identify the factors key to colon cancer metastasis. They showed that when tumour stem cells reach the liver, a common target of colon cancer metastasis, they release a molecule called TGF-beta into the microenvironment. The surrounding cells, including macrophages, leukocytes, fibroblasts and [endothelial cells](#), respond by releasing a different set of molecules. The researchers found that the cells in the tumour microenvironment produce interleukin-11 (IL11) and cause a series of [genetic changes](#) in the tumour stem cells that allow it to survive in the foreign organ.

"This study proposes a change in paradigm", explains Batlle. "Until now, if we wanted to know whether a colon cancer patient was likely to develop metastasis, we would look at their tumour cells. This study has shown us that, instead of looking at the seed, we need to be looking at the earth. We can predict if a plant will grow if the ground, or substrate, in which the seed is planted is fertilized. TGF-beta is the fertilizer that changes the earth in which the tumour seed grows."

The scientists also observed that tumour cells in the original organ already possess the ability to change their microenvironment. "We can tell whether there will be metastasis through indirect means. If we see that the stroma is already modified in the primary tumour site in the colon, it means that the tumour [cells](#) will also be able to change the [microenvironment](#) when they disseminate to the liver," explains Alexandre Calon, a French postdoctoral fellow in Batlle's lab and first author of the study.



The epithelial cells of the colon (in blue) form a thin layer that covers the colon. Herein lie the cells which give rise to colon cancer. Credit: © E. Batlle lab, IRB Barcelona. Autor: Alexandre Calon

A test to predict relapse ready in five years

Colon cancer is the second cause of cancer deaths worldwide. Current treatment normally combines surgery and chemotherapy. After intervention, patients normally go into remission, which can last months or years. 30-40% will relapse, mostly in the form of metastasis primarily

to the liver or to the lung. Elena Sancho explains that "in about five years, we will likely have a test on the market that identifies those patients at risk of metastasis, allowing doctors to fine tune their treatment regimes."

The scientists have observed that about 15% of patients never develop metastasis and this is related to whether or not the stroma has been modified by TGF-beta. This means that armed with a diagnostic test that analyzes the genetic signature of the stroma (whether or not molecules including TGF-beta and interleukin-11 are present), doctors may be able to identify patients at risk of developing metastasis. If the data from this study are confirmed, between 10-15% of patients may no longer require chemotherapy, leading to direct benefits for their health and to a better use of resources. On the other hand, if the test predicts a high risk for metastasis, patients would be able to receive more aggressive treatment and undergo more thorough monitorization.

Validation of scientific results and future treatment for metastasis

The team of researchers also show in the *Cancer Cell* article that metastasis can be prevented from occurring by eliminating the TGF-beta signal in the stroma. They treated mice with aggressive colon tumours with a TGF-beta inhibitor that is already in clinical trials for other illnesses. Their tumours did not metastasize. "This experiment proves that TGF-beta and the tumour [stroma](#) must 'speak to each other' in order for metastasis to occur. Our results in mice also show that patients with activated TGF-beta, and who are in the initial phases of the disease, may benefit from taking a TGF-beta inhibitor", explains Battle.

As far as the researchers can tell, dependence on TGF-beta is limited to the initial phases of metastasis. Once metastasis takes hold in the foreign

organ, the administration of the inhibitor is no longer effective. "Even so, we must point out", says Batlle, "that the development of a drug to treat colon cancer metastasis is a complicated process." Today, the vast majority of inhibitors must first be tested in patients with irreversible prognosis. Clinical trials are designed to slow down tumour growth, while the molecules that we administered to mice don't act on [tumour](#) growth but at an earlier step. We have presented our evidence in this article, and we open the door to a future development of a TGF-beta based inhibitor".

This study was made possible thanks to the collaboration of physicians at the Hospital Clinic of Barcelona, the Hospital del Mar, the Hospital de Sant Pau and the group of researchers at the Memorial Sloan Kettering Cancer Center led by Joan Massagué. Massagué, who is also adjunct director of IRB Barcelona and fosters the research on cancer metastasis in the center, participated in the study as an expert on [metastasis](#) and TGF-beta.

Other collaborators in the study include David Rossell, Head of the Biostatistics and Bioinformatics Unit at IRB Barcelona, who played a key role in making sense of the enormous amount of genomic data generated in the study, as well as the team of chemist Antoni Riera, also from IRB Barcelona, who contributed work on the TGF-beta inhibitor.

More information: Dependency of Colorectal Cancer on a TGF-beta-Driven Program in Stromal Cells for Metastasis Initiation, Alexandre Calon, Elisa Espinet, Sergio Palomo-Ponce, Daniele V.F. Tauriello, Mar Iglesias, María Virtudes Céspedes, Marta Sevillano, Cristina Nadal, Peter Jung, Xiang H.-F. Zhang, Daniel Byrom, Antoni Riera, David Rossell, Ramon Mangués, Joan Massagué, Elena Sancho, Eduard Batlle. *Cancer Cell* (2012). November 13 (print issue)

Provided by Institute for Research in Biomedicine (IRB Barcelona)

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