



SCIENTISTS AT IRB BARCELONA DISCOVER A KEY PROCESS THAT ALLOWS COLON CANCER TO METASTASIZE

- The study, published in the prestigious journal *Cancer Cell*, reveals that tumour cells of the colon must form alliances with healthy cells in order to colonize other organs during metastasis.
- The presence of TGF-beta in the tumour's microenvironment forces healthy cells to produce interleukin-11 (IL-11), a protein that alters the genetic programme of the tumour cells and helps them to survive during metastasis.
- This discovery opens the doors to substantial improvements in the diagnosis and treatment of patients with colon cancer.

Barcelona, Monday, 12 November 2012.- 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 one of the two first co-authors of the study together with **Elisa Espinet**.

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 Batlle.

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.

Reference article:

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 13th (print issue)

KEY CONCEPTS IN STUDY

Tumour stem cells

Not all tumour cells have the same properties. Many of them, although they are tumour cells, only serve to form the mass of the tumour. There exists a hierarchy within the different types of tumour cells, at the top of which are stem cells. These cells have the ability to regenerate a tumour and cause metastasis in a distant organ.

Stroma

Stroma is the microenvironment that surrounds tumour cells. Stroma is formed by different types of cells that are recruited by cancer cells, and include: *endothelial cells*: - flat cells that cover the inside of blood vessels; *macrophages* - cells with immunological capacities that serve to clean and protect tissues; *fibroblasts* - cells within tissues responsible for synthesizing the components of the matrix; *leukocytes* - immune response blood cells responsible for defending an organism against foreign substances or infectious agents.

Tumours are able to alter the function of these cells for their own benefit. In this study, the researchers discovered the fundamental role that the stroma plays in allowing tumour cells from the colon to cause a metastasis in the liver.

TGF-beta

Transforming growth factor-beta. TGF-beta is a protein that controls proliferation (growth and cell division) and cell differentiation (the specialization of a cell into a specific type) in most cells. It is a type of cytokine that is associated with immune system deficiencies, cancer, heart disease, diabetes, Parkinsons, Marfan syndrome, Loeys-Dietz syndrome and AIDS.

One of the leading experts on TGF-beta is Joan Massagué. The IRB Barcelona adjunct director is recognized internationally for having described the signalling cascade of this protein and created the basis for studying its deregulation in disease.

The deregulation of TGF-beta can result in tumour development. TGF-beta acts as a tumour suppressor that malignant cells must evade in order to maintain their malignancy. TGF-beta also alters processes such as cell invasion, immune system regulation, and modification of the microenvironment that malignant cells can exploit to their own benefit. In 2008, Joan Massagué determined the key role that TGF-beta plays in allowing breast cancer cells to metastasize. This study, which included the participation of IRB Barcelona, showed that TGF-beta causes changes in tumour cells that allows them to break free from the primary organ and enter the blood stream. The study showed that TGF-beta corrupts the tumour stroma so that it helps the tumour to metastasize.

Interleukin-11

Interleukin-11 is a protein produced by the stroma cells. The study by Batlle and Sancho in *Cancer Cell* assigns it a fundamental role in the modification of tumour cells. Thanks to the interleukin-11 signal, tumour cells can activate a series of genes that allow the cells to survive in a hostile organ during metastasis. Without interleukin-11, the tumour cells that have spread to other organs will die before being able to produce the metastasis.

Metastasis

Metastasis is the process by which tumour cells are able to generate new tumours in distant organs. Colon cancer tends to metastasize to the liver and lung.

Right from the earliest stages, tumours release cells that have the potential to cause metastasis into the blood stream. Metastasis is an inefficient process, however, given that only a very small number of cells are able to survive the trip to a distant organ (organisms have many defense mechanisms), and because the new organ provides a hostile environment. Unfortunately, when metastasis occurs, prognosis for the patient is poor. Epidemiologists estimate that 90% of deaths by cancer are caused by metastasis.

For more information:

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INSTITUTE FOR RESEARCH IN BIOMEDICINE (IRB BARCELONA)

Founded in 2005 by the Government of Catalonia and the University of Barcelona, the Institute for Research in Biomedicine (IRB Barcelona) is one of eight centres in Spain to be recognised by the Ministry of Economy and Competitiveness as a “Severo Ochoa Centre of Excellence”. The 28 groups hosted by the institute are devoted to basic and applied research at the interface between molecular and cellular biology, structural and computational biology, and chemistry, with experts in proteomics, genomics, biostatistics, and advanced digital microscopy. The research at IRB Barcelona is organised into five programmes, which work together with the common goal of conducting multidisciplinary projects that address important biomedical problems affecting our society, with special emphasis on cancer and metastasis. The institute is home to approximately 470 employees from 37 countries. IRB Barcelona's ultimate objective is to translate research results to the clinic and has already established three biotechnology spin-off companies to this end. The institute is located in the Barcelona Science Park (PCB), in the Diagonal Campus of the University of Barcelona. Director: Dr. Joan J. Guinovart. Adjunct director: Dr. Joan Massagué. <http://www.irbbarcelona.org>

Access to scientific images, 3D animation of colon cancer metastasis and video images of Eduard Batlle, Elena Sancho and Alexandre Calon in Batlle's lab at IRB Barcelona:

<http://www.irbbarcelona.org/press>

Scientific images caption:

_Colon_cancer_cells&stroma.tif

Microscopy images of growing colon cancer cells surrounded by stroma cells, mainly fibroblasts (in green)

© E. Batlle lab, IRB Barcelona. Autor: Alexandre Calon

_Colon_epithelial_cells.tif

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.

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_Fibroblast.tif

Stroma cells, such as the fibroblasts in this image, help colon cancer cells to metastasize.

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