PRIZE ESSAY

FINALIST
Daniele V. F. Tauriello
Daniele Tauriello studied at Utrecht University, Netherlands, and earned his Ph.D. at the University Medical Centre Utrecht. Dr. Tauriello has been a postdoctoral fellow at IRB Barcelona, Spain, working on the role of TGFβ in the tumor immune microenvironment in colorectal cancer metastasis. This year, he will set up his lab at the Radboudumc, Radboud Institute for Molecular Life Sciences, in Nijmegen, Netherlands.
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REGENERATIVE MEDICINE

From poor prognosis to promising treatment

A better mouse model sheds light on immunotherapy's potential for treating metastatic cancer

By **Daniele V. F. Tauriello**[1,2]

Over the past several decades, evidence has accumulated that stromal cells—the nonmutated cells that surround malignant cancer cells—are not mere bystanders in tumorigenesis. Instead, they play a crucial role in cancer progression. We now know that metastatic cancer cells must reprogram the tumor stroma, or tumor microenvironment (TME), before they can metastasize (*1*–*3*). They must also contend with the immune system that strives to limit tumor spreading. If the road to metastasis is full of intense obstacles, how can this disease be so devastating?

The answer probably lies in the fact that as cancer cells reorganize the microenvironment, they thoroughly manipulate the stroma to not just shut down any recruited immune cells but also to suppress the mobilization of an effective immune response in the first place. Yet there is hope. In the 1990s, the labs of Tasuku Honjo and James Allison each discovered a mechanism of immune regulation that turned out to be inhibitors of immune responses. When these signals were later found to be hijacked by cancers to evade immunity, a new path toward reinvigorating the immune system to fight cancer was revealed (*4*–*7*).

Indeed, from the relatively speedy implementation of these therapies in humans to impressive cases in which cancers have been eradicated, this new treatment option has been very close to a miracle for many patients. However, only a fraction of patients respond to this breakthrough, and immunotherapy does not yet work in all cancer types. But we are starting to learn why.

TGFβ: CORRUPTING THE STROMA

In 2011, I joined the lab of Eduard Batlle, at the Institute for Research in Biomedicine (IRB) in Barcelona and began investigating colorectal cancer (CRC) metastasis. When I arrived, there was a small group of scientists studying the CRC stroma in mouse models. They had just discovered that a molecule called transforming growth factor–β (TGFβ) was associated with a bad prognosis in patients. This had puzzled them, as the same molecule can block tumor growth in culture. It turned out that in vivo, TGFβ also acts on the stroma and somehow promotes tumor growth and metastasis.

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While I learned animal handling from them, they published a paper, showing that TGFβ signaling in the TME was involved in boosting metastatic initiation (*8*). They used patient CRC cells, which could be injected only in immunodeficient mice, otherwise they would reject the tumor. We clearly needed a better model, one with an intact immune system—so, together with Sergio Palomo-Ponce in the lab, I started a project to generate one.

RECONSTITUTING CRC IN MICE

We used a very simple concept, but one that proved to be almost prohibitively tedious: crossing multiple key CRC mutations into one mouse. Three years later, we achieved mouse strains with between one and four of the mutations. With every added mutation, the tumors became more aggressive. [We anticipated this, as similar results had already been shown more elegantly in a different system (*9*, *10*).]

Out of the strains we developed, only the one with all four mutations experienced liver or lung metastases, closely replicating common disease progression in humans. This model also had all the telltale signs of activated TGFβ signaling in the TME. In the end, we generated a mouse model that recapitulated just about all the relevant characteristics of human metastatic CRC with poor prognosis (*11*).

[1]*Institute for Research in Biomedicine (IRB Barcelona), The Barcelona Institute of Science and Technology, Baldiri i Reixac 10, 08028 Barcelona, Spain.* [2]*Centro de Investigación Biomédica en Red de Cáncer (CIBERONC), 28029 Madrid, Spain. Email: daniele.tauriello@irbbarcelona.org*

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A TRANSPLANTABLE MODALITY

Next, I embarked on another big project: putting the tumors generated using my new model into culture using state-of-the-art organoid technology. Once I succeeded in this endeavor, Sergio and I tried injecting the organoids back into mice. The organoids struggled to grow in the mouse strain in which they were generated; however, just as the human cancer cells had, they grew much better in immunodeficient mice.

Because the organoids came from the exact same genetic background as the new host, it could not simply be transplant rejection. Instead, it seemed to suggest that the immune system was, in principle, capable of recognizing and eliminating CRC. Could something be blocking these immune responses during tumor progression?

BLOCKING TGFβ TO BOOST CANCER IMMUNITY

Studying the successfully transplanted mouse tumor organoids, I again found cancers with high stromal TGFβ levels. TGFβ must be the immune suppressor, I decided, potentially explaining its link to poor prognosis. Using a pharmacological TGFβ inhibitor, I was able to completely prevent metastasis initiation, inducing immune rejection (*11*). I also showed that this therapeutic effect depends on T lymphocytes, the same cells that are often targeted in immunotherapy treatment regimes.

Approximately one in three patients with cancer is either diagnosed with metastatic disease or develops metastasis after surgical removal of the primary tumor, so I wanted to know whether TGFβ inhibition could be used to treat established liver metastases in my model. Unfortunately, TGFβ inhibition was not effective when initiated at a late stage of the disease. Although T lymphocytes were recruited and activated, something was preventing them from killing the cancer. Inspired by the work of Honjo and Allison, I tested the combination of TGFβ inhibition with their therapy regime and cured the majority of mice in my study (*11*). One of the first mice I cured is still alive and has been cancer-free for more than 2 years.

With the finding that TGFβ hinders immune responses in cancer progression, we may be able to prevent metastatic initiation by blocking this pathway in the TME. Moreover, our work opens the door to efficacious combinatory immunotherapy for a large group of patients with late-stage disease who currently have no effective therapeutic options. ■

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