

Cédric Blanpain: The stories stem cells tell

Blanpain studies stem cell maintenance and repair of embryonic and adult tissues.

Although the stem cells found in adult tissues produce a more limited range of cell types than those found in the early embryo, they are absolutely essential to replace cells lost to turnover or tissue damage. Understanding and harnessing the biology of these cells would yield amazing therapeutic benefits. But to realize such benefits, it's necessary to study as many kinds of stem cells as possible because, just as each tissue performs different functions in the body, the stem cells that maintain these tissues each possess their own unique features.

Cédric Blanpain started working on epithelial stem cells when the field was still in its infancy. His efforts have helped illuminate the complex and sometimes idiosyncratic behavior of stem cell populations in the skin (1–3), heart (4), and other tissues (5). Now, he's working to extend findings from stem cell biology into other fields such as cancer biology (6, 7), as he explained when we reached him at his office at the Free University of Brussels.

OPENING CHAPTER

You started out working in a very different field than you're in now...

My mother was an MD, and I remember reading her medical journals, which were always sitting on the table.

At the end of high school, I decided I wanted to be an MD because I wanted to help people, in particular people who were suffering. So I went to medical school and even performed a residency in internal medicine before doing a PhD in Marc Parmentier's lab, where I was studying how the chemokine receptor CCR5 interacts with its ligand and how it modulates HIV entry.

I had decided to do a PhD because I had done research rotations as an undergraduate and medical student and really enjoyed them. I joined Marc's lab because,

around that time, he had made the seminal discovery that a mutation in CCR5 can completely prevent HIV infection. That was obviously very exciting from both a basic research and therapeutic standpoint. And it was a local lab next door that was doing this fascinating research. I was really excited about their work.

What motivated the switch you made as a postdoc?

I wanted to do research that could also be potentially useful for patients. This was a little more than ten years ago, really just as epithelial stem cell biology was getting started, and there was a lot of excitement about it. I chose to join Elaine Fuchs' lab at The Rockefeller University, which was in retrospect an excellent choice for several reasons. First, because at that time everyone was still working out how to perform stem cell isolation and how to do assays to assess stem cell potential. So we all felt that we were pioneers, establishing all the protocols and working out the bugs. It was also an excellent choice because I was surrounded by a lot of super-smart people in a very intense scientific atmosphere. And then also because Elaine is a fantastic mentor. She really taught me most of what I know today.

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How did you isolate stem cells without knowing their markers?

One thing that was known at that time was that there is a portion of the hair follicle, called the bulge, in which cells cycle less frequently than they do in the rest of the epidermis. Tudorita Tumber and Elaine had the brilliant

idea to create a new mouse model to isolate the living cells that cycle the least during a certain period of time. Using this totally new method, we could isolate almost pure bulge stem cells and then do transcriptional profiling on them



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Cédric Blanpain

to uncover new markers. Using new cell surface markers, I was able to isolate the follicle stem cell and show that the progeny of a single bulge stem cell are able to give rise to all the lineages of the skin epidermis.

MAIN CHARACTERS

Are bulge stem cells the only stem cells in the epidermis?

During homeostasis, the bulge stem cells essentially contribute to the regeneration of the hair follicle lineage. Upon injury, they are rapidly activated, migrate to the wound region, and contribute to the repair of the skin. But this activity is only transient. We have shown recently that the interfollicular epidermis also contains a pool of more quiescent stem cells that can participate in repairing the epidermis following injury.

Is skin a bad place to be a stem cell? Don't such long-lived cells receive lots of mutagenic insults there?

One of the questions that we are interested in is how the different cell types of the skin respond to DNA damage. By studying this, we realized that actually bulge stem cells are highly resistant to DNA damage-induced cell death because they express a higher amount of anti-apoptotic molecules such as Bcl-2. They are also

very resistant to DNA damage, and they repair DNA much faster than other cells. But they repair their DNA through a mechanism that is not completely faithful and can be error prone. This ensures the immediate preservation of the tissue because that's probably the most important thing for survival, but maintaining the tissue function has the cost of potentially letting the cells accumulate DNA damage over time.

There could be many other mechanisms that help bulge stem cells keep mutations in check during the normal growth cycle. We are still studying this question to see whether different DNA repair mechanisms are differentially active depending upon whether the hair follicle stem cells are in a quiescent or active state, or if we look at them during different stages of development or morphogenesis.

PLOT TWISTS

Your work is not confined only to skin stem cells...

Many people in my lab now work on cardiac stem cells, which is something I started working on as a kind of side project. While I was still in Elaine's lab, I was approached by a young cardiologist, Antoine Bondue, who wanted to understand the mechanisms that regulate specification of the cardiovascular lineage during stem

cell differentiation. That project turned out to be so successful that lots of students want to continue working on it.

We have also expanded our interests to include the stem cells of glandular epithelia—for example, the mammary glands and the prostate. The technique that we are using the most in these studies,

"The markers tumors express can be completely misleading in extrapolating their cellular origin."

and the one that I believe is best suited to following the fate and the potential of stem cells within their natural environment, is lineage tracing. For example, last year we published a study where we generated new mouse lines to let us trace the different cell lineages of the mammary gland. We realized that, in contrast to what we were

expecting, we did not find any evidence for multipotent stem cells in the mammary epithelia of adult or young mice but only for different types of unipotent stem cells. We just recently completed studies showing that this switch from multipotency to unipotency also occurs in the prostate and sweat gland.

Although we could not find any evidence of multipotent cells under physiological conditions in these different adult epithelia, we do not exclude that, under some pathological conditions, you can stimulate some unipotent cells to adopt a multipotent fate. We have now used a lineage-tracing strategy to investigate how tumors grow

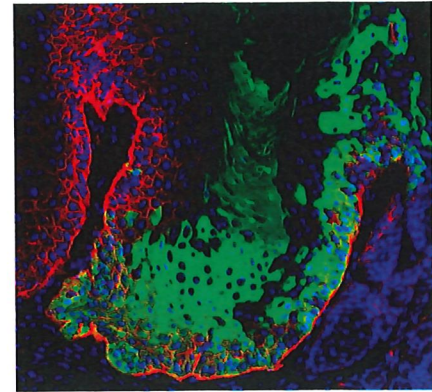


IMAGE COURTESY OF GREGORY DRIESSENS

The progeny of a single labeled tumor stem cell (green) fuel tumor growth in a benign papilloma.

in their natural environment and found that early skin tumors contain stem and progenitor cells that fuel tumor growth, reminiscent of the hierarchy found in the normal epidermis.

Do stem cells contribute to cancer initiation?

Although the mutations leading to cancer are relatively well known, the cellular origin of cancer has remained elusive for a long time. We have used lineage tracing to study the origins of different epithelial cancers, for example in basal cell carcinomas and in papillomas. In medical textbooks, you'll find that people thought that the cell at the origin of the cancer is a cell that expresses the same markers as in the tumors they find. What we found in our studies is that the markers tumors express can be completely misleading in extrapolating their cellular origin. If we can understand which cells are competent to initiate cancer and which cells are resistant to cancer initiation, this could help us to understand the step of cancer initiation, which was clearly not possible before.



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The Blanpain lab

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