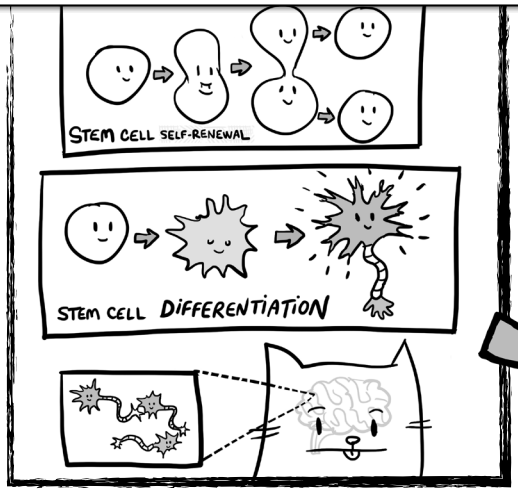
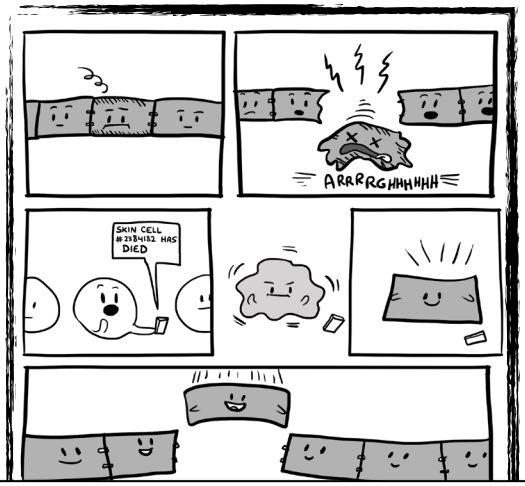
The Elixir of Life and Our Skin

1 In our bodies, we have a type of cells called stem cells that are special because: 1) they can self-renew (make more stem cells) and 2) they can change into other different types of cells. Only stem cells have these abilities. This is key for living creatures to grow from single cells.

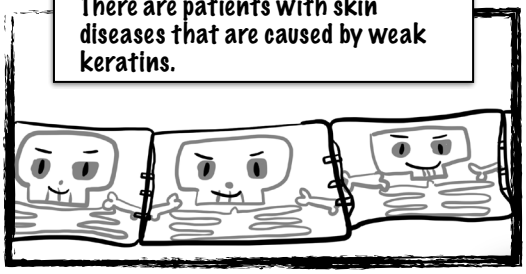


2

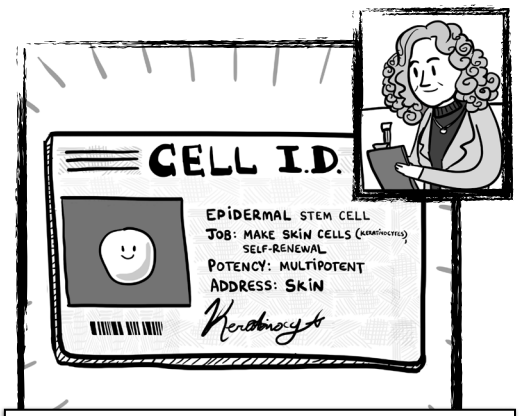


There are stem cells within our skin which help replace dying cells and repair wounds. They divide and then become all the different types of skin cells needed to form our skin.

3 Our skin is resistant to outside forces thanks to a network built by these chain-like structures (kind of like a skeleton) called keratins. There are patients with skin diseases that are caused by weak keratins.

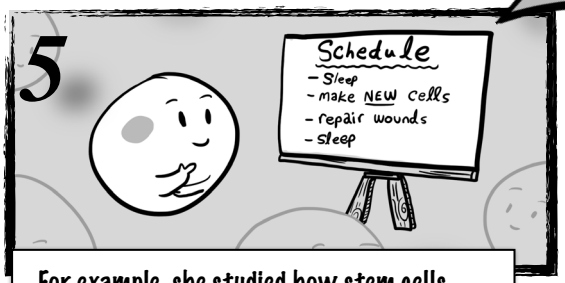


4



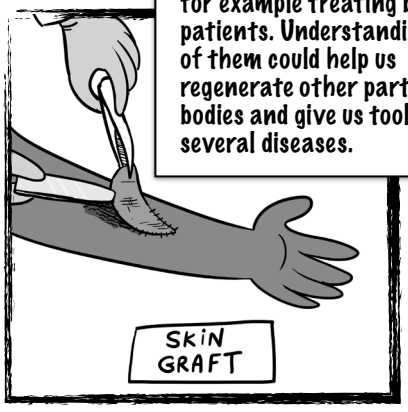
Professor Elaine Fuchs has investigated skin diseases -and other diseases- by trying to learn everything about stem cells.

5



For example, she studied how stem cells experience cycles of rest and action: sometimes they sleep, sometimes they work to make new cells. One time they become active is when they repair wounds.

6 Stem cells have helped us regenerate parts of our bodies, for example treating burn patients. Understanding more of them could help us regenerate other parts of our bodies and give us tools to fight several diseases.



Art by Armin Mortazavi and text by Daniela Salas Acosta. October 2020

The Elixir of Life and Our Skin

Studying the cells of our skin, paved the way for science that explores the possibility of regeneration in medicine.

Written by Daniela Salas Acosta
Art by Armin Mortazavi

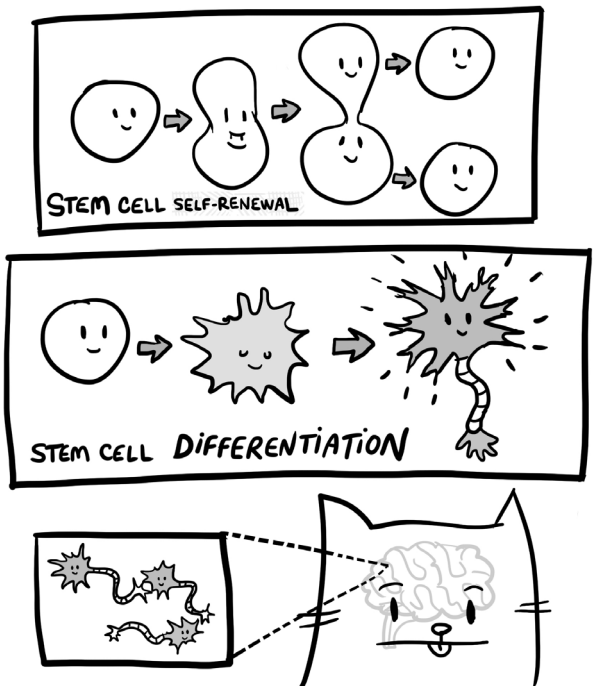
October 2020

Real life examples of fairy tales are everywhere if you look through the right glasses – or in this case, through laboratory lenses. For example, there is actually an elixir of life of sorts, which is even able to regenerate parts of our bodies. And for those who were looking, this incredible possibility was found within our own cells.

What we are really talking about are **stem cells**. These are very special because they have two main abilities. One, they have **potency** – this is the ability to develop, or **differentiate** (kind of like growing up) – into many different kinds of cell types with different kinds of functions. It's as if these cells have enormous potential to become many different things - they haven't committed to any one path yet. Secondly, stem cells can also **self renew** – that is, they have the ability to continually divide into more stem cells which are able to retain their special potency status.

If you think about it, because of these two powerful features, a lot of fundamental biology can happen with stem cells. And here, they play a crucial role in how a *single* cell can grow into mixtures of different cell types, and are able to develop into complex structures such as organs or even an entire organism.

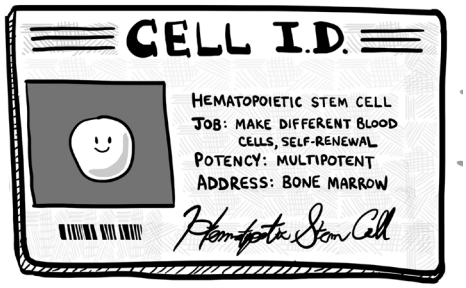
Note that this is very different to the overwhelming majority of cells in your body. Most cells in your body have already differentiated, and have therefore already become specialized. This status means that they have lost potency, in that they are committed to being only that one type of cell. This also tends to mean that your differentiated cells have limited regenerative abilities. This is why stem cells are so special.



This is also where the work of Dr. Elaine Fuchs, a professor at Rockefeller University in New York and one of the 2020 Canadian Gairdner Award winners, comes in. She has dedicated her entire career to studying stem cells, and in particular, the adult stem cells in our skin (or epidermis).

Fuchs was originally a chemist and had never taken a biology or genetics course, but she found herself wanting to work on research related to medicine. She says, "In physical chemistry, you

*Sidebar: There are different types of stem cells according to their potency. A stem cell is more potent if it can differentiate into more cell types. The most potent of all stem cells are called **totipotent** because they can make all the cells required to form a complete organism and also cells that can become placental cells. **Pluripotent** cells can make all the cells of an organism, but they cannot make those needed to form placentas. Sometimes, totipotent and pluripotent cells are referred to as **embryonic cells**, because they tend to only exist in the most early stages of an organism's life.*



***Multipotent** cells is a term for a more restrictive type of stem cell that can also produce many cells, but where they tend to belong to a family with closely related function. However, these aren't limited to early stages of life, and can be found in different parts of the body at any stage of our lives. An example of multipotency are the **hematopoietic stem cells** in our bone marrow, which produce all of our different blood cells. Multipotent stem cells are also often **adult stem cells**.*

can feel that you've answered a question, or you can solve an equation, but in biology, there are so many questions to solve that you can only approximate. And with those approximations, come more questions. It took me a while to recognize that this was what I really loved about biology."

During that transition from chemistry to biology, she attended a research presentation by Prof. Howard Green. He was visiting from MIT to give a seminar about a special type of skin cell. Dr. Green had taken pieces of human skin and had put this tissue in a culture dish. Under the right conditions, he found that he could propagate the cells endlessly, making more and more tissue. These sheets of skin were used to successfully treat patients with terrible burn wounds.

These skin cells could differentiate to make the many different cells found in skin tissue and they could also self-renew. Initially, these skin cells were not known as stem cells but were called **human epidermal keratinocytes**. Today, these keratinocytes would be considered **multipotent adult stem cells** (see sidebar above). Fuchs vividly remembers: "I listened to that talk and I was just enthralled, and I decided soon after that [Dr. Green] was the person I really wanted to work with."

One of Dr. Green's discoveries was that these skin stem cells needed the presence of other cells to grow properly. And so his lab developed techniques where stem cells would be grown layered on top of regular cells. After Fuchs learned how to do this, she used these techniques to become familiar with skin cells and focused her attention on a class of proteins known as **keratins**. Keratins are important because they give our skin the strength to withstand the stress it endures from the environment. "If you rub your skin, you wouldn't expect to see your skin cells ruined after that", says Fuchs, "but if you do the same to your liver, you'll probably ruin your liver".

Her work discovered that these keratin proteins organize in pairs, which in turn further organize in larger numbers to build networks. Furthermore, by understanding the DNA code of keratin, she could do experiments that introduced errors (called mutations) into the keratin proteins. With this, she attempted to examine how those organized networks could become disrupted. And whilst looking at

these disrupted cells, she started to wonder if these types of genetic errors could result in certain human diseases. Fuchs remembers thinking: "There must be patients that have defects in their keratins, but we didn't know where or how to look".

To help pinpoint the genetic causes of disease, Fuchs pioneered a strategy called **reverse genetics**. Basically, this term describes the process of observing the outcomes and symptoms of targeted mutations and *then* attempting to connect those observations with the diagnosis of a disease. It works backwards, or the reverse, of the then common way of figuring out the genetics of a disease. Before reverse genetics, scientists would start with the diseased patients and use their samples to hunt for the mutations responsible. This was not very efficient because they would generally have to compare many genes from many diseased and healthy patients, all with the hope of finding interesting genetic differences.

With her reverse genetics strategy, Fuchs introduced the keratin mutations into a mouse and observed the effects on the animal. In this case, the mouse would be seen to form blisters coming from the layer of mutated stem cells in the skin. She then worked to correlate those symptoms with existing skin diseases. Because she didn't have a medical degree, Fuchs and her team searched the medical literature. "We bought a dermatology textbook," she recalls, "and compared the symptoms point by point, and found a disorder called epidermolysis bullosa simplex that would cause blistering just from washing your face." The similarities were so striking that she knew that this disease was related to those keratins.

Fuchs' work on keratins was a breakthrough on its own right but her subsequent contributions were equally important and were more focused on the very fundamentals of stem cell biology. In particular, she was inspired by observations noted from the burn patients who were treated with the healthy sheets of skin. She noticed that the skin sheets continued to grow tissue that looked and behaved like skin, but that they were missing certain functions: specifically, they couldn't produce hair or sweat. She surmised that there had to be other sources of stem cells found within the skin that are in charge of producing the hair follicles and sweat glands.

Fuchs and colleagues isolated and identified hair follicle stem cells in the skin, and through their study, also helped confirm predictions that stem cells exist in a state of **frequent cycling**. What this means, is that stem cells can go through cycles of work and rest, whereby there are mechanisms that allow these cells to grow at higher rates when needed, but to also slow down or pause when necessary.

It turns out that these stem cells, found in skin, were an ideal model to study this cycling phenomenon, especially since skin is really good at replacing dead cells, and repairing wounds. Fuchs' work noted how these stem cells could decide when to make new cells and when to stop. For example, she observed that when skin was wounded, stem cells not only became more active, but that they also kept a memory of the wounding, and reacted faster when wounded again.

But why do cells keep this memory? The answer might be in the stem cells' job of repairing wounds. Fuchs' work demonstrated that a wound heals faster if inflicted in a spot that had previously seen inflammation. In essence, the cells' ability to remember might help them do their job quicker.

With so many connections to disease and health,

Sidebar: Because wounds normally produce inflammation, Fuchs did experiments to induce inflammation in the skin and to then look for effects in the cells. Strikingly, cells affected by inflammation showed a great number of changes in how their DNA was packaged. Most of these changes reverted back after inflammation, but many remained like a memory - some of them even after six months. However, this memory also appears to lead to quicker inflammation, which in certain diseases, can result in more damage.

Furthermore, this work might also be important in the fight against cancer. Fuchs currently wonders about the relationship between this disease with wound healing and inflammation.. She explains, "The reason why we became increasingly interested is that every time we generated mice that healed their wounds faster, those mice were also more susceptible to develop tumors". With such intriguing results, Fuchs' team is now actively trying to understand the mechanics of this.

stem cell biology is a truly fascinating and complex field, and Fuchs' discoveries and techniques have been a crucial part of this journey. It is already science that sometimes works like an elixir of life, and further work will continue to lead to new exciting possibilities in human medicine.