Listening to the signals

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Manuela Baccarini's research revolves around cell signaling. Credit: Universität Wien

If something tickles our nose, we sneeze. Behind this simple biological output lies a cascade of cell communication. In an interview with uni:view, Manuela Baccarini, molecular biologist at Max F. Perutz Laboratories, explains why cell signaling resembles a WhatsApp group and how we can prevent cell damage.

In order to work properly, the cells in our body need to communicate with each other. You did a lot of research on this process called cell signaling. Why is it so important?

Manuela Baccarini: Life is adaption and we adapt as an organism because each one of our cells adapts and communicates with the environment. Every second, every cell receives a tremendous amount of signals that need to be integrated in a meaningful biological response. If you ask me a question, I will react to it. If I give a good answer, you will write it down. If I give a stupid answer, I'll probably be allowed to scratch that, but a cell may not be able to do so and something bad might happen to that cell or to the whole organism. The way that cells receive and interpret a signal and react to it with a biological output is central to life. The basic process of signaling is a kind of network, like a network of people in a WhatsApp group. One member starts with the news of a wedding and then everybody answers in a different way. A cell tries to integrate all of the answers into an output. Hopefully, the outcome will be a nice wedding gift or – on a cell level – a positive reaction.

How do cells communicate?

Baccarini: Cells communicate through chemical or mechanical signals. They need receptors to be able to listen to these signals. Receptors are molecules that – as the word suggests – receive a signal and connect with other molecules in the cell. So a ligand that comes in and binds to the receptor will change its conformation, meaning that it will change its shape or appearance. A lot of signaling proteins present in the cell are continuously monitoring the receptor to figure out whether it is free or bound. If it is bound, the proteins themselves will be changed physically. It is as if the receptor would paint a "red dot" on a waiting protein – once this happens, the other proteins will recognize that protein as changed –

as activated – and will react accordingly. It works like a cascade, or like a domino if you wish.

What does it mean for the cell if a reaction starts?

Baccarini: The reactions can be of different nature. There are very fast reactions, involving for instance changes in the shape of a cells; but there are also longer-lasting reactions that involve changes in the whole landscape of the cell. This happens when some of the proteins that are activated when the receptor is bound go to the nucleus of the cell to induce the transcription of specific genes. The cell can then undergo dramatic changes, which could culminate in a complete change of identity. For instance, there are signals that transform immature cells into a mature cells, and signals that cause cells to die.

Can your way of living affect how your cell signaling works?

Baccarini: Absolutely. In fact your way of living exposes you to different signals and elicits different responses from your body. If you lead a healthy life, if you eat plenty of vegetables, your cells will be exposed to anti-oxidant substances which prevent ageing. Cells react to the amount of oxygen radicals they are exposed to. Eating healthy food and exercising can protect cells from the harmful effects of the environment, but of course your genes are just as important. Some people smoke throughout their entire life and get sick very late in their life, others lead a very healthy life and get sick earlier on. But that's no excuse for smoking three packs a day. I would not rely on my genes.

What happens to this signaling system, if something goes wrong, for instance in the case of cancer?

Baccarini: There are several hallmarks of cancer. The first and best-

known is uncontrolled proliferation. The second one is that affected cells become sort of immortal. They cannot be made to die, which is bad because cells should die. And the third hallmark of cancer cells is that they stop differentiating. The cell stops responding to signals that tell it to die or that tell it to go further in the differentiation. What is really important with cancer cells is that the "red dot" I mentioned earlier, the activation signal, cannot be removed from some proteins involved in these basic processes. Signaling should always be reversible, otherwise the cell is locked in a state where it can only fire. Even though the network tries to make the protein listen to reason, the protein has been changed intrinsically so that nobody can stop it anymore. The "red dot" is on all the time. This happens mostly due to mutation. And if that happens to a powerful molecule, very high in the hierarchy of the cell, you have a big problem. Many of the mutations observed in cancer activate key signaling proteins. This means that these proteins, called oncogenes, gain the ability to put red dots on a number of other molecules. If you activate one of these key molecules, you will immediately activate many others.

Is it possible to stop this cascade?

Baccarini: Researchers have developed inhibitors to stop the activity of specific oncogenes promoting proliferation. The inhibitors will modify the oncogenes, preventing them from putting red dots on others and stopping the cascade. Unfortunately, since the cell uses this WhatsApp-like system, it eventually becomes resistant to the inhibitor. Somebody else in the group will do something that will reactivate the proliferation – a tumor resistance mechanism is born. Tumors are able to do this because they are genetically unstable. The genomes of cancer cells undergo many mutations and through this process they become able to activate another pathway – even though you are inhibiting the oncogene initially driving tumor proliferation.

Could stem cells be part of the solution?

Baccarini: Stem cells are very important when conducting research on cancer because their undifferentiated state resembles the state of a cancer cell, although they are very strictly regulated in their proliferation potential. If you study their differentiation, you are bound to better understand what mechanisms make a cell differentiate. And if you can make a cell differentiate, you might also be able to at least halt tumor progression, meaning the tumor becoming more malignant. The other thing I really like about stem cells is their potential for regeneration. With the population growing older and older, it is important to find ways for people to age well. Stem cells of old people are no longer able to renew themselves or to produce new differentiated cells. If we were to understand why they stopped doing that and if we were able to push them out of that state, we would be tapping into a natural resource for spare parts.

Our current semester question is "Health from the lab – What is possible?". What is your answer to this question?

Baccarini: Whatever the major future advances in health will be, they are going to come from the lab. I don't think there is any major innovation without research. I strongly believe that research is the way forward and this has also been shown by the many successes that research has brought to people. Many of the things we now take for granted actually came from a lab. Besides the inhibitors mentioned above, many of which are in the clinic for cancer treatment, all new methods to diagnose cancer in its very early stages came from a physics lab. Or programmes that enable physicians to follow their patients remotely came from bioinformatics labs. There is no innovation without research.

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