Talking to neurons

It was still dark when she called me:

-Mr. Cage, let's go?

-What time is it now?

- Five o'clock. But you need to go to radiology first, remember?

I didn't, but said "yes".

This story started 9 years ago. I was preparing myself for five concerts in South America. I felt excited, but my right hand seemed not to understand Beethoven's wishes. My hand was slow and trembling. "It must be stress", I thought. But it wasn't, unfortunately. The tremor got worse and my right arm was moving slowly, as if it were freezing. The doctors said at that point, they could not be 100% sure of the diagnosis, but I should try some medication. I tried it and it worked very well. The happiness didn't last long. This good response brought me closer to the diagnosis of Parkinson's Disease.

Well, the years went by, the diagnosis was became certain and the symptoms got worse. It seemed that at every visit to the neurologist he would add more pills to my daily diet. The tremors and rigidity also spread to my left side. Walking was quite difficult and even eating was a big challenge. And, if – in exceptional cases- I intended to smile, nobody would notice. I sometimes felt like a statue. One evening my son asked me: "Daddy, why are you dancing like that?" Children can observe and say things an adult wouldn't. These involuntary "dancing-like" movements happened in association with my medication as a collateral effect. At a certain point, I didn't know which was worse: the disease or the drugs against it. And precisely at this point, surgery was proposed. After thousands of questions and fulfilling requirements, I was finally a candidate for brain surgery for Parkinson's Disease. The idea the neurosurgeon told me, was to insert an electrode, connected by a wire under my skin to a pacemaker that would rest in my chest, in my brain. This pacemaker would provide the electrode with the necessary electricity to inhibit some areas in my brain that were working more than they should. And as far as I understood, these areas were overexcited because the brain region that normally inhibits them was slowly dying. It was roughly comparable to kids in a classroom. If the teacher leaves, they can be very excited. So, my pacemaker would return these kids to order, relieve the symptoms and allow me to take fewer pills. The side effects of the medication should then be reduced.

And there I was, going to the radiology department to have a metal frame fixed on my skull and get some nice pictures of my brain with this crown. The neurosurgeon told me about this as if it was the most natural procedure on earth. And I believed it so, until the moment I saw the pins that were about to be screwed in my head. With some humor left, I thought: "Torture instruments from the Middle Ages must be somehow nicer than this one". Yes, it was as bad as it seemed. Not properly painful, as local anesthesia was applied. But the tremor was really

intense, since I had taken no medication and it usually increases in stressful situations. It was not easy to fasten the frame, and not easy at all to hold still inside the tomograph.

Back to the Neurosurgery Department, everyone was waiting for me, as they used to before one of my concerts. The anesthesiologist spoke to me, and even though I knew that I was going to be awake during the procedure, but he assured that I would get some sleep until the doctors needed to talk to me.

Done as spoken, the next sound I heard was the sound of a broken radio, and my doctor's voice:

-Hey James, everything fine?

-As far as it can be, yes, doc. I would not mind if you could just put some music on this radio instead of static…

He laughed and said:

-I understand that for a musician this can be just noise. But these are the sounds of your neurons, James.

-Hum…

I wasn't really in a state that allowed me great discussions, but I could hear and understand well, and he kept explaining.

-So, your neurons communicate with each other using electric signals, as if they released many small sparks each second. Each group of neurons in your brain fires these sparks at a specific rate, and this electrode we are inserting in your brain can transform these electric signals into these sounds you are listening to and you can also see them also on that screen, in the form of waves.

-Keep talking, doc. It is interesting…

- So, in the case of your disease, the neurons of the specific area we are targeting are firing too much, as we said before. The electrode should be placed there so it can inhibit them from firing.

-And how will you know we are at the right place?

-Listening and talking to them…you will see.

Listening to sparse popping of my neurons intercalated with strange questions such as "Are you seeing blue lights?" and the movement of my hand and leg followed over the next few hours.

But suddenly this noise rose as fireworks celebrating the New Year. As the neurologist moved my hand and leg, the noise changed clearly. And, with a single word of the neurosurgeon, the tremor in my right hand stopped and the neurologist could readily move my hand and leg as I haven't done in years.

-I think we are at the right place, doc - I said.

-We agree, James. We found the place indeed. Everything is going to be all right. Thanks for your cooperation and patience, I know it is not easy, but it must be like this. Now you are going to sleep a little bit and wake up in your room. Have sweet dreams!

And I did. But they were not as sweet as the reality of writing this story with my own hand.

Eduardo Joaquim Lopes Alho

Heart Break: A Literal Perspective

A romantic heart break situation: guy meets girl, he likes her and in that instant- Cupid's arrow strikes the cord. In an animated movie this would lead to 'happily ever after,' with many lucky people, it happens in real life too! However, an unhappy ending with a heart break is also not very uncommon. The same is true for a condition called 'Myocarditis'. Myocarditis happens when our own immune system strikes our heart, cells responsible for killing the pathogen break into our heart muscle causing massive edema (swelling in the heart muscle). Symptoms experienced are rapid heartbeat, shortness of breath, swollen joints and tingling chest pain. Of course some of these symptoms are the same for an individual falling in or out of love, except with myocarditis, treatment cost will be covered by insurance. Myocarditis is often followed by viral cold, that is why doctors recommend full recovery before resuming any physical activity.

After heart break, people display emotions like intense anger and anxiety, or the bereavement of the loss might even, in extreme situations, force an individual to commit suicide! Though suicide is an extreme step and happens rarely, it does happen. During myocarditis, our immune cells try to remove the virus or any other pathogen in a very aggressive manner, with the cells being so 'angry' that they penetrate their own organs looking for it. Now, a concept many of us might know of already, is when a baby is conceived, the heart is one of the first organs to develop and the immune system much later. So when immune cells look inside the heart for the first time while seeking a pathogen, they realize that it is something unusual, something foreign, which is clearly its misunderstanding. It is like finding an octopus under the couch in your living room. Any sensible human being will get rid of it at any cost. In the same way, our angry army of immune cells starts accumulating and getting rid of the body's own heart muscle, or at least destroy it extensively. When our immune cells are successful in completely destroying the heart function irreversibly, it causes sudden death. Unexpected death due to myocarditis in kids is up to 20%. In most cases, people recover from myocarditis without any noticeable damage, but sometimes it leaves a scar in the heart muscle. It is exactly like an unfortunate end to a romance, or a break up, when a person might go through intense pain but recover, sometimes with bad memories.

In another scenario, what happens to people who never recover after losing love? On similar terms, what happens to the heart if the immune cells remain angry- angry enough to destroy heart muscle in a slow and consistent fashion? It causes 'Dilated Cardiomyopathy.' If myocarditis is a reaction of an angry teenager who experienced his first heart break then dilated cardiomyopathy is a reaction of a psychopath who has experienced it consistently. Myocarditis is a rapid acute form, whereas cardiomyopathy is a chronic painful form. Symptoms of cardiomyopathy appear when heart muscle is irreversibly damaged and nothing much can be done about it. This eventually creates the need for a heart transplant.

In this condition, over years, our immune system destroys heart cells in a sluggish manner and our body keeps replacing these cells, but the replaced cells are not heart cells. Heart cells are special, they have the ability to contract and relax, which is essentially one's heart beat. The replaced cells are like skin cells, a natural bandage. These skin-like cells will remain there, will

repair the damage superficially, but they will not beat like original heart cells. Thus the heart loses all its ability to function and becomes enlarged (dilated).

Friedrich Nietzsche once said ‘That which does not kill us makes us stronger’. Whoever experienced an emotional heart break will agree that even though it was hard to get through, it was worth it! This is the only thing which might not be comparable to myocarditis. Myocarditis, if treated at the right time in a proper manner, then increases the chances that the immune system becomes familiar with heart cells, accepts them, and never destroys them again. Unlike emotional heart break, myocarditis happens to relatively few number of people and it will never be worth it to have this condition. So, finish all the doses of antibiotics prescribed by the doctor during bacterial infections, take proper rest during those viral colds (especially kids) and exercise regularly to have a healthy heart.

One life, one heart and one destiny!

Priya Panjwani
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Garden on a coverslip

Communicating science to non-scientists often results in confused looks and statements like “This is too complicated.” Often, however, it’s not too complicated but not put in a context they will understand. For example, cell culture is a lot like gardening. Unbelievable? We’ll see …

One topic we’re working on is culturing spiral ganglion neurons to study their dependency on neurotrophic factors. Spiral ganglion neurons are important cells at the interface between the acoustic presentation of sound to the ear and its electrical transmission to the brain. Like other cells, they depend on growth factors, so-called neurotrophins. Since some hearing disorders are caused by a dysfunction of this interface, studying these neurons in a cell culture system might yield new insights into the causes of these diseases.

Therefore, after manual preparation, we can grow spiral ganglion neurons on coverslips. Coverslips are coated with laminin to gain better adherence of the ne urons to the glass surface. Laminin is a protein which is also a major component of the basal lamina in cells and organs, like a scaffold. Coverslips are thus comparable to jiffy pellets which are usually used to start growing plants before replanting them into bigger pots. However, that last part isn’t necessary in growing neurons.

The next step to make sure your plants grow well is, of course, watering and manuring. For us this means regularly exchanging the growing medium, an aqueous solution with several ingredients to prevent the growth of fungus as well as additional factors like the aforementioned neurotrophins. Those work like the nitrogen-phosphorus-potassium combination found in every modern fertilizer. And if one of them is missing or in short supply? Well of course that leads to

stunted growth or none at all.

And what is one aspect every gardener can be spooked with? Weeds! And, believe it or not, this is a problem in cell culture too. Cultures do not solely consist of neurons, but in fact a major portion is composed of glial cells. These cells are important for homeostasis and also constitute part of the myelin, an insulating and protecting layer for the axon of neurons. Glial cells also secrete neurotrophins; however, their secretion can't be controlled and thus might lead to inconsistent results regarding the neurons. Another undesirable behavior is that they proliferate in culture, unlike spiral ganglion neurons, and therefore indeed behave like weeds overgrowing an untended garden. So there are two reasons to get rid of excess glial cells. In a garden the best solution to fight weeds is to rip them out. In contrast, in cell cultures the call is to prevent glial cells from taking over. Therefore, Cytosin-β-D-arabinofuranosid, short AraC, can be added to the medium. AraC acts like a herbicide. It forms a complex with Topoisomerase 1, an enzyme which cuts double-stranded DNA. They start DNA fragmentation and therefore block the replication of glial cells. This helps to keep the number of unwanted cells down.

Another substance we use is Leukemia Inhibitory Factor, LIF, a cytokine which is mostly used in stem cell cultures of mice because it keeps cells in an undifferentiated state but still permits them to proliferate. It lets the neurons grow longer, even better than other neurotrophins do. It can be compared to a plant hormone. Normally, plant growth is controlled by a finely tuned ratio between cytokinin and auxin, both plant hormones. However when auxin concentration drops, for example due to trimming the top of the plant where it is produced (a trick often used by gardeners), vertical growth is reduced and the plant becomes more bushy. This may induce also budding. Therefore, LIF acts in cell culturse similar to auxin in plants.

Nonetheless, all chemical help is in vain if one important part of cell culture is not

mastered and that is the preparation of the desired cells. Likewise, a gardener will not enjoy flowers in full bloom if he doesn't know his weeds from his wisterias. So, a good cell culture composition of many spiral ganglions and few glial cells is also dependent on manual skill. And the latter can only be perfected by practice, which is true for every field that requires manual work.

So, it can be quite tricky to get flowers to grow or achieve a clean cell culture but nevertheless it works on the same principles even though this may seems far-fetched at first. Now, if you'll excuse me, I have to tend to my garden … on a coverslip.