ANTIBODIES,

THOSE PARTY POOPERS

RODRIGO GARCÍA VALIENTE

Prelude - Lots of pathogens, lots of fun

Imagine you are a pathogen, a microorganism (a virus, a bacteria, a fungi, a protozoan, or even some algae!) or a multicellular organism (as a hookworm) that can produce a disease to another organism, your host.

Pick your favourite and then imagine you are the best of your family saga. Your ancestors diseased many hosts and went through a lot, but they always survived thanks to having the best genes and incorporating the best mutations on them. And lucky you inherited those when you were born, perhaps even adding some new good mutations in the process.

So there you are, ready to start your life in a much bigger organism, let's say a human!

Nature is harsh for everyone, and your victim is going to learn the lesson.

Chapter 1: The fun starts

You can enter your human through a wound, the intestine, the lungs... whatever your speciality is. It doesn't matter that much once you are inside.

But your host has defences to fight you: the immune system. Some are used as-is against all the invaders (innate immune system) and some are trained specifically against each unique invader (adaptive immune system).

But, oh boy or girl, aren't you lucky? Your host has never been attacked by any organism that even remotely resembles you. So the adaptive defences of your host have not been trained against you. It doesn't know your weaknesses!

Nor the host's cells nor you can't see, but you all can interact with the environment. Your external membranes are covered by surface proteins (to each its own, made according to the instructions contained on the genes each). Some of them tell you where to go, where to bind, where to feed. Others can help you escape the defenders, perhaps even mimicking host cells or hiding inside them.

Once inside, you start feeding on the host and using it to multiply and produce your offspring. Because of that you need to harm your host, but it's a small price after all.

Nature is harsh for everyone but you, you are TOO good.

Chapter 2: The neighbours are calling the cops

The host reacts to the harm. It uses its innate immune system mechanisms to block your way out of wherever you are. The area gets inflamed and you can't move as easily, everything gets narrower and hard to navigate. The temperature rises (fever!) so you don't work that well. And even worse, the inflammation attracts macrophages, the gluttons of the body, and they eat any damaged or foreign organism (your offspring!) they find. More cells come, as the T killer cells that destroy infected cells.

But even then, most of your offspring survive. They inherited your great genes, and some of them had mutations on them that improved them. Still, these are tough times.

Nature is harsh for everyone, and you are starting to realise.

Chapter 3: Antibodies, those party poopers

There is something floating towards you. It is not alive, small and looks like a Y. It is a small protein called antibody, because it binds to (small) bodies through its short poles (the Fabs). And this particular antibody... is going to bind to you. Well, more correctly, to one specific part of one type of your surface proteins.

And this antibody is not coming alone. Thousands of copies of the same antibody are also coming. And along with them, thousands of different antibodies that are going to bind to the same or other parts of your surface proteins, the ones that were helping you survive this whole time.

So after a while you are all covered in antibodies that are bound to you. They don't let you move that well, they don't let your surface proteins interact well with the environment and it is very annoying. Once bound, they will use their long pole (the Fc) to signal macrophages and other cells to come to attack you.

Things are not looking well.

Nature is harsh for everyone, and you are no exception.

Interlude - Mom, where do antibodies come from?

Antibodies stick great to their target through their Fabs, but the price for that is that their target has to be a very specific structure, and sometimes small or big changes (mutations) in the target can make it bind worse or none at all.

There are "infinite" possible pathogens in the world, each with their own proteins and each with many possible mutations... Does the host have infinite DNA with infinite genes to produce enough antibodies to match this?

No! Even better.

Everything starts with the so-called naïve B cells. Each one produces an unique antibody, created by using genes made from joining genes each picked from a different big pool of antibody-parts genes. And to add more variety, they are not always joined in the same way.

The antibodies produced by B cells are firstly bound to their surface and not released to the medium because they still have a lot of room to improve. They need to go first to the lymph nodes, to structures called germinal centres.

Germinal centres are extremely hardcore schools. Naïve B cells are the students, the cells called FDCs (big and covered in the digested proteins of the pathogen, brought by the macrophages) are the books and the so-called T helper cells are the T-eachers.

In one part of the school, the **dark-zone**, they divide and multiply and "study" (mutate randomly the parts of the antibody that bind the pathogen, sometimes improving the antibody, sometimes worsening it). They multiply so much and occupy so much space that this is why sometimes your lymph nodes are swollen when you are sick.

In the other part, the **light-zone**, they take an "antibody exam" (so they retrieve from the FDCs the more parts of the pathogen's proteins they are able to, the maximum of "books") and are later "evaluated": if they get don't' get enough parts, the T helper cells "fail" them and they have to die (apoptosis) but if they get a decent number of parts, they "pass" and can move back to the dark-zone to continue the cycle. When they are very good and get a lot of parts (a "high grade") they can leave the germinal centres in the shape of plasma cells or memory B cells to then start releasing their unique and uniquely-mutated antibodies to the medium.

Easy-peasy, right?!

Nature is harsh for everyone, so we need to be ready for anything.

Chapter 4: Hey, can we have a second chance?

Perhaps some of your offspring left the host on time and will invade it again in the future. Will they have it as (initially) easy as yourself? No-but-maybe!

Once the party is over, some of the cells that produce antibodies or the T cells will "hibernate" in the body, and be kept sleeping for quite some time until they are needed again. So all the training will not go to waste.

But if your offspring mutate enough... they can bypass these defences! Enough mutations in the target protein can make the host antibody useless. The COVID-19 virus mutated its surface proteins many times and therefore the cells trained with the former vaccines lost their efficiency against new varieties of the virus.

Nature is harsh for everyone, so we need to be ready for anything. That's why we have antibodies.

Afterthought - Real life and the Science of the antibodies

In real life pathogens do not decide what to do, who to attack, how to defend. They are programmed to do so, and they are very well programmed. Our body does the same.

Programmes can fail at some point. Our body has many mechanisms to avoid producing antibodies that bind to our own proteins, but they sometimes fail, as it happens in many autoimmune diseases.

But, **more importantly, programmes can also be improved**.

Imagine easily designing individually customised vaccines to have the best antibodies against a pathogen.

Imagine producing antibodies to attack our cancers (which are made of our own cells, and, as said before, the body avoids producing antibodies against our own cells!).

Imagine using antibodies to deliver drugs directly to their targets. A guided missile against the disease, not harming anywhere else.

Imagine Frankenstein-like antibodies made from two antibodies that can stick to and force to interact to two different cells (tumour-destroying cell and tumour cell) or two proteins in the same cell (that can start a reaction of interest).

Imagine knowing which pathogens and dangers you have been exposed to just by analysing your antibodies and making a prediction using highly-sophisticated computer programmes.

Now **stop imagining, because scientists all around the world are working on this**. It is not easy at all and it will take time until we see this applied to all the possible cases, but it is already happening.

Nature is harsh for everyone and that’s why we have antibodies.

But antibodies are not perfect, and that’s why we have scientists.