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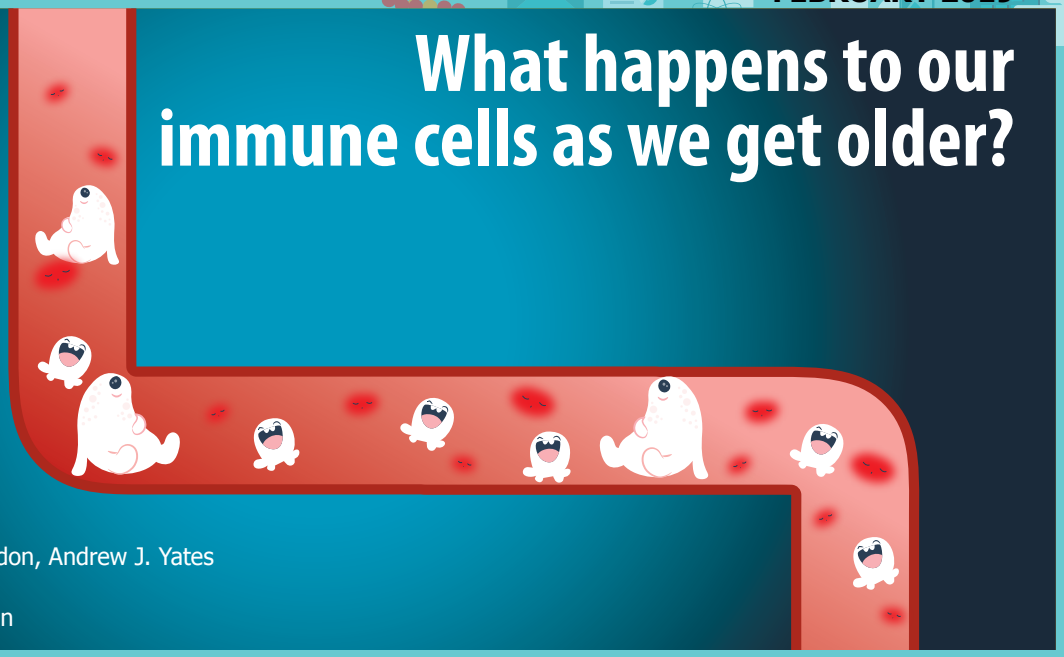
What happens to our immune cells as we get older?



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Abstract

Our *immune system* fights off lots of infections which could harm us. *T cells* are an important part of the immune system. They recognize different infections and protect us from them. Our body makes lots of T cells when we are young, but slows down production after puberty. Nevertheless, the numbers of these cells in our body stays the same even when we are old. We wanted to know how T cell numbers manage to stay so stable. We used data from experiments performed on mice to test a variety of potential ways they might do this, using mathematical models. Our experiments and models show that T cells gradually increase their ability to survive the longer they stay in the blood system.

Introduction

There are disease-causing *pathogens* all around us, things such as viruses, bacteria, and parasites. So why are we not sick all of the time? We have our immune system to thank for that – it combats harmful *microbes* with several lines of defense. What's more, the immune system can remember the infections we get so that if they return, it knows how to fight them off straight away.

The immune system does this by making various types of cells (Fig.1), and the ones we find in the blood are known as *white blood cells*. Different white cells do different jobs. *Granulocytes* kill anything that looks obviously shady, whilst others, like *B cells* and *T cells*, are more clever about how they recognize infections. The immature versions of both B and T cells are made in the middle of our bones (the bone marrow). Whilst B cells mature there as well, T cells grow up in the *thymus* (a gland in the chest), and from there the newly made T cells (which we call naive T cells) circulate constantly through the blood, lymph nodes, and the spleen. Naive T cells do not live forever (in humans they die after a few years, in mice after a few weeks) so it is important that new ones get made all the time to replace the ones that die. Our thymus makes lots of new naive T cells early in life, but it makes fewer and fewer each day as the thymus slowly wears out after puberty.

Despite the slow down in the production of T cells, the total number we have in our bodies stays pretty much the same as we age. What is the reason for this? And how might our naive T cells change throughout our lives? Do they adapt over time, perhaps improving their survival skills or their ability to replenish themselves? Or are some T cells intrinsically fitter than others, simply outlasting the weaker ones? And finally, do T cells compete with each other? These are the questions we wanted to answer.

Figure 1:
Electron microscope image of healthy human blood.
Source: National Cancer Institute

Methods

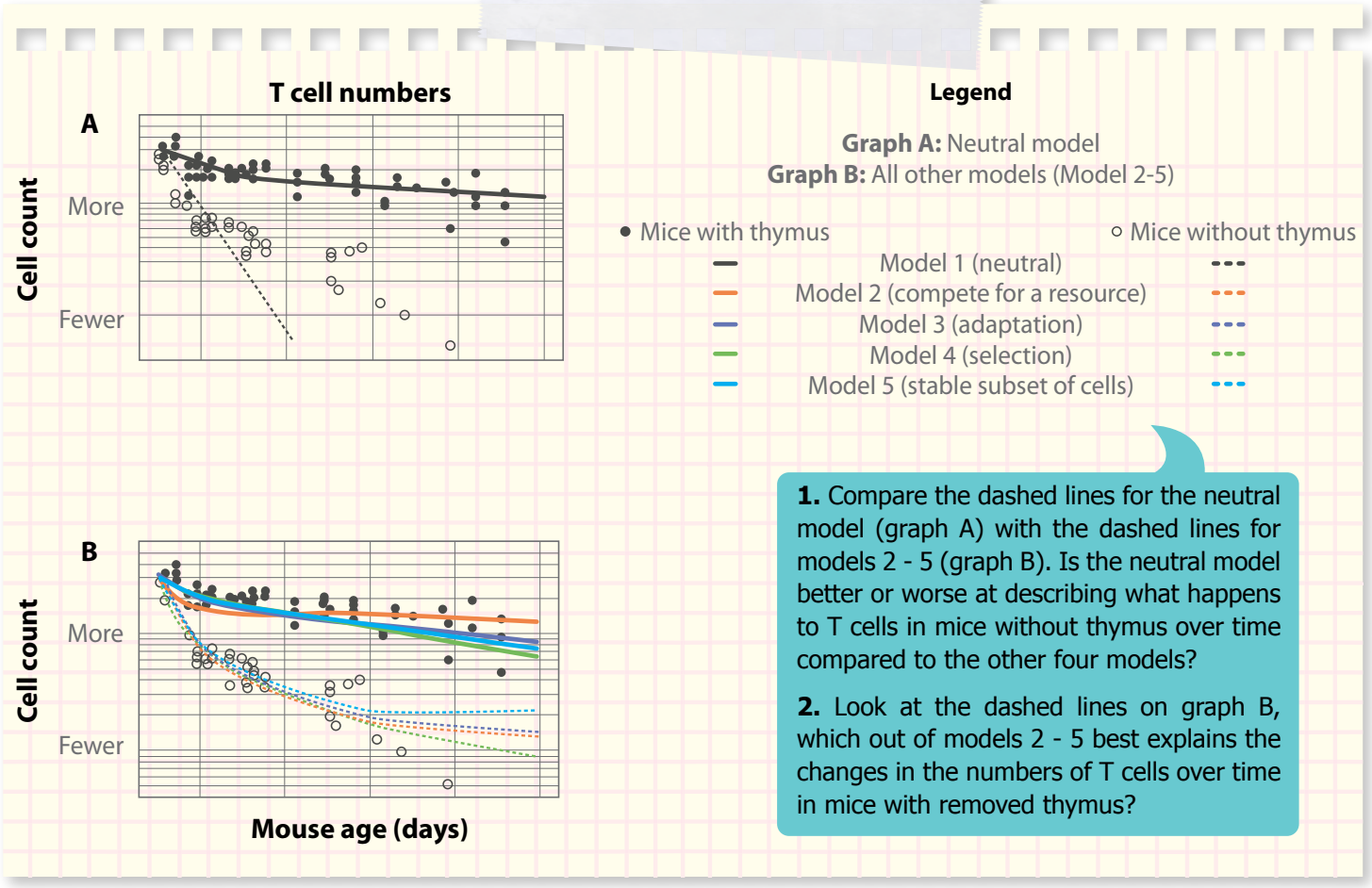
We used five mathematical models to help us understand what is going on with T cells. Each model measures *cell fitness* - the difference between how many cells are being lost and how many are being produced by *cell division*.

- **Model 1** – the neutral model: all T cells have equal fitness, they arise and die at constant rates.
- **Model 2** – the cells' rates of division and loss depend on how many of them there are in the body (i.e. they are competing).
- **Model 3** – the T cells circulating in the body adapt over time, so their fitness increases. This leads to a build-up of older cells over time.
- **Model 4** – T cells are subject to selection (strong ones survive, weak ones die), and cells with higher fitness build up over time
- **Model 5** – we consider the possibility that there are two different sets of T cells: a small stable set, and a larger set of cells which newly created T cells can replace.

To test these models we used data from lots of different experiments with mice (Fig. 2):

- We used data from a study which measured the numbers of T cells for over a year in healthy mice and in mice whose thymus had been removed.
- We did experiments to test how newly developed T cells replace older ones in mice. We carefully monitored new T cells as they were made from the thymus, and watched how the new T cells gradually replaced all the old ones in the rest of the body.
- We used results from a study where the researchers took T cells from either old or young mice, and put them back into young mice and watched how well the different aged T cells could survive.

Figure 2:
Comparison of the ability of the five models to explain how T-cells behave in mice with a thymus and in mice without a thymus.



1. Compare the dashed lines for the neutral model (graph A) with the dashed lines for models 2 - 5 (graph B). Is the neutral model better or worse at describing what happens to T cells in mice without thymus over time compared to the other four models?

2. Look at the dashed lines on graph B, which out of models 2 - 5 best explains the changes in the numbers of T cells over time in mice with removed thymus?

Results

All models did a good job of describing how T cells behave in healthy mice. The neutral model, however, was not able to show what happens to T cells when the thymus is removed.

When we watched how new T cells mixed in with the old T cells, we saw that older host T cells were replaced by newer donor T cells. However, not all of the old T cells got replaced with the new ones. This looked as if certain T cells created early in life can resist being replaced by new T cells generated later in life (Model 5). However, when we watched how new T cells mixed up with old T cells in mice that were young and old, Models 3 and 4 best showed how T cells were being replaced (i.e. T cells were adapting and the fittest were surviving whilst the weakest died away).

In the dataset where T cells were transferred into young host mice, the T cells from the older mice were a lot better at surviving than those from the younger ones. Only Model 3 was able to explain and show what happened with T cells in these cases.

Discussion

Many studies have concluded that the way T cells behave depends on competition for limited resources that keep them alive – for example when there are fewer immune system cells in the body, T cells start to grow and divide more often and increase their lifespan, i.e. they become fitter. T cells are a diverse mixture of individuals though - some of them live longer than others. We asked if this is because T cells are naturally made with a mixture of different fitness levels, or if individual T cells can adapt to their environment in the body and make themselves fitter, or indeed because of competition for limited resources. The model in which cells adapt (their fitness increases as they age - Model 3), was the best way to explain all the different experimental data.

Having said that, even though the adaptation model seemed the most reliable, it is also possible that adaptation works in combination with other mechanisms, like a hardwired selection for fitter cells, or competition for limited resources.

Either way, T cells get more likely to stick around as they age. Is it good for us to have lots of old fit T cells? We are not sure! On one hand, the thymus makes fewer and fewer new T cells as we age, so it's good that there are lots of long-lasting T cells in our bodies. On the other hand, older T cells may not work as well as younger ones. Over time, this might lead to a weaker immune system.

Conclusion

As we age we make fewer new T cells. Older T cells die less often than younger T cells do. We found that the most likely explanation for this is that T cells become better adapted to their environment as they age. Like seasoned warriors, these older T cells are tougher than their youthful counterparts.

To look after your T cells you have to look after your immune system! Scientists are still exploring how the immune system works, but a good start in caring for it is to take care of yourself:

- Get enough sleep
- Eat lots of fruit and vegetables
- Drink a good amount of water each day
- Take regular exercise

Glossary of Key Terms

B cells – a type of white blood cell which is part of the immune system. They recognize specific infections and pathogens and produce antibodies which defend us. B cells mature in the bone marrow (unlike T cells which mature in the thymus).

Bone marrow – tissue which fills the cavity of bones. Blood cells are produced there.

Cell division – the process by which a 'parent' cell divides into two or more cells, known as 'daughter' cells.

Cell fitness – cells' rate of growth (i.e. division minus loss).

Granulocyte – a type of white blood cell which fights infections. They are produced in the bone marrow (see *bone marrow*).

Immune system – a collection of different types of cells in our body who work together to recognize and fight diseases so that you don't get sick.

Lymph nodes – organs, found throughout our body in which B and T cells reside.

Microbes – tiny life forms that surround us - they are too small to be seen by the naked eye. They are found in water, soil, air, and our bodies. Some microbes make us sick, whilst others are vital for our health.

Naive T cell – T cells that have not (yet) been exposed to pathogens are called naive. Immature T cells in the thymus mature to become naive T cells. T cells can stay naive even when they are old and have spent years in our system.

Pathogen – a virus, bacterium or other microorganisms that can cause disease in another organism. For example, HIV, which causes AIDS; or *Vibrio cholerae*, which causes cholera.

Spleen – an organ near the stomach which removes old red blood cells and holds a large pool of white blood cells.

T cell – a type of white blood cell which makes up part of our immune system. They recognize specific infections and pathogens and protect us from them. They are produced in the bone marrow and mature in the thymus.

Thymus – a gland at the back of the neck. T cells mature in the thymus but in time this organ wastes away.

White blood cells (aka leukocytes) – one of the types of cells contained in the blood. They help to defend the body against infectious diseases as part of the immune system.

Check your understanding

1. What would happen if you had an impaired immune system, e.g. you had HIV or another autoimmune disease?
2. According to our study which mechanism best explains the ability of older T cells to live longer in the body outside of the thymus?
3. Why do newly developed T cells decline in number after puberty?
4. Do T cells attack specific pathogens or do they attack anything and everything that looks suspicious and foreign to the body? What about B cells?

REFERENCES

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