**A *gut feeling -* the adventure of immune training**

Every now and then, in your body, an immune cell arrives at the gut. This is what happened to Lilly the T-cell, a young immune cell who studied at the Thymus school. She travelled through the blood until something exciting made her stop. **“The wonderful gut.”** She had heard amazing stories about this place. After wandering around for a while, she had a “gut feeling” that something else was going on in there, deep inside. Lilly the T-cell knew about the rumours of the Great Wall of the gut (which is even bigger than the skin!). The other immune cells told her that this was one of the most dangerous places, because millions of bugs live on the other side of the Great Wall. Any adult cell would have run away from such a place, but Lilly was young, naïve, and adventurous. She had to see it for herself.

As Lilly got away from the blood vessels of the gut and approached the Great Wall, the “gut feeling” of excitement increased, making her a bit nervous and alert. She felt the danger. It was right there, at the border. The cells of the gut that form the Great Wall, called epithelial cells, were constantly shaking, constantly working. Lilly couldn’t see through; they were all packed together. She wanted to know what was happening, so desperately that she started shouting:

* Hey! Gut cells! What are you hiding behind you?!

All the cells around started to look at her a bit angry. *“Go shout somewhere else, kid”*, said one of them. *“Nothing to see here, little T-cell, shut up and leave”*. “*How could these cells be so relaxed with all the noise and excitement around?*” thought Lilly, “*They must be hiding something. I need to know. I must know!*” Lilly was young, but not stupid. She was a top student of the Thymus, and she knew that it was her duty to investigate and to uncover any dangerous stranger. To protect the body. She shouted again:

* Hey! Hey! Who is out there?!

For a moment, all the activity around ceased. Lilly was surprised, she didn’t know she had such power. The epithelial cells were scared, they didn’t know what to say. “*I know nothing, there is only mucus at the other side*”, whispered many of them.

* What is mucus? Is it an enemy? – asked Lilly.
* No! I am making the mucus –a shy epithelial cell replied, hiding between her colleagues on the wall.
* Why are you making disgusting mucus?! Where are the bugs? Show me the bugs! – ordered Lilly.

Lilly had never been so agitated. “*How is it possible that millions of bugs are threatening the gut and these cells are doing nothing about it?*” she thought.

Suddenly, Lilly felt someone behind her. She turned around, raised fists, ready to attack. But before she could do anything, the “gut feeling” changed.

* Hi, young lady. Welcome to the gut – said a relaxing voice. Lilly recognised that kind of immune cell. It was a macrophage. - It is better to keep the voice down. There is already enough noise with everything that’s going on here. We don’t want any misunderstanding, do we?

As far as Lilly knew, macrophages were in the middle rank of the immune army. They do not receive such good training as T-cells do but, at least, they had better control than the first-line fighters, the granulocytes. Macrophages live in the organs, so they know each tissue pretty well, and can help control the immune army. “*However, that is no reason for a middle-rank soldier to talk to her like this*”, thought Lilly. “*I am a T-cell Major*”. But before Lilly could complain, the macrophage extended his hand and introduced himself. His name was Mark.

* How much do you know about the gut? Do you want to hear its story? – asked Mark, the macrophage.

“*I am not a kid anymore. I need no stories. I am student of the Thymus*” thought Lilly, raising her head with pride. But again, she couldn´t reply. Somehow, Mark calmed her again. So, she decided to hear what Mark had to say. Also, Lilly loved stories. Who doesn’t?

Mark the macrophage and Lilly the T-cell went for a walk along the Great Wall of the gut. That walk, and that story, changed Lilly’s life. She never thought she could learn so much from a middle-rank soldier like Mark. That was probably the first lesson: “*Always listen to your colleagues. They may not be as clever as you think you are, but they have valuable experiences*.”

Mark told her that the gut was one of the first organs to exist, when living beings made of one cell evolved to become the big multicellular animals. “*That´s how the cells of the gut became “masters of feeding”, building the Great Wall and providing all the nutrients and energy for the rest of the cells of the body. With their help, other cells had the opportunity to specialize in more specific tasks, such as the protective immune cells. But the gut didn´t do everything alone. It started to work with little*

*bugs, the microorganisms that live inside of the gut that we call “microbiota”. They help us digest food, and in return, they live inside us. The gut is a warm and perfect home for them. As the animals became more complex, with multiple types of cells and friendly bugs, it became more and more difficult for the immune system to recognise who is a friend and who is an enemy.*” Lilly knew that part of the story, of course. She was a Major of the immune army, trained to recognise the molecules that differentiate the cells of the body from dangerous strangers. But she never thought about those friendly bugs. Probably that’s why she got so nervous before. Lilly stopped for a moment and started thinking.

* + Mark, how can I recognise one bug from another? How could I know if they are good or bad? It’s impossible! – asked Lilly.
  + I am not going to lie. It is not easy. I know you have a good memory, but you don’t have to do this alone. We are all here to help. Even the epithelial cells, they are not just standing there. They keep the bugs away with their mucus, and they alert us when there is a breach in the wall… we all have our roles.

Lilly was one of the bravest T-cells, but she felt overwhelmed with all the hard work required to protect the gut. “*I wish I had gone to an easier place*”, she thought. Her job was to study the molecules, called antigens, that help differentiate friends from enemies, and to find the one destined for her. Once she could find her antigen, she would become an expert; she would know what to do and remember it forever. *“But with millions of cells and bugs living in the gut, each of them with multiple antigens… how could she find the destined antigen?”* Lilly was worried. *“It is very easy for bad bugs to hide in that chaos”.* Mark calmed her again, giving his last advice before leaving:

* + We are not here because it is easy. We are here because it is important, to protect us all. There are moments when some of us get tired or stressed. It’s OK. Look around. We are not alone. Others will have the strength to help. And one day, you will have that strength too, and you will know what to do. As long as we all do our part, peace will reign within the gut.

Mark left, and Lilly continued exploring the gut, admiring the Great Wall, and learning its many secrets. The gut was such a great place to learn, that it didn’t take long until Lilly found her “destined antigen”. Another macrophage helped her find it. He extended his hand to the other side of the wall, picked something, and showed it to her. *“Look what I found!”* Lilly couldn´t be happier: It was not from an enemy, but

from a good bug that lived and worked on the other side. She became one of those T-cells that keep other immune cells calm, as Mark did for her.

For the young immune cells that were constantly arriving at the gut, all bugs were a danger, a reason to shout and attack. One day, Lilly found another macrophage. He was younger than the previous ones. It was his first day at the gut. He was nervous, even angry, shouting and calling to arms. But the Great Wall was intact, with the epithelial cells happily tight together. Lilly knew what she had to do. She put her hand in that young macrophage and said:

* I know this world seems scary and threatening. But let me show you the truth. We are all friends here. You are not alone, trust me. Walk with me and I will tell you the story of the gut.

Lilly the T-cell smiled, remembering the last words of Mark the macrophage: “*As long as we all do our part, peace will reign within the gut.”*