COMMENTARY

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Symbiotic Life is a Success of Immunity

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"If you shut the door to all errors, truth will be shut out."
R. Tagore

Abstract

Microorganisms (including viruses) have shaped the evolution of all living creatures since the beginning of life on Earth 3.8 billion years ago. They still put pressure on all living organisms. Because life is symbiotic (i.e., all life depends on other lives), the initial primitive border protection of single cells had to be developed against transgressive microorganisms. Thus, all organisms needed to discriminate self from non-self. With time, this simple recognition system developed into highly complex immunological mechanisms. In the symbiotic relationship, all animals take in and feed trillions of microorganisms in their body, mainly in the gut, to help digest food but also to train their immune system. We need to understand that microorganisms are neither our enemies nor friends. Survival of all life forms depends on maintaining a delicate balance between self and non-self, i.e., microorganisms. Understanding the symbiotic nature of life on Earth might help prevent further destruction of nature.

Keywords: Microorganisms, symbiosis, immune system, evolution, microbiota, environmental balance

Introduction

Not so long ago, a tiny virus has turned our lives upside down. We witnessed how our civilization can fall to its knees so easily. After infecting 770 million individuals and killing over 7 million people across the globe, COVID-19 is still with us. Previously, I shortly examined the coronavirus pandemic from an evolutionary perspective (1, 2). It looks like SARS-CoV-2 is going to stay with us longer (3, 4).

In this "opinion" article, I wish to examine not just coronaviruses but the co-evolution of all organisms and the pivotal role immune systems play. I will first remind you of some basics of the evolution of life, then will go into obligatory partnership and deal with the immune system, which keeps all life in balance. By understanding the begin-

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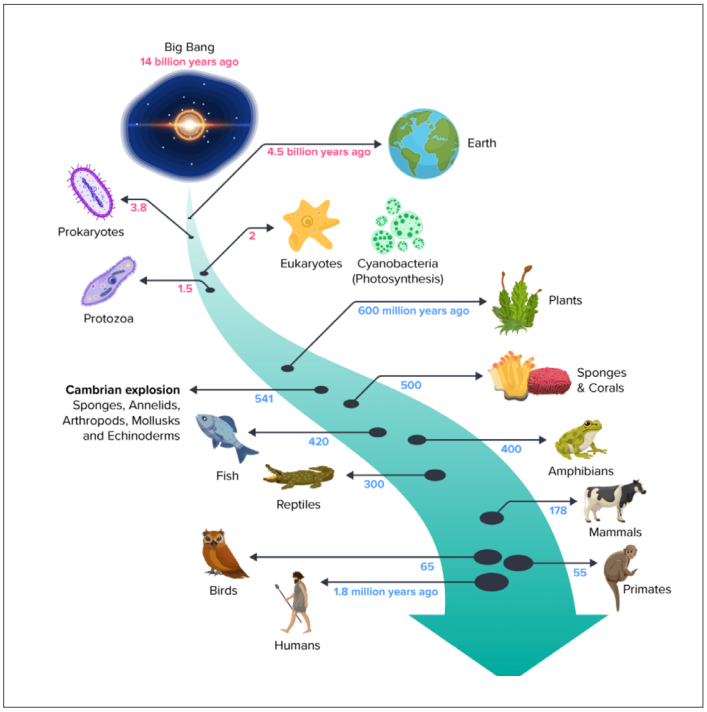

Figure 1. Timeline of evolution. (From Flex Books 2.0. CK-12) (6). nings of

Box 1: Life on Earth in short

- The world is run by microorganisms
- All creatures have to live together/help each other
- Evolution is not a chain reaction
- The engine of evolution is mutation
- Changes (mutations) can disrupt the established balance
- Change survives if it fits to the environment
- Change creates new border disputes between living beings
- Immune systems protect the borders

life on Earth and supporting the conditions of symbiotic life (5), we might reduce unnecessary suffering.

I think humanity has a lot to learn from the microorganisms that are neither our enemies nor our friends. We do not have to hate or love them; we only need to understand them because all other life forms need them. It is only through a deep understanding of the evolutionary process that we can appreciate the value of symbiotic life.

Figure 2. A teaspoon of soil probably contains more life than humans on Earth (9).

Evolution in Short

As shown in Figure 1, the world's first owners are tiny creatures. We have 3.8 billion years of joined history with these first owners of Earth, and their evolutionary superiority continues because microorganisms not only reproduce rapidly but also mutate frequently and exchange genes (by mechanisms such as conjugation, transformation, and transduction). Thus, they keep their superiority in natural selection. They still rule the world for this and other reasons, such as the production of our food and oxygen (algae).

Metagenomic Revolution

Metagenomics refers to the application of sequencing techniques to analyze the totality of the genomic material present in a sample (7). It allows us to characterize the entire communities of microbes in any given environment. Thus, it enables us to understand the complex interactions between different micro/macro-organisms and their environments, including our bodies.

The vital value of Earth has been recognized very early in Turkish culture; “My faithful half is black soil,” said the late Turkish folk poet Aşık Veysel (blinded by smallpox infection, 1894 –1973), who is famous for his love for nature, soil, and people (8). Thanks to the metagenomic revolution, we now know that Earth's value mainly comes from microorganisms; one teaspoon of soil contains more living organisms than people in the world (Figure 2).

Thanks to metagenomic technologies, we now have an idea of the number of microorganisms found in our soil, sea, and atmosphere (Figure 3).

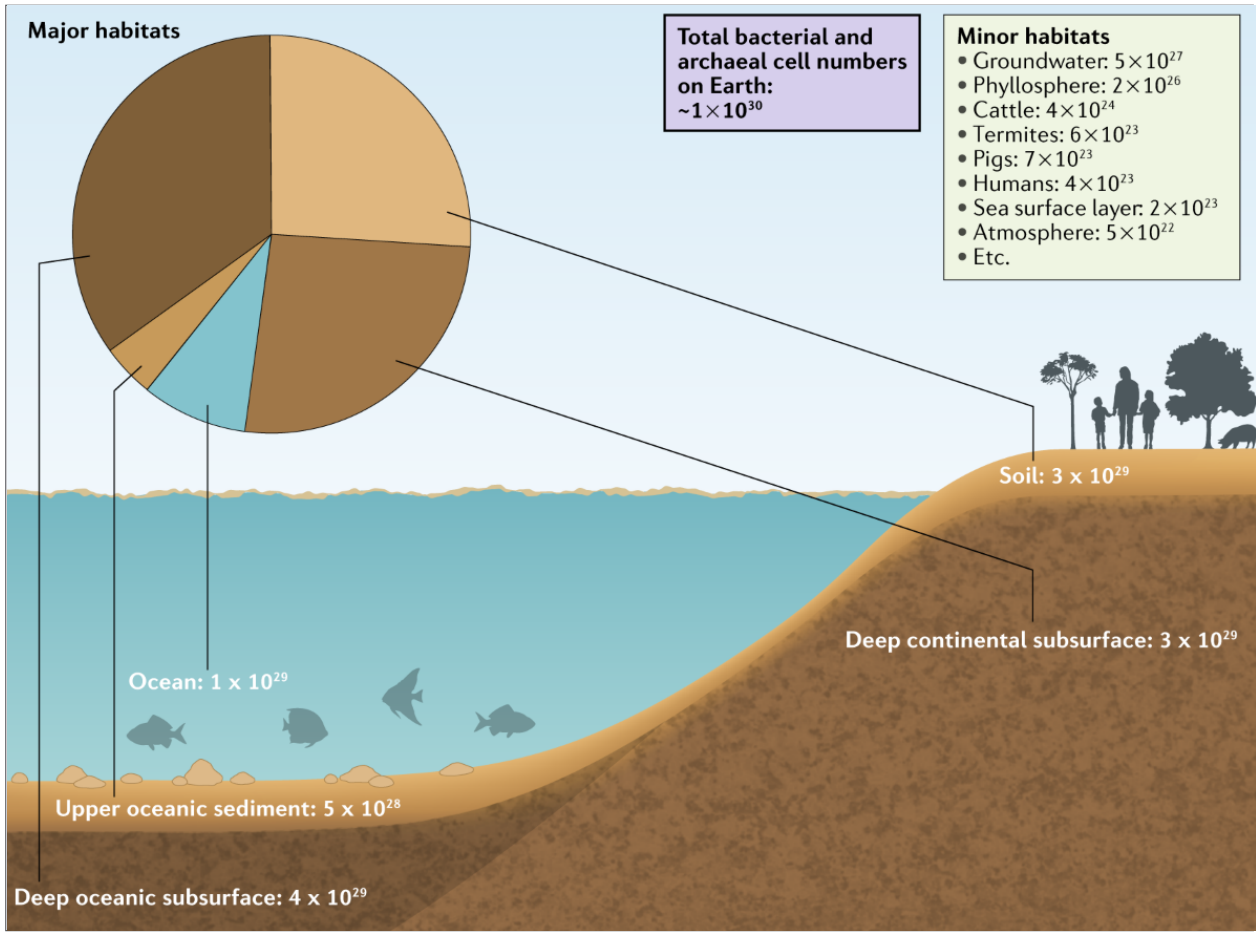

Figure 3. Estimated numbers of microorganisms found in our soil, sea, and atmosphere (10).

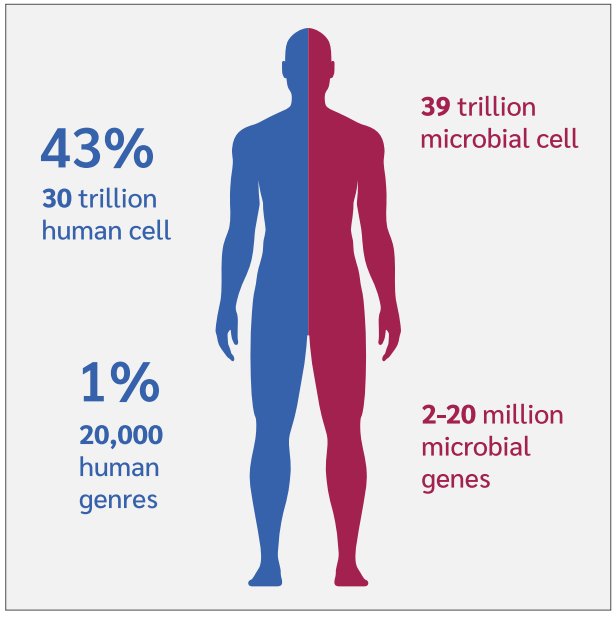

Figure 4. A normal human body contains more foreign cells and much more foreign genetic material than mammalian cells (13).

Microbiome/ Microbiota

These two words are sometimes used interchangeably, but they have subtle differences. **Microbiome** refers to the collection of **genomes** from all the microorganisms in a given environment. Meanwhile, **microbiota** refers to microorganisms that are found within a specific environment. Think of our bodies; there are localized differences in each person's microbiota. Also, our gut microbiota differs greatly from the skin, mouth, etc. Predominant bacterial genera in the oral cavity, respiratory tract, skin, gut, and vagina are unique (11).

The human body consists of an estimated about 40 trillion cells (Figure 4), and only about 40 % belong to us (12). If we look at genetic material in our bodies, 99% of it belongs to microbiota.

Our microbiome is crucial to our health (13). Our microbiota is in symbiosis with us, contributing to homeostasis

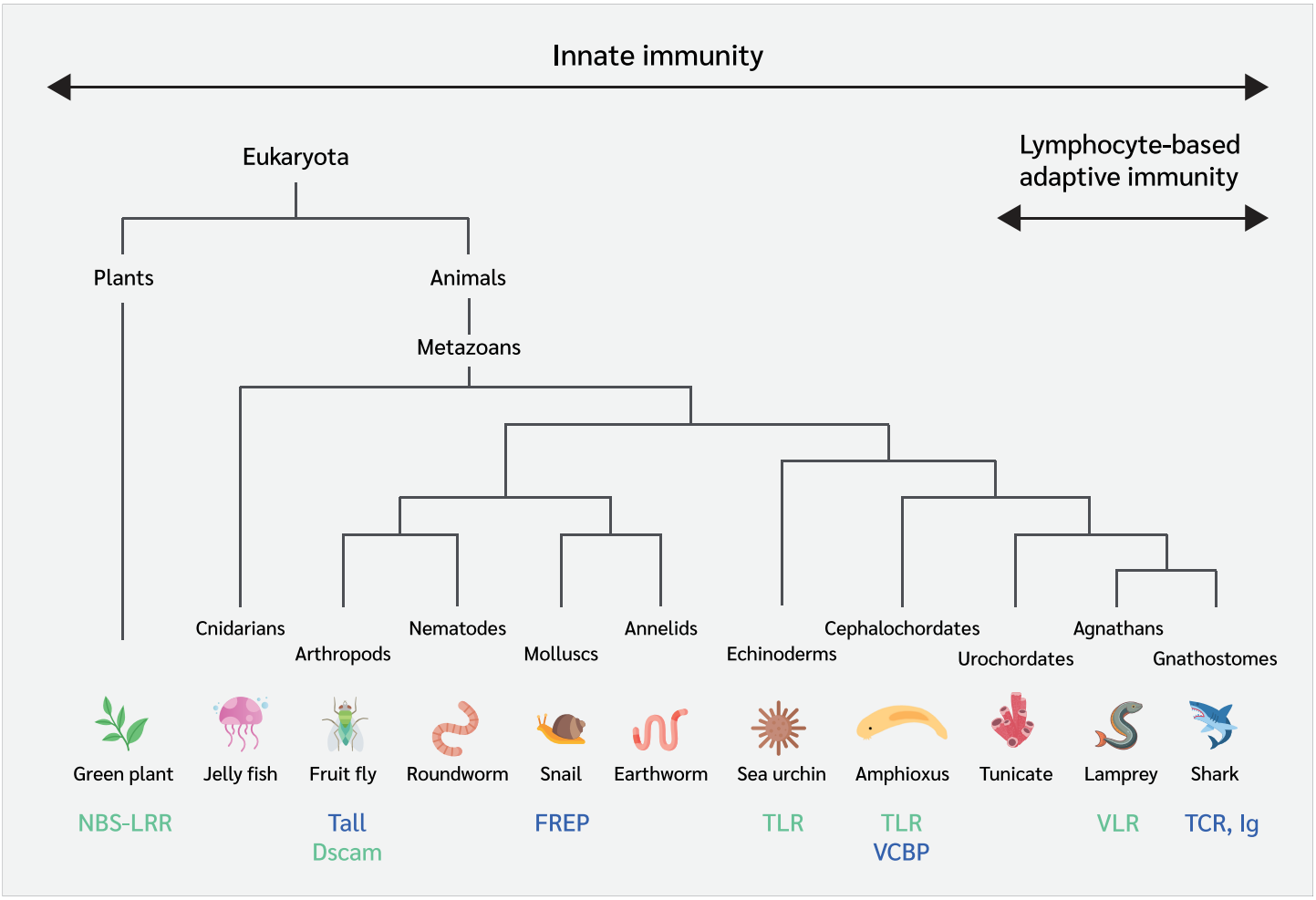

Figure 5. Evolution of defense systems (20).

and regulating immune function. Microbiota dysbiosis can lead to dysregulation of bodily functions and cause diseases. These microbes shape our metabolism and susceptibility to allergic and inflammatory diseases. As it became clear that microorganisms are no longer common germs or pathogens to be avoided—they are a crucial part of what makes us human, there is an explosion of literature that deals with why the gut microbiota is so important, its impact on human health, effect on allergies, or we use microbiota to treat disease, etc. Since the microbiota topic has been intensely reviewed, I only refer to some recent review articles (14-17).

Immunity- A Peace Keeping Organ?

The interaction of different life forms on Earth can be described as a) commensalism, b) mutualism, or c) parasitism. Since all organisms need to protect their cell/body borders, they must have defense systems. In fact, the first immune deference mechanism started in bacteria against viruses millions of years ago. Recently discovered CRISPR system protects bacteria against invading viruses (*bacteriophages*). CRISPR has become a powerful gene editing technology that is now revolutionizing biomedical research and clinical medicine (18). This kind of trillions of years of old protective mechanism,

Box 2: Immunity in short

- Gathers information
- Solves problems; fast (innate) and slow (acquired)
- Keeps records (short and long-term memory)
- Communicates with brain using a common language; hormones, cytokines
- Evolves; changes, is selected, matures over

i.e., foreign RNA/DNA recognition, still operates in our mammalian cells. If a mammalian cell is infected with a virus, that cell protects its neighbor cells by releasing interferon molecules (19).

As shown in Figure 5, starting from plants, metazoans all have an innate immune system that recognizes self and non-self. Only after fish, animals developed adaptive immunity. All jawed vertebrates assemble their antigen-receptor genes through combinatorial rearrangement of different immunoglobulin or T cell receptor gene segments. In humans, this sophisticated mechanism of "somatic mutations" has become so good that they can recognize an almost limitless number of antigens.

Conclusion

"There is no 'final knowledge obsession' in science..."
R. Feynman

If one wishes to understand what life is, one must look at the world under the light of evolution (21, 22). Fast-evolving microorganisms and very slowly evolving multicellular organisms like us must live together. In fact, our bodies are multispecies cell society living together. Therefore, there will always be border disputes (diseases).

Viruses and microorganisms are always one step ahead in evolution. Viruses are always at the center of inheritance (gene) wars and are strong, blind, and ruthless representatives of natural selection in evolution. Since the beginning of life on Earth, viruses and other microorganisms probably have shaped the evolution of all creatures. Recognizing strangers and protecting oneself started in single-celled organisms, evolved over time, and became more complex. The human immune system constantly evolves under the pressure of microbes. The immune system can be viewed as an army that lives together, watches over the borders, and tries to keep peace between multispecies cell populations.

In the natural world, an intricate and diverse web of life exists. It encompasses the interconnectedness of all living organisms, their habitats, and the ecosystems they form (23, 24). If this harmony is destroyed by the current rate of pollution, climate change, etc., consequences will be more frequent pandemics, which most people's immune systems cannot handle.

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