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OPINION

The Immune Response as a Model of Random Natural Selection, from Charles Darwin to Susumo Tonegawa: A (Provocative) Text for Non-Immunologists

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ABSTRACT

The beginning and the maturation of the immune response emulates quite precisely what Darwin wrote in the XIX century about the Natural Selection and the Evolution of the Species. The fierce competition between species made some of them disappear and some changed during evolution, taking this process several thousand years. Incredibly, it is still under discussion by some in our XXI century. Looking at how the immune system maturates its response to a given antigen, one can see striking similarities between this maturation process and what we learned from Darwin's observations, with the biggest difference being the speed. Instead of thousands of years, the immune response evolves in a matter of days or a few weeks, using essentially the same competition mechanisms.

Descriptors: Darwinism; Evolution; Natural selection; Immune response; Immune

A resposta Imunológica como um Modelo de Seleção Natural Aleatória, de Charles Darwin a Susumo Tonegawa: Um Texto (Provocativo) para não Imunologistas

RESUMO

O início e a maturação da resposta imune emulam precisamente o que Darwin escreveu no século XIX sobre a Seleção Natural e a Evolução das Espécies. A competição feroz entre espécies fez algumas desaparecerem e algumas mudarem durante a evolução, levando esse processo vários milhares de anos. Incrivelmente, ainda está em discussão por alguns em nosso século XXI. Observando como o sistema imunológico amadurece sua resposta a um determinado antígeno, podem-se ver semelhanças impressionantes entre esse processo de maturação e o que aprendemos com as observações de Darwin, com a maior diferença sendo a velocidade. Em vez de milhares de anos, a resposta imune evolui em questão de dias ou algumas semanas, usando essencialmente os mesmos mecanismos de competição.

Descritores: Darwinismo; Evolução; Seleção natural; Resposta imune; Maturação imune.

> *"Natural selection acts solely through the preservation of variations in some way advantageous, which consequently endure."*[1]

Since the discovery of genes by Mendel in 1866, a dogma in genetics was established: one gene would be responsible for one protein. This dogma was very logical, considering what was known at the time and what was learned in the many decades that followed. However, it did not answer a question that worried immunologists. Since the concept of antibody was formulated by Erlich at the end of the 19th century, it has been known that each individual must possess an enormous capacity to build different specificities of these agents. With an average repertoire today estimated at well over ten million different antibodies that one person can produce, even if

our entire genome were directed to produce these proteins, we would not have enough genes to generate so many different antibodies.

For decades, this puzzled immunologists and geneticists. It was evident that only a small fraction of our genome could be dedicated to this task. But how can we make so many different proteins with just a small number of genes?

For several years, no proposed theory was accepted due to an absolute lack of consistency. However, at the end of the 1960s, one that finally could explain so many different proteins from a limited number of genes emerged: gene recombination.

Susumo Tonegawa, while working at the Basel Institute of Immunology, was urged to use his experience in molecular biology to elucidate this issue. His approach was to demonstrate that a stem cell in the bone marrow suffers losses and rearrangements in its DNA at the moment it begins to differentiate into a lymphocyte. He proved that these losses were related to a certain group of genes responsible for the production of antibodies in B lymphocytes or in the production of T lymphocyte receptors (shown much later). These findings resulted in a rare publication without coauthors, which in 1987 earned him the Nobel Prize in Medicine, awarded for his discovery.[2]

What Tonegawa proved was that a single gene was not responsible for the synthesis of immunoglobulin, but several. He demonstrated that two important genetic mechanisms do contribute to the generation of antibody diversity.

The first mechanism is the rearrangement itself. Just the shuffling of the V, D, and J genes, as we now know, can produce over 1.2 million different antibodies. This shuffling is entirely antigen-independent.[2]

After that comes another mechanism for generating diversity, also presented by Tonegawa. This one is driven by antigens and much more interesting from the point of view of natural selection.

Mature B cells residing in secondary lymphoid organs are constantly challenged by antigens presented to them. The antibody on the surface of the B lymphocyte acts as a receptor for this cell. Most cells in this repertoire—with their receptor antibodies—do not recognize these potential targets, remain inactive, and will eventually disappear. However, some of these cells, via their antibody/receptor, may experience some interaction with this potential target. In this case, information is sent to the nucleus of these cells, triggering division and multiplication.[2]

Here begins a fascinating mechanism. With each division, this B lymphocyte is subjected to a process called somatic hypermutation. There is no site in the whole organism more prone to mutations than the one that encodes the variable/hypervariable region of immunoglobulin.

The result is that the daughter cell's antibody will often be different from the original mother's antibody initially stimulated. Some possibilities open up:

1. The mutation is silent, and the protein/antibody is the same;
2. The mutation results in a dysfunctional antibody, and the cell is eliminated;
3. The mutation produces an antibody that, while still functional, is less efficient than that of the originally stimulated cell;
4. The mutation produces an antibody that has greater specificity and/or affinity to the target antigen.

As long as this second generation of B cells remains exposed to the antigen that triggered the process, some possibilities are opened. The cell 2, with the dysfunctional mutation, leaves the fray because it has lost the ability to interact with the antigen. Cell 1 will receive the same stimulus load as the previous generation and will continue to expand for another generation at the same pace as previously. Cell 3 will receive less stimulus for producing a less efficient antibody and will multiply less. Cell 4, in turn, for having an antibody/receptor more capable of interacting with the antigen, or more avid for it, will receive a greater stimulus to multiply and consequently will generate more daughter cells.[2]

In a new cycle of division, this whole process is repeated, always with an advantage for the cell, which, through mutation, produces an antibody better in its ability to interact with the antigen. After a few generations, the antibody produced is much more efficient than the original one, which was generated randomly in the bone marrow. This is the main mechanism of maturation of the acquired immune response, in general very similar between B and T lymphocytes.[2]

And what does all this have to do with Charles Darwin?

Is this not a model of natural selection? Is this not the mechanism of *Survival of the Fittest*, in Darwin's words? He wrote:

> [...] in an area fully stocked with inhabitants; … as the favoured forms increase in numbers, so, generally, will the less favoured decrease and become rare. Rarity, as geology tells us, is the precursor of extinction.
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> We have seen that the species which are most numerous in individuals have the best chance of producing favourable variations within any given period. … Hence, rare species will be less quickly modified or improved within any given period; they will consequently be beaten in the race for life by the modified and improved descendants of the commoner species.
>
> [...] in the chapter on the Struggle for Existence that it is the most closely-allied forms,—varieties of the same species … —which, from having nearly the same structure, constitution, and habits, generally come into the severest competition with

> each other; consequently, each new variety or species, during the progress of its formation, will generally press hardest on its nearest kindred, and tend to exterminate them.[2]

The maturation of the adaptive immune response, therefore, follows exactly the model of Darwinian natural selection, where we can replace the word "species" with "B (or T) lymphocyte clone." In both cases, randomness plays a fundamental role, producing mutations that may or may not bring a competitive advantage. Once the advantage is obtained, it will inevitably lead to the disappearance of the species, or lymphocyte clone, which has lost competitiveness for survival.

The Theory of Natural Selection took decades to begin to be taken seriously. Its universal acceptance still faces resistance and depends on meticulous observations and findings, mostly in fossils. It took millions of years of evolution caused by mutations and selection to reach the current stage where we are.

The adaptive immune response is a model of natural selection that can be observed over a period of weeks. The selection and improvement mechanisms are the same. It is the Darwinian selection in *warp speed*.

CONFLICT OF INTEREST

Nothing to declare.

DATA AVAILABILITY STATEMENT

All data sets were generated or analyzed in the current study.

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REFERENCES

1. Darwin C. On the origin of species by means of natural selection, or the preservation of favored races in the struggle for life. Norwalk: Easton Press; 1991. p. 83-4.
2. Tonegawa S. Somatic generation of antibody diversity. Nature 1983;302:575-81. https://doi.org/10.1038/302575a0