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LETTER TO THE EDITOR

The Immune Response as a Model of (Really?) Random Natural Selection

A Resposta Imune Como um Modelo de Seleção Natural (Realmente?) Aleatória

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Dear editor,

We read with great interest Jorge Neumann's provocative text, "The Immune Response as a Model of Random Natural Selection, from Charles Darwin to Susumu Tonegawa." The analogy about how the maturation of the adaptive immune response results in a more efficient antibody population, similar to "survival of the fittest," is quite interesting and thought-provoking.[1]

However, as immunologists, we noticed that this elegant view hides an even greater complexity regarding lymphocyte memory responses. Just as in life, where the fittest does not always win, in immunology, the selection of memory T lymphocytes is not a simple race where the hungriest wins. Actually, the immune system memory acts as a sophisticated strategist that prioritizes diversity over maximum affinity to ensure long-term protection.

While the effector response, which fights the current infection, is dominated by high-affinity T cells, which are considered the "best" for such an immediate task, the establishment of memory cells, those which would be able to fight future reinfections, follows different rules. In fact, memory, instead of keeping the high-affinity and highly specific lymphocytes, will save lymphocytes with intermediate behaviors, not the worst/weak fighters, but also not the best/very skilled and specific ones. Although at first glance this may not seem to be a good strategy, it is, in fact, an approach that perfectly fits a world where pathogens could mutate, being capable of even altering antigenic epitopes. If the memory cell pool were composed only of cells with the highest specificity and avidity towards the original antigen, a small mutation in the pathogen could render such memory useless.

Studies point to this complex relationship between affinity and memory cell formation: reduced antigenic affinity, combined with a decrease in T cell receptor (TCR) signal intensity, can lead to enhanced and accelerated development of memory T cells, suggesting that the selection of these cells is not a simple competition, but a process fine-tuned by multiple factors acting together.[2]

Recent research, such as that described by Kavazović et al.,[3] demonstrates that low-affinity T cells, which otherwise would be suppressed in the effector phase of the immune response, follow an intrinsic survival mechanism that allows them to become memory cells. They do not proliferate as rapidly as high-affinity cells, but are protected by a transcription factor called Eomes, which promotes the expression of the Bcl-2 protein, preventing cell apoptosis and ensuring the survival of a wide range of cells, with different affinities towards the original selective factor. Actually, the absence of Eomes leads to a less diverse pool of memory cells that, while responding well to the original pathogen, are significantly less effective against mutant variants. This demonstrates that a more permissive selection for the memory pool, which includes "less avid" T lymphocytes, is actually an evolutionary strategy of the immune system itself.[3]

In conclusion, the immune response is, in fact, a model of natural selection; however, its complexity forces us to go beyond mere "survival of the fittest." Actually, we could argue that a new layer of selection should be envisaged, "diversifying selection", where distinct needs (effector response versus immunological memory) will represent different selective drivers. In effect, it shows us that diversity trumps extreme specialization when it comes to ensuring the long-term survival of a species.

CONFLICT OF INTEREST

Nothing to declare.

AUTHOR'S CONTRIBUTION

Substantive scientific and intellectual contributions to the study: Mayer AM, Chies JAB. **Conception and design:** Chies JAB. **Data analysis and interpretation:** Mayer AM, Chies JAB. **Article writing:** Mayer AM. **Critical revision:** Chies JAB. **Final approval:** Mayer AM, Chies JAB.

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