Thermodynamics as the driving principle behind the immune system

A termodinâmica como princípio motriz do sistema imune

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ABSTRACT

Over the last 120 years, few things contributed more to our understanding of immune system than the study of its behavior in the host/parasite relationship. Despite the advances though, a few questions remain, such as what drives the immune system? What are its guiding principles? If we ask these questions randomly, most will immediately answer "defend the body from external threats," but what exactly do we defend ourselves from? How do these threats harm us? What criteria define what constitutes a threat? On the other hand, if the immune system evolved to defend us against external threats, how does its action against "internal" processes, such as neoplasms, qualify? Why do we die from cancer? Or from infection? Or even, why do we die at all? These apparently obvious questions are nor simple neither trivial, and the difficulty answering them reveals the complex reality that the immune system handles. The objective of this article is to articulate for the reader something that he instinctively already knows: that the decisions of the immune system are thermodynamically driven. Additionally, we will discuss how this apparent change in paradigm alters concepts such as health, disease, and therapeutics.

Keywords: Immunology; Physiopathology; Thermodynamics; Ecology; Therapeutics

RESUMO

Nos últimos 120 anos, poucas coisas contribuíram tanto para a compreensão do funcionamento do sistema imune quanto o estudo de seu comportamento na relação hospedeiro/parasita. Apesar do avanço, algumas questões permanecem sem resposta clara, como, por exemplo: qual o objetivo do sistema imune? Qual o princípio de sua atuação? Se perguntarmos aleatoriamente, a maioria imediatamente responderá: "defender o organismo contra invasores externos", mas exatamente do que nos defendemos? Como esses invasores nos prejudicam? Quais critérios determinam o que é um invasor? Por outro lado, se o sistema imune existe para nos defender de invasores externos, como qualificar sua atuação contra processos "internos", como as neoplasias? Por que morremos de câncer? Ou de infecção? Ou mesmo: por que morremos? Essas perguntas aparentemente óbvias não são simples nem triviais e a dificuldade em respondê-las revela a complexa realidade que o sistema imune administra. O objetivo deste artigo foi articular, para o leitor, algo que ele instintivamente já sabe: que as decisões do sistema imune são tomadas segundo princípios termodinâmicos. Adicionalmente, discutiremos como esta aparente mudança de paradigma altera conceitos como saúde, doença e terapêutica.

Descritores: Imunologia; Fisiopatologia; Termodinâmica; Ecologia; Terapêutica

A thermodynamic perspective of life

Immunity presupposes coexistence for, were there only a single organism on Earth, it would be unnecessary. However, our planetary reality is exactly the opposite. Whether in deep-sea volcanoes[1] or in a crevasse 3.5km below Earth's surface[2], there seems to be no niche not colonized by one or more organisms. In some cases, this cohabitation leads to the establishment of relations such as commensalism and mutualism, where one or many benefits and in others, to their counterparts: parasitism and predation, in which one benefits in detriment of the other. But at the root, what is the essence driving the relationships between these beings? At their core, these relations are based on an organism's ability to acquire energy and retain it to itself. When we mention "energy", we mean the chemical potential energy stored in the bonds of high-energy molecules, such as carbohydrates or triphosphate nucleosides continually used to maintain the chemical cycle we call "metabolism." The role of metabolism, on the other hand, is to enable the synthesis and/or modification of the compounds necessary for structuring the body of this organism, the degradation

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of undesirable compounds, and the chemical reactions required to keep it functional. This observation is critical because, from bacteria to whales, what we recognize as Life is precisely the presence of an active metabolism.

Like any other process, metabolism is subject to the same thermodynamic laws valid for the entire universe such that, without replenishment of the energy used to perform work or lost as entropy, it decelerates until it stops. This is also the reason why all organisms need to continuously search for this replenishment, either by autonomously producing high-energy compounds via sequestration of energy radiated from natural sources (autotrophism), or by acquisition of these compounds from other organisms (heterotrophism).

Given that metabolism evolved chaotic and randomly, far from perfect, it assembles as an infinitely complex set of chemical modules connected by trial and error, and operating together in a symphony refined over eons to the point where multiple evolutionary solutions, such as proteic catalysts (enzymes) and energy transporters (triphosphate compounds) allowed different possibilities to, in the end, defuse the unavoidable energy bottlenecks. As a matter of fact, it is noteworthy that optimization of the acquisition, retention and allocation of energy is the very driving principle behind Darwinian natural selection. All that nature created and selected had, as their purpose, the enhancement of these traits.

Concretely, this means that were it possible an energetically perfect and 100% efficient metabolism, its owner would need very little nourishment and would be near immortal and eternal. As, in reality, all metabolisms are full of inefficiencies, their upkeep demands significant and continuous energy expenditure. Once enough energy is available, the organism has no problems forfeiting the energy debt required to keep its vital processes within acceptable homeostatic parameters, or, in other words, to sustain that dynamic balance we call "health." If, however, energy becomes scarce, it is more difficult to pay this debt and the organism is forced to prioritize vital metabolic pathways in detriment of others. These options force the reorganization of the homeostatic equilibrium to a new arrangement, almost certainly inferior to the previous one, and the metabolic and functional substrates of the neglected pathways start causing local and/or systemic dysfunctions recognized as signs and symptoms. In other words, what we call "disease" is nothing but the tangible reflection of the sacrifices made by the organism to prevent the collapse of its metabolism. The greater the inefficiency, the bigger the debt thus, the harder to forfeit it and therefore, the graver the disease. Finally, when the debt becomes unpayable, the cycle is interrupted and life ceases.

A natural conclusion of this rationale is that surviving a challenge depends more on the ability of an organism to collect, mobilize and allocate adequate energy resources, than on the nature or intensity of the challenge itself.

Evolutionary dividends of an immune system

Whether as restriction enzymes in bacteria, antimicrobials in fungi, antibodies in mammals, or coelomocytes in sea urchins, there is no organism devoid of some sort of immunity, no exceptions. This observation indicates that, despite representing a hefty investment of energy, immunity pays high dividends. What then would be the evolutionary benefit of an immune system?

Briefly, the immune system exists because it is the most economical way an organism can use to guarantee for itself the integrity and monopoly of its energy reserves for its own needs. In other words, its function is to eliminate any element that insists on remaining unresponsive to the organism's homeostatic controls and/or causes unproductive energy expenditure. Thus, bacteria consuming nutrients in the internal environment, toxins hindering the adequate function of an organ, or tumors proliferating in spite of the homeostatic limits are indistinguishable for the immune system. They all represent unproductive energy expenditure, which makes them intolerable and marked for elimination. Only the methods vary.

In conclusion: wherever the control of energy reigns as supreme indicator of evolutionary success, having an efficient immune system represents an invaluable advantage.

Health, disease and treatment from the thermodynamic perspective

The particularities of the thermodynamic rationale are better appreciated when contrasted with what we shall call the "hygienic perspective": a different approach on the relationship between organisms with an anthropocentric bias, that tends to consider harmful the presence of microorganisms. For example, if we analyze the definition of parasitism proposed by Markell, it states that "parasitism is an intimate and prolonged relationship in which an organism, the host, is harmed to a certain degree by the activities of another organism, the parasite"[(3)]. Note that the very definition of parasite involves damage to the host. It is an absolute definition, with no room for debate or attenuating factors.

In the thermodynamic approach, exactly as postulated in Hess' law, the number and nature of the organisms involved is totally irrelevant, and only thing that matters is the final balance of energy (or Gibbs' free energy). Since this approach allows flow in either direction, concepts become relative.

To better illustrate it, let us consider *Ascaris lumbricoides*, an organism which few would deny as being the "prototype of a parasite." By the hygienic perspective, ascaridiasis is a disease and demands treatment. By the thermodynamic perspective, one needs to weigh the numbers before drawing conclusions. If the host is a healthy organism, ascaridiasis truly represents a small but unnecessary and unproductive drain of energy. Its presence contributes to an unfavorable balance of energy and therefore, it is immunologically unacceptable. On the other hand, in the process of adapting to life as a parasite, ascaris learned to downmodulate its host's immune response, reducing its inflammatory potential and therefore, if we consider this very same infection in patients with inflammatory bowel disease, we will perceive a significant improvement of the autoimmune inflammation, with an economy of the energy wasted unproductively by the disease. One could conclude, then, that the infection represents an improvement in the balance of energy, with direct benefit to the host, so, in stark contrast with the hygienic perspective, ascaris should no longer be classified as a parasite, but as a mutualist.

Other examples mark this difference: the infusion of the Calmette-Guérin bacillus as treatment for bladder tumors[4], the use of larvae for debridement of necrotic tissue[5], fasciotomy in the treatment of compartment syndrome or even a surgery to excise a tumor. Looking deeper into this last example, the only justification for submitting someone to a procedure of this nature is the promise that the elimination of this neoplastic energy drain will allow an energy surplus, that will be used by the patient's physiology to promote the reestablishment of homeostasis and cure, that is, the very rationale behind the principle of risk/benefit that guides medical practice is thermodynamic.

In conclusion, according to this thermodynamic premise, a therapeutic intervention is only justified if, in the end, it improves the energy balance of the organism, and this can only be done in two ways: a) by unequivocally identifying an energy bottleneck that can be corrected (for example: iron-deficiency anemia), or b) an energy drain that can be eliminated (for example, tumors or infections). To believe that, beyond these two possibilities, we are able to make our infinitely complex and predominantly unbeknownst metabolism perform better than stipulated in its internal program, continually tested and refined over 3.5 billion years, represents dangerous hubris.

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