ARQUIVOS DE ASMA, ALERGIA E IMUNOLOGIA

Review Article

Evolutionary aspects of immunopathological phenomena with emphasis on COVID-19

Aspectos evolutivos dos fenômenos imunopatológicos com ênfase na COVID-19

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ABSTRACT

Natural selection is the main mechanism by which species evolve, and it favors phenotypes associated with an effective immune defense against pathogens. However, human immune responses and the occurrence of immunopathological phenomena vary considerably from individual to individual. Infection with SARS-CoV-2, a virus of the *Coronaviridae* family causing the disease known as COVID-19, induces exacerbated inflammatory immune responses and cytokine storm in severe cases. In this review, we discuss, in the light of Evolution, this apparent paradox between the immune responses and the 3 main factors contributing to the maintenance of hyperactive phenotypes: the cost-effectiveness of immune responses, coevolution, and the life history of the species.

Keywords: SARS-CoV-2, cytokines, biological evolution.

RESUMO

A seleção natural é o principal mecanismo da evolução das espécies, e favorece fenótipos com defesas imunes efetivas contra patógenos. Entretanto, há uma grande variação das respostas imunes entre os indivíduos da espécie humana e a ocorrência de fenômenos imunopatológicos. A infecção com o vírus da família *Coronaviridae*, SARS-CoV-2, responsável pela doença conhecida como COVID-19, induz a respostas imunes inflamatórias exacerbadas e à tempestade de citocinas, nos casos graves. Nesta revisão discutiremos, à luz da Evolução, esse aparente paradoxo entre as respostas imunes, e os três principais fatores que contribuem para a manutenção dos fenótipos hiperativos: o custo-benefício das respostas imunes, a coevolução e a história de vida da espécie.

Descritores: SARS-CoV-2, citocinas, evolução biológica.

Introduction

The 1st International Symposium of Immunopathology, held in 1958, gathered for the first time researchers interested in the impact of immunology on medical practice. After this symposium, immunopathology was defined as the study field on immune reactions that cause, modify, or follow pathological states.[1] In a teaching monography published in 1978 by the *American Journal of Pathology*,[2] Stewart Sell called attention to the ambiguity of the word immunopathology, composed of two terms with different meanings: immunity, which refers to protective immune responses against external agents, and pathology, which is the study of diseases.[2] Pathological conditions such autoimmune diseases, hypersensitivity, and allergies to innocuous substances or foods, and pathogen-induced immunopathological phenomena result from inappropriate immune responses. Optimal immune response results in pathogen elimination and reestablishment of organism's homeostasis without causing cell and tissue damage.[3,4]

There is an apparent paradox in the immune system of the human species, because natural selection, the main mechanism of Evolution, should select phenotypes with effective immune defenses against pathogens; however, human immune

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responses and the occurrence of immunopathological phenomena vary considerably from individual to individual.[4,5] Infection with SARS-CoV-2, a virus of the *Coronaviridae* family, responsible for the disease known as coronavirus disease (COVID-19) and for the pandemic experienced recently,[6,7] is one example of this paradox. Mortality rates from this disease are approximately 3.7%, reaching 50% in critically ill patients.[8] The main symptoms associated with COVID-19 are fever (98% of patients), cough (76%), dyspnea (55%), and myalgia or fatigue (44%). Severe disease is characterized by pneumonia and severe acute respiratory syndrome (SARS).[8]

The SARS-CoV-2 virus colonizes upper airways and the nasopharyngeal cavity.[9] The innate immune system is involved in initial response to infections, with the participation of Toll-like receptor (TLR)-3, TLR-4 and TLR-7, which bind the following viral molecules, present in the cytoplasm of the infected epithelial cells: dsRNA, Spike protein, and ssRNA, respectively, resulting in the production of various cytokines with antiviral effects, such as interferons (IFNs) and interleukin-6 (IL-6), an inflammatory cytokine (Figure 1). Adaptive immune response, which is critical for viral clearance, has the participation of T CD4, T CD8, and B lymphocytes and antibodies.[8,9] With the migration of the dendritic cells that internalized viral antigens to regional lymph nodes, there is activation of T lymphocytes (Figure 1). These proliferate and migrate to the lung, inducing local cytokine production and cell recruitment.[8,9] However, antiviral immunological responses may result in immunopathology, when high levels of inflammatory cytokines and chemokines, such as IL-1β, IL-6, IL-8, IL-12, tumor necrotizing factor (TNF-α), and IFNs are systematically produced in the lung, leading to increased immune activation and inflammation and creating a positive feedback loop, which results in extensive tissue lysis and loss of organ function (Figure 1).[8-10]

Although the severity of clinical manifestations of COVID-19 is related to systemic conditions manifested in infected individuals,[6] the intensity and reactivity

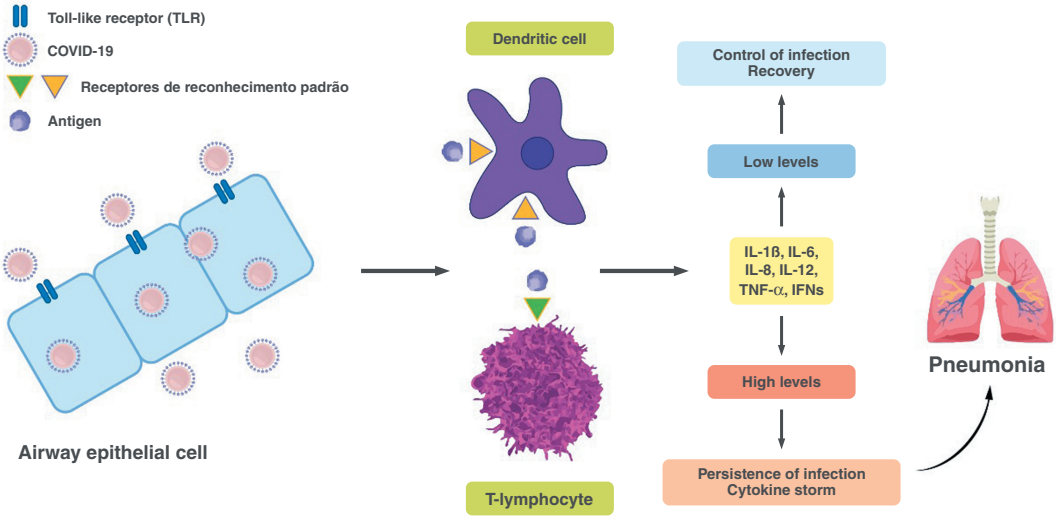

Figure 1
Schematic representation of immune responses against the SARS-CoV-2 virus

The virus interacts with Toll-like receptors (TLR) in airway epithelial cells, inducing the production of cytokines. Dendritic cells transporting viral antigens migrate to regional lymph nodes, present these antigens, and activate T lymphocytes, which migrate to the lungs. Individuals may exhibit different immune response profiles: one leading to the production of controlled levels of inflammatory cytokines, which results in viral clearance and recovery of the infected individual; and another leading to the production of very high levels of inflammatory cytokines, which causes persistence of viral infection and pneumonia

of immune responses, and consequently disease outcomes, vary among infected individuals. Uncontrolled inflammation, known as hyperinflammatory syndrome or cytokine storm, is directly associated with mortality and results in SARS.[8] This review aims to discuss, in the light of Evolution, the following question: why are exacerbated immune responses, such as uncontrolled production of inflammatory cytokines, observed in COVID-19 and also in septic shock and malaria,[13] maintained in the population?

In Evolutionary Medicine, the theory of Evolution is applied to the understanding of health problems and improvement of medical approaches.[14] Initially, one may consider that immunopathological phenomena conflict with Darwinism and Evolution,[4,12] because natural selection operates in the immune system to optimize it and maintain the phenotype most adapted to the environment where an organism lives.[4,5,11] However, natural selection also favors "defective" immune responses, which result in immunopathological phenomena, i.e., in phenotypes with propensity to excessive inflammatory responses. The three main factors that contribute to the maintenance of phenotypes with hyper-reactive responses are: cost-effectiveness, coevolution, and the life history of the species.[4,5,11,12] In this review, we discuss these factors and answer the aforementioned question.

Data sources

A non-systematic literature review was performed, with search and selection of articles available in the PubMed, SciELO, Web of Science, and Google Scholar System databases and published from 1957 to 2022, in English or Portuguese, with no location restrictions, using the following words: "SARS-CoV-2", "COVID-19", "immunopathology", "inflammation", "cytokines" or "Biologic Evolution". The literature search was conducted in January 2022.

Cost-effectiveness

Although fine adjustments of immune reactions to stressful situations occur frequently, the intensity of immune responses varies considerably from individual to individual, ranging from sterile protective responses to hyper-inflammation, a fact that can be explained by trade-off.[5,15,16] The concept of trade-off refers to selective conflicts in which a species, by following an advantageous evolutionary pathway, "will pay a price" for it, i.e., there will be some disadvantages associated with this biological innovation.[5,17,18] For example, the costs for complete viral clearance are tissue damages caused by immune system cells when combating the pathogen.[5] Mathematical models of several situations related to infections[5,19,20,21] indicate that the risk of death due to infections with virus species that has a transmission pattern similar to that of SARS-CoV-2 is higher than the risk of death due to immunopathological phenomena resulting from immune responses. Natural selection will favor more reactive and intense immune defenses, even with some risk of death to the host.[5,22] However, there are two additional costs: the possibility of errors in antigen recognition (self-recognition, causing autoimmune diseases) and collateral damage exacerbated in the infected tissue.[5,20-23]

A meta-analysis of 86 studies of cytokine gene knockout mice showed that the risk of death due to infection is higher than that due to immunopathological phenomena.[24] For example, animals IL-10$^{-/-}$, i.e., which did not produce this anti-inflammatory cytokine, infected with the murine cytomegalovirus showed a decrease in immunopathological effects in the liver, whereas viral replication and mortality rates increased.[26] Therefore, increased viral load was directly associated with increased mortality in these animals. In evolutionary terms, the persistence of immunopathological phenomena and their possible cost exist because immunological response (protection) brings immediate benefits, such as pathogen elimination.[24]

Coevolution

Another factor that contributes to the persistence of intense immune responses in individuals of the human species is coevolution, and this section is intended to make a brief description of this contribution. The immune system results from the simultaneous evolution (coevolution) of hosts, pathogens, and symbionts.[4,5,11,22]

So far, the human species has two important epidemiological transitions.[27] The first one happened in the Paleolithic period (10,000 BC), in which hunters/gatherers lived in small groups and were nomads, having contact with helminths, saprophytic bacteria, *Salmonella*, and *Toxoplasma*.[27] After the Neolithic period (3,300 BC), they started to live in highly populated settlements and together with farm animals, in frequent contact with feces, mud,

untreated water, and organisms transmitted via the fecal-oral route, such as helminths, as well as *Mycobacterium tuberculosis*, and the bacteria causing typhus and cholera.[27,28] The second epidemiological transmission, in turn, occurred later, in the 1800s, when the human species progressively starts to live in large urban agglomerations, with access to treated water and hygiene habits, thus interacting less with farm animals, in addition to using anthelmintics and antibiotics and to consuming industrialized food.[27,28] The consequence of these changes was reduced contact with helminths and pseudocommensal bacteria, known as "old friends", present in mud and untreated water, which results in a more homogeneous intestinal microbiota.[27,28]

With reduced exposure to various pathogens and symbionts (old friends), the microenvironment of the immune system has also changed, and consequently, its regulatory profile, which became less inflammatory. This is the case of helminths, which developed very competent immune regulatory mechanisms during coevolution with their hosts.[29] For example, *Brugia malayi* has molecules that mimic the macrophage-migration inhibition factor (MIF) and transforming growth factor-beta (TGF-β) cytokines, which, among various functions, are anti-inflammatory.[27-29] *Schistosoma mansoni*, an intestinal parasite, produces phosphatidylserine, phosphorylcholine, and various glycans, which interact with dendritic cells and activate TH2 and regulatory lymphocytes in their hosts. Onchocystatin, from *Onchocerca volvulus*, prevents the activation of T-lymphocytes and increases the production of anti-inflammatory cytokines.[29] These strategies adopted by helminth parasites result in regulatory and less inflammatory immune responses, thus facilitating their survival for a prolonged time in their hosts and, consequently, leading to the chronic infections observed in helminthiasis. Furthermore, this contributed to the presence of a less reactive and less inflammatory immunological profile in the host population.[27-29]

As previously seen, natural selection favors hosts that develop reactive and intense immune responses, and the main coevolutionary legacy of "old friends" was the modulation of these immune responses. With the loss of "old friends," i.e., reduced contact with parasites and symbionts, immune regulations cease to occur, and the more reactive and inflammatory immunological profile prevails in the population. Indeed, epidemiological data indicate a high incidence of chronic diseases with inflammatory profile, such as diabetes, asthma, and autoimmune diseases in the urban populations of industrialized countries.[27,28]

Other factors involved in the onset/maintenance of the "inflammatory" phenotype in urban populations are the prevalence of obesity, a condition characterized by increased levels of inflammatory cytokines; deficiency of vitamin D, a molecule involved in immune regulation, due to lack of sun exposure; and contact with pollutants such as dioxin, which activates inflammatory TH17 lymphocytes.[27,28,30]

Life history

The life history of a biological species is characterized by aspects that directly affect its reproductive success, such as anatomy, reproductive lifespan, size of the offspring, parental investment, maturation time, life expectancy, and behavior.[5,16,31] Reproductive and survival processes through which organisms of a given species complete their life cycle, as well as the energy allocated in each phase of their development, define the aspects of each stage of life. Limitation of environmental resources imposes trade-offs and restrictions and, thus, no individual can develop, reproduce rapidly, and invest on longevity at the same time.[5,11,16,31] It is necessary to prioritize a set of traits/functions to which energy will be allocated in each phase of organism's life.[31] Furthermore, life history explains why species have different patterns of reproduction, development, and longevity, which are determined by the allocation of resources to maximize reproductive success. The events that occur during the life of an organism are also shaped by demographic aspects.[31] Human beings are characterized by long lives, few offspring, and a long post-natal phase of nutritional dependency, with high parental investment. There is also a strong selective pressure in the early stage of species development, because the adaptive cost of juvenile mortality is higher than that of the mortality of older individuals, who do not reproduce anymore.[22,30,31] Therefore, the early stage of development should privilege a very reactive immune system, with memory and plasticity, which is indeed observed in our species. The genes involved in reactive and intense immune responses, which combat pathogens and benefit individuals in the early years of life, may be detrimental in the maturity stage, because these genes induce immunopathological phenomena.[5,19,23,32,33] The genetic traits selected in the early life development may have negative effects in other stages.

More empirical, experimental and theoretical investigations are needed; however, studies have undoubtedly advanced in the definition of evolutionary and adaptive aspects that result in the immunopathological phenomena experienced by the human species.

Conclusions

In this brief review, we assessed, in the light of Evolution, the apparent paradox of immune responses in the human species, immune reactions that should control infections, but that can result in irreversible immunopathological damages (e.g., cytokine storm, which occurs in severe cases of COVID-19). There is the understanding that the cost-effectiveness of exacerbated immune responses partially explains the maintenance of this trait during evolution: the risks of death due to infections exert a higher selective pressure than the risks of death due to immunopathological phenomena.

Coevolution of pathogens, symbionts, and hosts contributed to the emergence of immune regulatory responses, and epidemiological transitions of the human species contributed to the emergence of less immunoregulatory and more inflammatory phenotypes. Furthermore, the life history of our species reveals how demographic contexts and resource allocation are determining factors for the maintenance of a more reactive immune system. Additionally, knowledge on the evolutionary bases of immune response variability will help reinterpret immunopathological phenomena and formulate additional prevention and treatment strategies.

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