



# Understanding the Struggle Between Viruses and the Immune System: A Quintessential Grand Challenge

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## WHERE WE'VE BEEN AND WHERE WE ARE GOING

Medical students who trained in the 80s often tell of being discouraged by older professors from entering the infectious diseases (ID) field. ID was an ancient specialty, they said, that would soon become extinct: once antibiotics had taken care of infections, there would soon be no further need for the ID specialist. This positivistic and illuminist way of looking at scientific progress as an unstoppable trajectory generating an endless flow of solutions to our problems, was shattered by the emergence of human immunodeficiency virus (HIV) (1–4), even if residues of positivistic expectations of medicine still believed that the HIV pandemic would very rapidly be stopped by vaccines. We are still waiting for an HIV vaccine, but thanks to scientific progress, a score of antiretroviral molecules have been created, allowing HIV infection to become a chronic, manageable disease (5). This success inspired a stream of reviews from public health experts suggesting that the health systems of developed nations could be profoundly modified: acute, emergency medicine should be greatly reduced to focus on chronic conditions and rehabilitation (6, 7). Then SARS-CoV-2 arrived in the winter of 2019 (8), took the world by storm, and once again showed us that pathogens, in particular viruses, and the infectious diseases they provoke are far from being defeated.

Pathogens, in our case viruses, infect hosts. Infections are faced, fought, and if everything goes well, defeated to restore health by the immune system. Viruses appeared on earth more than 3 billion years ago along with the first cells; they survived by constantly mutating and adapting to plants, insects, animals and humans. Viruses are transmitted through an immense variety of vectors, from mosquitoes to primates, and are responsible for an only partially understood panoply of diseases: from acute and short-lasting systemic infections to tumors. Viruses and the immune response are engaged in a constant arm-to-arm race. Viruses employ an extended array of mechanisms and mutate to escape immune recognition and/or develop mechanisms that will allow them to establish more successful, more diffuse infections. Molecules, proteins and cells that are part of the immune system constantly hone their ability to recognize pathogens, diminishing their ability to penetrate into cells and replicate within the host (9, 10). We currently understand a minuscule portion of this race; to abuse an overused metaphor, we have barely explored the tip of the iceberg, but, as COVID has shown us, knowledge needs to be accumulated to allow the rapid development of novel therapeutic and vaccinal approaches.

## OPEN QUESTIONS

Open questions are many, and can be summarized as follows: (1) How can we better, more efficiently and more rapidly study viral variants and virus evolution and clarify how they impact immune response? A corollary regards the problem of the origin of animal viruses that jump

## OPEN ACCESS

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species. The emergence of SARS-CoV-2, whose original and intermediate hosts have not yet been identified, brought this aspect fully to light (11, 12). Notably, these types of viruses are widely considered to be the most dangerous of all pathogens, at least in part because the immune response is caught completely blindsided. Viral jumps across species into humans are feared to become more and more frequent in the near future, a consequence of overcrowding, massive farming, and other yet undetermined factors; it is foreseeable that this field of investigation will gain more importance. (2) How do innate immune responses prevent infection and, alternatively, how do viruses evade these responses and establish primary infection? Amongst the most exciting and revolutionary recent findings in this field are the individuation of so-called interferon-stimulated genes (ISG) and the discovery of a family of proteins globally termed restriction factors. ISGs include hundreds of genes that are stimulated by the production of  $\alpha$  interferon, and generate an only partially explored variety of early proteins that hamper initial viral replication [reviewed in Yang and Li (13), Bourdon et al. (14)]. Restriction factors, from the progenitor Apobec family of proteins on (15), are a complex and still barely understood family of endocellular proteins that form a first line of defense in blocking viral replication and propagation [reviewed in Paludan et al. (16)]. These findings have revolutionized our concept of innate immunity, rendering this type of immunity immensely more complex and sophisticated than was previously believed. A more in-depth knowledge of the structure–single nucleotide polymorphisms in restriction factor genes have been shown to influence the antiviral ability of such proteins— and the function of these two families of mediators would greatly enrich our therapeutic arsenal of antiviral compounds.

(3) How do acquired immune responses evolve to eliminate acute viral infections and, on the other hand, how do viruses avoid immune recognition and immune effector mechanisms, to kill the host or reach an equilibrium and generate chronic infections. Of pivotal importance, when the latter is the case, is the emerging knowledge of the possible role of chronic viral infections in the pathogenesis of neurodegenerative disorders (17). Recently observed evidence has renewed attention from the scientific community on the old hypothesis of a direct correlation between chronic herpes simplex infection and Alzheimer's disease (18). Chronic infections with other viruses as well as the reactivation of endogenous retroviruses, a whole different and often overlooked story—let's not forget that endogenous retrovirus genes make up at least 10% of the genome in our cells—[reviewed in Grandi and Tramontano (19)] have been suggested to be important in other neurologic diseases, as well as in the process of unhealthy aging. These are important and urgent questions that need to be addressed scientifically. (4) What possible role is played by mucosal immunity, which has moved center stage in recent years? This is a consequence of increased understanding of the importance of microbiota in determining human health and of the realization that the great majority of immune cells in the body are localized inside the gastrointestinal (GI) tract, making the GI tract the most important immune organ [reviewed in Malard et al. (20)]. Yet whereas our knowledge of the microbioma and its variations in disease

is rapidly expanding, very limited results are available on the virome, the population of viruses that colonize the GI tract [reviewed in Neil and Cadwell (21)]. The continuous interaction between virome and microbiome is a dynamic, ongoing process whose outcome determines the quality of the immune response. This field of research needs to be greatly expanded.

## OPEN CONTROVERSIES

Herein I would like to discuss two topics that still raise controversies amongst the scientific community. The first is the status of individuals that are exposed to a pathogen, and in particular to a virus, but do not become infected or develop an asymptomatic infection, and thus acquire immunity in the absence of either disease or vaccination. The second is the expanding role that viruses play in the pathogenesis of human neoplasia.

None of the epidemics that have ravaged humankind have been able to destroy our species, even the horrific black death, the plague that stunned the world during the fourteenth century, killed an estimated 50% of the residents of overcrowded medioeval cities. The phenomenon of seronegative exposure to viruses became a hot topic in HIV research, when different groups simultaneously described the existence of cohorts of HIV-exposed but uninfected individuals in whom HIV-specific T lymphocytes, but not antibodies, were observed (22, 23). Epidemiological studies suggested that these individuals could be resistant to HIV; a series of results indicated that this might indeed be the case and that susceptibility to HIV infection is modulated both by immunologic and genetic factors [reviewed in Fenizia et al. (24)]. This field of research epitomizes the complexity of the immune system/virus interaction, indicating that different outcomes are possible when the immune system is challenged by a pathogen. This type of research should be pursued, as clarification of the mechanisms responsible for the possible development of resistance to infection is the key to designing novel therapeutic and vaccinal approaches to viral infections.

The concept that viruses could cause cancers was initially suggested by Epstein and collaborators who identified the first human oncovirus in Burkitt's lymphoma cells (25), and gained greater momentum when zur Hausen published the hypothesis that HPV plays an important role in the causes of cervical cancer [reviewed in zur Hausen (26)]. It nevertheless took years for the scientific community to finally accept the concept that some viruses have an oncogenic role. More than 30% of human cancers, from Burkitt's lymphoma to hepatocarcinoma, are currently believed to be associated with viral infection; the majority of scientists are nevertheless convinced that the percentage of human cancers originating from viral infection is much higher than what is actually known. Innovative research and more sophisticated technologies will allow us to verify whether this is indeed the case. The interface between tumoral and immune cells, in the meantime, has become immensely more complicated. The discovery of so-called immune checkpoint molecules has shown us that the way in which viruses and

tumors manipulate the immune response to their advantage is astonishingly complex [reviewed in Palm and Medzhitov (27)]; the creation of therapeutic molecules that counteract such manipulation, on the other hand, has changed the outlook of many tumors [reviewed in Sharma and Allison (28)], and needs to be further exported in viral diseases.

## OPEN PROBLEMS

One of the biggest problems in infectious diseases is that, whereas a number of different antibiotics are available to treat bacterial infections, the therapeutic options that can be used for viral infections are indeed very limited. Notwithstanding the immense problem of rising resistance to antibiotics, it is distressing to realize that, with the curious exception of antiretrovirals, very few, mostly a specific drugs are available for viral infections. Conversely, whereas we can use a number of different molecules to suppress the immune response, we do not yet have at our

disposal anything that can augment immune responses in a solid and reliable matter. It is curious to realize that within a matter of months we managed to develop dozens of highly effective vaccines for the prevention of COVID-19, but we are still struggling in the attempt to understand how to treat patients suffering from severe SARS-CoV-2 infection. Full support needs to be provided for basic and translational research aiming at developing novel immunomodulants and antivirals; there is an urgent and impelling need to develop new therapeutic molecules that will allow us to directly target viruses, or maintain an edge in cases where the immune response is overwhelmed by viral infections. This section of the Journal will welcome all contributions that might help in this quest.

## AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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**Conflict of Interest:** The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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