Microbial evolution: The dilemma of direct and indirect viral self-camouflaging

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Abstract

Microbial immune escape represents the primary cause of induced pathogenesis in humans, and it represents a pivotal method used by viral agents to increase their load and suppress key mechanisms of the innate and adaptive immune system. This phenomenon represents the primary factor that led to the onset of the 1918-1920 A(H1N1) Influenza and 2020-2022 COVID-19 pandemics, and it possibly played a major role in the onset of the AIDS pandemic as well. Moreover, repeated incidents of immune evasion could be associated with higher rates of cellular aging (Jackson et al., 2017), most likely due to the consequent increased demands of energy consumption. Highly developed viral immune evasion ultimately indicates the high inner intelligence of human immunity due to reflective and imitative characteristics of reactions that are produced against initial actions. Ribonucleic acid-based viral genomes contain open reading frames, which consist of genes producing sixteen non-structural proteins. Such proteins play a considerable role in desensitizing first-line immunity during cellular infection, and non-structural proteins 1, 10 and 16 have the strongest effects against a healthy expression rate of Type I and Type III Interferon-encoding genes. Type I Interferons consist of IFN-alpha, -beta, -delta, -epsilon, -omega, -tau and -zeta, whilst Type III Interferons consist of IFN-lambda1, -lambda2 and -lambda3, and they act as stimulators of intracellular signalling cascades that in turn lead to the activation and expression of interferon-stimulated genes (Brown et al., 2022). The earlier the interferon-stimulated genes are activated, the lower the extent of pro-inflammatory mediation and overall, the more effective the antiviral immune response will be, given the exponential nature of the viral load increase. Non-structural protein 16 methylates the 5' cap of the virus, making the pathogen-associated molecular patterns less recognisable by pattern-recognition receptors, and it requires activation by bonding with non-structural protein 10. It is preserved in the S-Adenosyl-L-Methionine pocket of the SARS-CoV-2 genome. Non-structural protein 1 (NS1) directly cleaves the host cell mRNA producing Type I and possibly Type III Interferons, thereby preventing a translation process of the immune proteins. NS1 has recently been found

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to often be packaged into exosomes once secreted by the viral genome in the cytosol, meaning that exocytosis and paracrine signalling to neighbouring cells before their actual infection is possible. As a result, NS1 is highly capable of silencing the first-line immune responses of uninfected neighbouring cells as well, thereby highlighting the need to adjust the focus of therapeutics and vaccinology toward first-line immunity and further indicating its foundational importance in the support for the development of precise and balanced defenses against microbial agents of concern (EL SAFADI et al., 2022).

Introduction

The concept of viral self-camouflaging and innate immune escape is fairly novel in the scientific community. Despite the foundational roles that innate immunity plays in the overall development of immune responses against microbes of concern, traditional medicine and vaccinology placed a voluminous extent of focus upon sharpening adaptive immune responses and upon offering the immune system a proto-type of a weak or dead version of a pathogen by means of training it to destroy normal specimens without resulting in the onset of moderate or severe disease. Nevertheless, we have not managed to fully limit the onset of flu-like diseases, despite previous repetitive development of vaccines. It is rather impossible to vaccinate the human body against polymorphic viruses like (A) H1N1 Influenza and SARS-CoV-2 by using live-attenuated prototypes or fragments of the pathogen to stimulate the production of IgM and IgG antibodies, and nor is it significantly possible to develop nasal vaccination methods using the same materials, despite the purpose of innate and mucosal immunity training. The deeper explanation to this would be the fact that such polymorphic viruses are also capable of direct and indirect self-camouflaging, which can significantly down-regulate the expression of Type I and Type III Interferon-encoding genes. A significant down-regulation of Interferon I and III during the first few days of viral infection can make a major difference in the outcome of the overall quality of the immune response, given the exponential manner of viral load and infected cell count increases. Ultimately, the more cells are infected, the more Type I and III Interferon proteins will be produced, which will lead to the production of more pro-inflammatory mediators. A threshold level of synthesized pro-inflammatory mediator will significantly decrease the quality of the overall immune response, despite its increased power and extent. In worse case scenarios, the immune system may become overwhelmed and may also produce auto-antibodies, leading to the onset of a phenomenon known as viral disease-associated autoimmunity. Likewise, it is probable that the ability of a virus to escape innate immunity is proportional with the incidence of autoantibody synthesis. Given that viral immune escape leads to significant extents of Interferon I and III downregulation, there will be disruptions in the activation processes of all areas of the immune system, including the recruitment of antigen-presenting cells, as well as of natural and adaptive lymphocytes, which in turn will disrupt the synthesis rate of Type II Interferon (interferon-gamma).

Interferons represent glycoproteins produced by many kinds of cells (i.e. dendritic cells) in the human organism and they are part of the innate immune system. They consist of three classes (Type I, Type II and Type III), and the first and third classes are part of the first-line immunity,

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whilst the second class is part of the second-line immunity. The majority of the immune responses induced by Type I and III Interferons are anti-inflammatory in nature and mostly play neuroprotective roles, although exaggerated signals are associated with neuroinflammation and neuronal damages (Tan et al., 2022), whilst the majority of the immune responses induced by Type II Interferons are pro-inflammatory and play a more direct role in stimulating neurogenesis. Type I and III Interferons play a role in simulating intracellular infection and cross-stimulating the expression of Interferon-Stimulated Genes, which in turn lead to the production of anti-inflammatory and pro-inflammatory chemokines, such as CCL2, CCL5, CXCL10, IL-6 and TNF-alpha.

The pathogenic non-structural protein 1 is likely the most concerning element inducing viral infection-related first line immune-evasion and not only is it capable of silencing the Type I Interferon-encoding genes of the infected cell, but it may also be capable of cross-silencing the Interferon I-encoding genes of neighbouring uninfected cells, due to their likely exocytosis via exosomes. Type I Interferons undergo autocrine and paracrine signalling once translated, modified, packaged and exocytosed, and they bind to the IFNAR1 and IFNAR2 receptors to induce the signalling cascade leading to the activation of the Interferon-Stimulated Genes. Once produced and signalled, pro-inflammatory chemokines recruit diverse groups of Natural Killer Cells, which in turn will produce interferon-gamma. Likewise, a delayed production of Interferon I and III is associated with exaggerated recruitment of NK cells and interferon-gamma signalling, which in turn will continue the process of exaggerating pro-inflammatory immune responses. The process may be equivalent to the increase of financial interest in case of debt in relation to time; the higher the extent of waiting for debt repayment, the higher the financial interest becomes. A similar situation applies to the delay of Type I and III Interferons during an infection with a virus that has its reproductive rate higher than 1. Furthermore, a similar trend applies for the average decrease of the strength and quality of the herd immunity, particularly in countries where strict lockdown measures persisted throughout 2022 and where the mass vaccination campaigns were mandatory, as a decrease of the general quality of immune responses almost always implies a decrease of the sensitivity of first-line immunity in relation to many pathogens, which in turn favors a higher incidence of immune escape (not just by allowing viruses to self-camouflage more, but also by encouraging further viral evolution for a given time), generally resulting in a further rise in the intracellular demand of energy consumption and, consequently, in a further increase of the speed of aging.

Given that the Theory of Relativity influences all areas of the physical matter, the limit between the germ and the terrain is relative. Furthermore, both the germ and the terrain are part of the natural world and, given that whichever element is not part of the germ automatically is part of the terrain, it is likely that the immune system constitutes part of the terrain. As a result, given the profound abilities of human first-line immunity to prevent pronounced increases of pathogenic loads or counts, it is possible that the full extent of power of the innate immune system as a potential constituent of the terrain has not been determined yet (Carp T. et al., 2022). As a result, the scientific community may have not paid a sufficient extent of attention to the lively dynamics of the terrain in its defense against the germ. Likewise, it is likely required to study the hidden powers and intelligence of first-line immune evasion by pathogenic agents before we will be able to study the depths of the terrain thoroughly, just as the knowledge of an action and of a reaction is necessary to be able to thoroughly study their aetiology.

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Methodology

We utilized the [MeSH] algorithm of the PubMed mega-database to channel the focus of our literature review toward relevant and qualitative scientific papers to reference. We included “viral immune evasion”, “non-structural protein”, “exosome”, “spike protein”, “interferon”, “cellular infection simulation”, “first-line immunity” and “adaptive immunity” in our key word list, and we selected peer-reviewed studies with outstanding and cutting-edge methodology of clinical and literature research. We expanded our focus to areas of relations between innate immunity and oncology by means of highlighting the criticality of innate immunity in projecting a heavier regulation of viral load and tumor cell count increases respectively. We analysed and referenced in-vitro and in-vivo clinical data further suggesting a causal correlation between first-line immune evasion by viruses and the onset of more severe forms of infectious disease. We also research scientific literature suggesting the likelihood of a causative relationship between errors in the lockdown measures and the COVID-19 mass vaccination campaigns, and higher extents of first-line immune evasion and severe infectious disease.

Results

All the scientific literature previewed and analysed suggests a causal relationship between first-line immune delays and a higher incidence of infectious disease. We projected a solid relationship between early innate immune responses and a lower incidence of the onset of major oncologic diseases. Furthermore, we found a significant number of scientific papers confirming the possibility of a causal relationship between prolonged and generalised lockdown measures and errors in mass vaccination campaigns with a higher incidence and magnitude of first-line immune evasion by viruses, leading to the analogous projection of the causality of a higher incidence of severe infectious disease. Overall, we determined the likely existence of a compelling association between a sensitized first-line immunity and a low incidence of immune escape-induced pathogenesis.

Discussion

There seems to be a form of intelligence, not just behind the central nervous system, but behind all other organs and organ systems, and particularly behind the immune system. The links between the central nervous system and the immune system are profound and the interdependent relationship between the two is evident. High levels of human cognitive abilities are generally associated with more qualitative and balanced immune responses during microbial infection. Given the visible reflective nature of any reaction to an initial action, all the first, second and third lines of immunity show some form of micro-intelligence, as it can be observed that viruses exhibit significant levels of micro-intelligence whilst evading first-line

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immunity. The efficacy of important sets of immune responses do not rely solely upon strength, but they most rely upon micro-intelligence on a much more foundational level. Likewise, the phenomenon of harmful immune escape represents a shift in the micro-intelligence-related evolutionary competition between the human organism and pathogenic agents of concern, and developing the adequate intellectual and physiological tools to tackle such pathogenic abilities may represent the only opportunity, not just for the evolutionary prevail of the human population against challenging microbes, but also for a substantial improvement of the general health and living conditions of humanity, which may include a visible increase of the average human lifespan on a long-term basis.

Have prolonged and generalized lockdowns favored viral immune escape?

Viral evolution has played a major part in the selection of viruses that led to considerable situational suppressions of both the innate and the adaptive immune systems. Scientists, doctors and health authorities became puzzled during the spread of the novel coronavirus in the world and the major pressure to act brought health authorities to follow the model presented by China; to implement a general and lasting lockdown to prevent the virus from overwhelming hospitals and especially intensive care units. Furthermore, a number of world governments have locally mandated people to wear face coverings in areas of lower public attendance, which may also have played a negative role in changing the sensitivity of human first-line immunity, which plays a foundational role in the fortification and preservation of the overall human immune system. During the continuous implementation of such public health measures, many scientists failed to pay specific attention upon the viral mechanisms of genome self-camouflage and interferon system-based immune suppression, which likely prevented the development of effective therapeutic and immunizing agents to significantly mitigate the effects of the pandemic and facilitate the necessary and progressive steps of eliminating such measures, which may have caused the human immune system to build first-line immune defenses in a slower manner and consequently, to allow evolved viral variants to further increase their strength of immune evasion. Experiencing fast-paced first-line immune defenses is critical in ensuring a lasting dominant relationship between the human host and naturally-selected microbes. Likewise, areas of the world that experienced longer and harsher restrictions may experience higher levels of infectious disease due to the lack of the necessary exposure to routine pathogens and to a threshold level of UVA and UVB radiation from the sun, which would overall stimulate the synthesis of a threshold concentration of cholecalciferol per cell and maintain the sensitivity of first-line immunity. Furthermore, the tendency of monopolizing a certain form of immunization response for the vast majority of the global population, during the midst of the COVID-19 pandemic, may represent another important folly that needs to be addressed within the overall scientific community, and rather robustly.

SARS-CoV-2 represents a type of coronavirus that has complex mechanisms of immune evasion and anatomically-widespread methods of pathogenesis induction, as the ACE2 target receptor is widely bioavailable within the human organism. The uncertainty regarding the impact of the virus in the society sent signals of urgency for public health authorities to implement

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measures of lockdown to contain the viral spread and protect important hospitals from becoming filled with patients. The urgency to prevent the spread of the pathogen and save lives was certainly valid, and the benefits of the measures were significantly stronger than the risks of negative implications due to isolation and lack of societal interaction. During such a timeframe, leading scientists around the world had a unique opportunity to innovate novel methods of therapy and immunisation to help the world start to return to normal, step by step. Nevertheless, this did not take place rapidly, and rather strict lockdown measures were implemented even six months after the start of the vaccine rollout in many world countries, including the ones where the vaccine rollout was quick. The mainstream journalistic institutions and scientific communities unfortunately failed to place a firm emphasis upon the biological need for people to be exposed to UVA and UVB radiation, alongside regular pathogens, in order to maintain the strength of herd immunity and play a visible part in preventing an unnecessary increase of other kinds of public health problems in the future years. Public health authorities instead placed an unnecessary emphasis upon locking down people of all age groups and health backgrounds continuously for several months, despite the voluminous difference of hospitalization and mortality rates according to both age and health condition sort of groups. As a result, it is both the immune system and mental health of many people that have been affected by the prolonged lack of environmental exposure, and the problem persisted through the vast majority of 2022 in countries with autocratic regimes, such as China. As a result, it is especially the interferon system that has been under trained during this time, which may lead to considerably higher susceptibilities to other pathogens, particularly in people with one or more underlying health conditions, although this novel problem will likely affect all members of society. Furthermore, the suppression of alternative therapies that was accompanied by a monopolized public health approach in an attempt to quell the harmful effects of the COVID-19 pandemic will likely contribute to an overall decrease of the general integrity of human immunity, unless a serious change of course in immunological therapeutics and vaccinology takes place soon. In order for a significant positive change to occur, dissenting scientific opinions and points of analysis seriously require listening, rather than shaming and suppression, and a scientific depoliticization is likely the only way for the rule of democracy to prevail in science and likewise, in medicine. The draconian lockdown measures in China should raise awareness of the collateral risks of a perfidious and induction of novel forms of dictatorship. As a unitary society, we should be able to discern necessary measures to protect each other from a significant pandemic disease, from a perpetuated state of unhealthy fear that will only take away the freedom to have full accountability, as Sir Benjamin Franklin once mentioned that giving up essential liberties in exchange or temporary security deserve neither freedom, nor security. Hence, unlike previous forms of dictatorship, such changes in power can affect the overall health state of the society more directly. Vitamin D3 deficiency was repeatedly shown to be highly associated with an increased rate of severe pathogenesis and death among COVID-19 patients. This is a matter of a correct prophylaxis and early therapy, and not of late treatment, as a wide exposure to Vitamin D3 before and during initial stages of SARS-CoV-2 infection is highly associated with a good prognosis of infected patients. This aspect is tricky in a number of situations, given that genetic backgrounds do influence the rate of Vitamin D3 intake following solar exposure. For example, human skin with higher concentrations of melanin are more impermeable for UVA and UVB radiation, making it more difficult for the synthesis of the mineral underneath the epidermal layer.

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As a result, many scientists and clinicians recommended people living in warm countries to have a regular oral intake of Vitamin D3 by means of keeping risks of significant pathogenesis following an eventual SARS-CoV-2 infection as low as possible. At the same time, positions of the sun in the sky making an angle with the horizon lower than 45 degrees were associated with a much lower ability of the human body to produce Vitamin D3 following exposure to the sun, meaning that the concentration of UVA and UVB radiation is much lower in the Northern hemisphere during the winter, particularly in Nordic countries and at lower altitudes. Likewise, recommendations for regular oral intake of the vitamin have also been given to the inhabitants of areas with temperate and cold climates. And it is in such situations that the human body requires to be exposed to regular pathogens to maintain a relatively high extent of immune training by means of keeping human first-line immunity in a relatively fast-paced manner.

SARS-CoV-2 mass vaccination campaigns - what went wrong?

The vaccinal spike protein is fully capable of spreading to neighboring cells and tissues, entering and breaking the endothelial barrier area, causing microbursts into major blood vessels and the formation of blood clots and micro clots, and spreading at the systemic level. A recent peer-reviewed study demonstrated that the blood of people who received two doses of the spike protein vaccine contained significant quantities of spike protein for at least 15 days after the administration of the second dose (Fertig et al., 2022). Following the injection of the mRNA encapsulated in a lipid nanoparticle layer, the molecule was found to be distributed from the local area of the deltoid muscle into the lymphatic system prior to the reach of the endothelial barrier and the bloodstream. Likewise, it is very possible that both the encapsulated mRNA copies are packaged into exosomes and transmitted to neighbouring cells, making a spread of the mRNA and of the spike protein at circulatory and systemic levels rather likely. This confirms the findings that hepatic cells underwent LINE-1 Reverse Transcriptase-induced genomic toxicity and mutations following spike protein vaccination, and this also highly suggests that the oral shedding of spike protein is possible, given that anti-spike protein IgA and IgG antibodies were found in the saliva of all participants in a cohort who received the second dose of the spike protein vaccine. And because it is enough for the bloodstream to carry the spike protein in nearly all important areas of the body within 24 hours, it is also entirely possible for the spike protein and even a number of encapsulated mRNA copies encoding the spike protein to spread to the oral cavity and be transmitted into the saliva of other people, particularly if there is a close relationship between the two persons in cause, and the process of inhalation would often keep the distributed spike proteins still intact.

It is important to note that the speed of blood flow is high enough for substances in the blood to spread in the majority of important body areas within a day, let alone two weeks. Because of this, it is entirely possible and facile for the spike protein to reach and often break through the blood-brain barrier, thereby affecting important neuronal regions severely. This explains the number of people who reported loss of motor coordination, sight and important cognitive abilities following their recent administration of the vaccine. The spike protein was shown to also affect important elements of the environment, including marine life. Likewise, it seems that the pathogenic protein in cause harms anything it touches, highlighting the evidence that it has

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unnatural and pronouncedly dangerous origins. As a result, it is critical to address such important concerns with regards to the speedy mass vaccination campaigns that came hand in hand with an unprecedented censorship of potentially important medical solutions that arose during the COVID-19 pandemic.

Given the unprecedented reports of vaccine-associated enhanced disease and autoimmunity following the COVID-19 mass vaccination campaigns, there are valid reasons to believe that they, alongside the prolonged and generalized lockdown measures, have allowed polymorphic viruses of concern to further evolve in relation to human first-line immunity. The lack of exposure to routine pathogens have also decreased the extent of first-line immunity training, which can only offer more room to viral self-camouflaging. It is also important to mention that the translational and post-translational processes of spike protein production and development takes place within the cytosol. As a result, the spike protein of the vaccine can still cause much considerable intracellular harm, not to mention how it is still fully capable of destroying cells from the extracellular matrix. Not to mention that the limitation of conclusive evidence by the emergency state of the COVID-19 vaccine clinical trials still makes it possible for the vaccine spike protein to often enter host cells and directly harm the cytosolic and nuclear layers of the cells.

Conclusion

The thorough investigation of evolved direct and indirect immune escape by microbes may ultimately lead the research communities to pay a much wider focus on the profound powers of the human immune system from the innate, first-line immune functions, but the condition is that the overall focus of research is held fast to a positive mindset, rather than to an unhealthy fear-based innovation approach. Due to the at least slightly reflective and imitative nature of reactions when designed against initial actions, we can observe that deeply developed viral intelligence ultimately points toward one precious aspect of human immunity; its almost indestructible inner light of defense and wise lytic operation system. Likewise, recent discoveries of dangerous methods of viral self-camouflage should not scare the scientific and research communities, but rather encourage further, more intelligent and wise attempts to develop cutting-edge immunizing and early therapeutic approaches. Evolution primarily operates on a long-term basis, meaning that the development of an approach that brings a definitive effect of evolutionary shift of the human species in front of self-camouflaging germs is actually possible. In other words, we are capable of developing a medical approach that will protect the vast majority of the world population from deadly diseases caused by pathogenic immune evasion for at least three centuries. The only possible requirement is for us to ensure there is a fluid change of mind, as problems cannot be resolved with the same mindset we had when it first occurred, according to Albert Einstein, and this is only possible by maintaining a humble approach in scientific and medical research. A fluid change of mind will allow us to also hold fast to discernment and collectively build a path of progress that will lead mankind to a destination of balance and wellbeing.

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