

Review

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Review

Calibrating Human Immunity in the Context of Advanced Microbial Evolution and Self-Camouflaging

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Abstract: The concept of microbial evolution has become progressively intriguing for the immunological side of scientific research, as the ongoing evolutionary battle between microbial agents and animal immunity, which comprises a set of single-nucleotide polymorphisms (SNPs) for both the microbes and the host organisms by means of adaptation to environmental changes, has started including weak points within the innate host immunity as well. Namely, it was discovered only later in the contemporary era that microbial agents tend to use a method of silencing first and second immune lines as an escaping route toward an abundant distribution of the microbial load without a significant restriction from the host organism at the time. Furthermore, it was discovered that the innate immune system displays visible traits of specificity and memory, and also that the adaptive immune system does contain areas of non-specificity as well, which makes it possible for vaccine-based research efforts to bring a wider inclusion of innate, first-line and second-line immune elements into the overall equation of development and possibly rollout as well, perhaps by using such elements as potential immunising agents as well. Additionally, it is possible for central elements of the adaptive immune system to be treated with major elements of the innate immune system by means of improving their overall function and long-term efficacy against pathogenic agents of potential health concern. Such a context may also be adapted for a potential delay in the onset of specific proteinopathies, such as Alzheimer's Disease and possibly Retinitis Pigmentosa as well. An overall approach as such may help the research area of vaccine development undergo potential updates that will potentially help save even more lives worldwide, through the development and application of a scientific concept known as "United Immune System", as it may be important to transform the smaller and less direct "road" between natural and adaptive immunity into a broader and more direct "highway" between the two immune departments. Such a clinical application may be combined with potential fresh updates into pathogen-derived vaccine development, by using inactivated or completely lysed microbial genomes either lacking the genes encoding microbial proteins with suppressive effects against the host innate immune system, or containing such genes as the only activated microbial genes, to stimulate the host immune system to build novel evolutionary pathways and particularly adapt to changes in the microbial genome that affect the innate immune system, such as the expression of Type I and Type III Interferons.

Introduction

The immune system represents the system of organs that is particularly responsible for defending the host organism from particles and microorganisms whose genetic or proteomic codes are foreign to the host organisms', operating through the Major Histocompatibility Complex (MHC), which in humans is known as the Human Leukocyte Antigen (HLA). Likewise, the immune system typically plays a role in separating "self" from "non-self" and consists of multiple departments, which are characterised according to location and function. With regards to location, it consists of the mucosal immunity and the systemic immunity. With regards to function, it consists of the innate immunity and the adaptive immunity. The mucosal immune system tends to implicate more elements from the innate immunity, whilst the systemic immune system tends to include a higher number of elements from the adaptive immunity. For example, mucosal immunity contains neutralising IgA antibodies among its principal elements, whilst systemic immunity contains IgG antibodies among its principal elements. Moreover, an immune response comprises three lines of defence: the first-line, the second-line and the third-line. The innate immune system covers the first two lines of defence, whilst the adaptive immune system covers the third line of defence. The innate

immune system includes the interferon and the complement systems as their main elements, whilst the adaptive immune system is centred around B- and T-Lymphocytes, alongside immunoglobulins (Igs). There are signs that the complement system is not completely autonomous from the interferon system, but that the first shows a degree of dependency upon the latter, as it was observed that the delayed activation and expression of Type I Interferon-encoding genes often resulted in an exaggerated manner of activation in the complement system, particularly via the C3a and the C5a pathways (Shibabaw T., 2020). Beforehand, it was apprehended that innate immune responses were unspecific and fast, whilst adaptive immune responses were specific and slow. Nevertheless, it was discovered that both innate and adaptive immunity display their own “memory” and “specificity”, that the innate immune “memory” displays traits of specificity, and simultaneously that adaptive immunity also displays “non-specificity”-like traits (Domínguez-Andrés, J. and Netea, M.G., 2020). Given the recent discovery of significant intersections between the specificity of innate immunity and the non-specificity of adaptive immunity, scientists have even deemed innate immunity as adaptive and adaptive immunity as innate (Černý, J. and Stríž, I., 2019). Likewise, it could be philosophically thought that the key words behind the ongoing evolutionary struggle between human immunity and microbial infection are “intelligence” and “counterintelligence”. Hence, there is more substantial evidence to state that the innate and the adaptive immune systems are interdependent, but that the timing and quality of developed adaptive immune responses are significantly dependent upon the timing and quality of developed innate immune responses. In other words, despite the fact that the adaptive immune system represents the central department of all immunity, the innate immunity representing the periphery of all immunity increasingly probably and in a paradoxical manner, plays a role of foundation with regards to a proper extent of immune activation. As a result, the adequate activation of innate immunity also plays a major role in maintaining a consistent process of immune evolution. Moreover, the above analysis makes it plausible that it is also chemokines, cytokines and cells characteristic of innate immunity that may produce effects of immunisation, and not only adaptive immune components of such structural nature. The first-line immune defences comprise the extracellular and intracellular receptors sensing microbial entry, the cGAS-STING transduction pathway, as well as the transcription factor of the genes that synthesise Type I and Type III Interferon glycoproteins, which are all mostly contained by plasmacytoid dendritic cells (pDCs). The second-line immune defences comprise the synthesised interferons, the target cells for the interferons, interferon-stimulated genes (ISGs), as well as the target cells for the products of the ISGs, which implicate natural and adaptive lymphocytes. In turn, natural lymphocytes become recruited and synthesise Type II Interferons, which in turn are exocytosed and signalled in a paracrine manner to adaptive lymphocytes. From the moment adaptive lymphocytes, such as B-Lymphocytes, helper CD4+ T-Lymphocytes and cytotoxic CD8+ T-Lymphocytes, become activated, the third line of immune defences start forming. Recruited B-Lymphocytes will then express their recombined antibody genes, whilst helper CD4+ T-Lymphocytes will support cytotoxic CD8+ T-Lymphocytes in their process of lysing infected cells.

Discussion

There are four important methods microbial agents utilise in their process of induced immune evasion; the double methylation of the 5' end of the microbial genome, the direct inhibition of the activation and expression of interferon-encoding genes (INGs) and interferon-stimulated genes (ISGs), the disruption of the metabolic processes started by mitochondria of the host cells, through the increased production rate of reactive oxygen species (ROS), as well as the viral utilisation of channelling nanotubes that are synthesised by many cells for the purpose of cell-to-cell paracrine signalling of various important proteins, with the purpose of facilitating the exocytosis and paracrine signalling of viral non-structural proteins that will inhibit the activation of interferon-encoding genes in neighbouring cells, before the virus even undergoes receptor-mediated endocytosis in the neighbouring, uninfected cells (Sherer N. M. et al., 2008). It is becoming highly probable that humanity is currently situated at a crossroads with regards to the ongoing evolutionary battle between human immunity and microbial self-camouflaging. Despite the fact that pathogen-derived

vaccines have been developed to help the immune system sense microbes with concerning public health effects before it may cause clinical symptoms of infectious disease, there is an increasing number of emerging pathogens that have developed outstanding evolutionary capabilities of preventing first-line and second-line, innate immunity-based signalling to third-line, adaptive immune elements. An important sign that we are situated at such a place in evolutionary history is the recent discovery that newly-developed pathogen-derived vaccines against the avian H5N1 strain of the Influenza A Virus accelerated the process of zoonosis, rather than making it slower. Additionally, it was observed that the rate of viral transmission and induction of virulence increased following the new round of vaccination of poultry against the life-threatening viral disease (Li B. et al., 2023). Similar patterns of immune evasion were observed toward the beginning of the 21st century, when the H5N1 IAV virus was situated in earlier zoonotic stages (Sitaras I. et al., 2014). Such a phenomenon represents a prevention of the proper bridging to the core elements of human immunity, which has resulted in polymorphic viruses evading previously-built immune memory with novel rounds of mutations. Furthermore, the scientific discovery that SARS-CoV-2 is highly adapted to the human host organism, as the spike glycoprotein displays a high proportion of homology with the human proteome, the viral protein displays a high binding affinity to the receptor binding domain of the human ACE2 and groups of four consecutive amino acids sharing the same electric charge in their side chains were found in the viral proteome (including the spike glycoprotein), instead of only groups of two and remotely of three such amino acids, further indicates that viral agents like SARS-CoV-2 and novel IAV strains are situated in an advanced stage of microbial evolution in relation to human immunity, and the situation seems to have no precedent in the history of the continuous human host - microbe evolutionary swing of struggle. Novel viruses and bacteria have developed advanced capabilities of molecular self-camouflaging, with the purpose of preventing the activation of the interferon system altogether. Interferons have been given such nomenclature due to their particular nature of “interfering” with viral replication and distribution of its load to neighbouring cells, via exocytosis and paracrine signalling. For example, several single-stranded RNA-based viruses produce sixteen non-structural proteins (NSPs) that, although are not responsible with a direct induction of pathophysiology, particularly target the activation process of first-line and second-line immunity. Among such proteins, NSP1, NSP2, NSP10, NSP14 and NSP16 have molecular actions that are most highly notable. Wider and more prolonged delays in the activation of the interferon system are generally associated with increased rates of severe infectious disease, given that the immune system will often become activated only when the viral load has reached more than one host organ systems, leading many times to the development of exaggerated pro-inflammatory responses, given that the amount of secreted cytokines, chemokines, as well as the count of recruited immune cells, will have to be proportional with the count of infected cells. Overall, such major delays in the activation of the interferon system will lead to the development of an immune response that will have a poor quality, leading to a contribution to pathophysiology and often even to the development of autoimmunity (Mattoo S.U.S. et al., 2022).

Viral NSPs are known to play various roles in preventing the activation of Pattern Recognition Receptors (PRRs), which are responsible for detecting molecules specific of microbial agents, known as Pathogen-Associated Molecular Patterns (PAMPs), as well as molecules that are produced as a result of induced cellular damage and lysis, which as known as Damage-Associated Molecular Patterns (DAMPs), and PRRs include the extracellular Toll-Like Receptors 3, 7 and 8 as well as the intracellular Melanoma-Differentiation Associated Protein 5 (MDA5), which is part of the RIG-I-like Receptor (RLR) family, inhibits the cGAS-STING pathway, which in turn results in the prevention of the activation and translocation of the Interferon-Regulatory Factors 3 and 7 (IRF3 and 7), and in some cases as well as of the Nuclear Factor kappa-light-enhancer of activated B-Lymphocytes (NF- κ B), as transcription factors for Type I and Type III Interferon-encoding genes (INGs), with the overall outcome of preventing the phosphorylation of transcription factors for Type I and possibly Type III Interferon-encoding genes, and they are also responsible with the prevention of ISG activation in several important cases, leading to the delayed and improper activation of important adaptive immune pathways, and NSP2 was found to aid the molecular activities of NSP1 (Amarante-Mendes,

G. P. et al., 2018). In other words, the implicated viral NSPs not only prevent the detection of molecular patterns characteristic of pathogenic agents, but also the detection of molecules produced as a result of pathogen-induced cellular damage and lysis. Furthermore, it was discovered that NSP1 results in the caspase-induced apoptosis of the cells it enters and that it undergoes virus-independent exocytosis and paracrine signalling into neighbouring cells, seemingly “imitating” the manner produced Type I and Type III Interferons are normally exocytosed and signalled in such a manner to neighbouring cells, where they normally undergo endocytosis mediated by IFNAR1/IFNAR2, as well as IFNLR1/IL10R2 surface receptors respectively. Likewise, NSP1 seems to induce an effect of “trace erasing”, aiding the virus in its unnoticed replication and distribution to several host tissues. Simultaneously, other NSPs are responsible with the process of transferring methyl groups to the NSP16, which becomes activated by joining NSP10, assembling the NSP10/16 methyltransferase complex, which is also known as the 2'-O-Methyltransferase enzyme complex and transfers in turn a methyl group to the 5' end of the viral ssRNA genome - which is known as the ^{7Me}GpppA_{2'-O'-Me} - alongside NSP14, which acts as a N7-Methyltransferase enzyme, in order to make it seem as if the viral genome is not a “foreign agent”, but part of the cell, resulting in the prevention of the cGAS-STING signalling transduction cascade to the transcription factors responsible for the activation of interferon-encoding genes (INGs) (Chang L. et al., 2021). NSP14 plays two functional roles, which are independent of each other. Namely, the protein can act as a C-terminal N7-MethylTransferase (N7-MTase), sending a methyl group to the 5' end of the viral mRNA alongside NSP16. In such a case, it does not require a molecular interaction and union with NSP10 to become activated as an effector enzyme. Nonetheless, when NSP14 plays the role of N-terminal 3'-5' exoribonuclease (ExoN), which is responsible for synthesising new RNA molecules for the virus to ensure the long-term validity of the viral genome, it requires activation by NSP10, forming the NSP10/14 enzyme complex. Although the manner the 5' end of the viral mRNA is capped is not fully understood, it can be deduced that two separate events of methyl transfer occur for a full modification of the 5' viral mRNA end. (Saramago M. et al., 2021).

In the case of the COVID-19 pandemic, which lasted from the 14th of March 2020 until the 5th of May 2023, the +ssRNA-based SARS-CoV-2 virus displayed substantial capabilities of molecular self-camouflaging with the help of the sixteen NSPs, and hypotheses have arisen regarding an existing proportionality between the length of the pre-symptomatic disease stage, and the severity of the clinical disease that would onset afterward. Alongside the four developed mRNA-based and adenoviral vectors 5 and 26-based vaccines, researchers have also placed unprecedented intellectual and clinical efforts in developing immunostimulatory approaches involving quicker activation of first-line immune signals. In several areas of the world, clinical trials regarding a nasal administration of a fairly low dose of human recombinant Type I and remotely, Type III Interferons, showed promising results with regards to prevention of clinical disease onset altogether. Preliminary medical studies have generally limited the low dosage of the human recombinant IFNs to a range between 200 and 500 International Units (IU), and substantial efficacy was displayed for all groups of age and health background that participated in the clinical trials. Using the collected data, researchers projected substantial effects of prophylaxis and early therapy by the recombinant interferons. Similar results of efficacy had been displayed in the case of other infectious diseases with life-threatening effects, such as HIV-induced AIDS, (A)H5N1 Influenza Virus-induced bird flu and (A)H1N1 Influenza Virus-induced swine flu, as well as oncological diseases, like hepatic melanomas and even pancreatic cancer. Another potential clinical approach could implicate the development of IgM super-immunoglobulins, clinically specialised into detecting and lysing NSP1, NSP14 and NSP16 proteins, would only be possible for remote administration given the costly clinical research process, despite a high need for such viral proteins to be detected and denatured. Other approaches would involve the development of pathogen-derived vaccine candidates, involving viral genomes with NSP-encoding genes that had artificially underwent loss-of-function mutation beforehand. Nonetheless, such an approach would probably still not guarantee that future viral variants would not evade IgM and IgG antibodies built for the previous variants, especially in the case of people with their immune system compromised by one or more underlying health conditions. Perhaps, scientists could also consider

the development of pathogen-derived vaccines implicating viruses with almost all genes having undergone whole inactivation beforehand, except for the non-structural protein-encoding ones, as well as a few genes responsible for viral replication, given the substantial and possibly even urgent need to stimulate the innate and the adaptive immune departments to outcompete the highly advanced capabilities of viruses to directly and indirectly undergo molecular self-camouflaging. In the case of SARS-CoV-2 infection, there may be two other major prophylactic and therapeutic approaches preventing the activation of NSP16. Namely, the first approach would involve the development of the small drug-like protein abbreviated as TP29, which would prevent the molecular interaction between NSP10 and NSP16, likewise resulting in the prevention of the transfer of the methyl group to the 5' end of the +ssRNA viral macromolecule. Such an approach is statistically likely to be successful because it displayed substantial rates of efficacy in the case of SARS-CoV-1 infection (Wang Y. et al., 2015). Other pharmaceutical components that could target the NSP16 protein are simefungin (SFG) and S-Adenosyl-Homocysteine (SAH), although more evidence is required to be collected to confirm such information. During the COVID-19 pandemic, clinical researchers determined that two other drug-like molecules may be capable of targeting and denaturing NSP16; carba-nicotinamide-adenine-dinucleotide and galuteolin (Vijayan V. et al., 2021). The second approach would involve the oral administration of the methioninase enzyme, for prophylactic or early therapeutic purposes as well, with the objective of digesting the S-Adenosyl-L-Methionine (SAM) pocket of the virus, which acts as a donor of methyl groups and stores the viral NSPs 10, 13, 14 and 16 (Hoffman R.M. and Han Q., 2020). The chemical reaction implicating the release of a methyl group from the SAM viral pocket is catalysed by the SAM-dependent Methyltransferase (MTase) enzyme. If such viral pocket is lysed, then it would be far less possible for the NSP16 to be activated and receive its methyl group, given that SAM-dependent MTases would no longer have chemical reactions to catalyse, thereby resulting in a substantially poorer ability of the virus to undergo molecular self-camouflaging.

Potential solutions to the dilemma of increased molecular self-camouflaging capabilities of diverse microbes could involve the administration of human recombinant Type I and Type III Interferons, possibly alongside recombinant plasmacytoid dendritic cells, as well as Natural Killer (NK), helper CD4+ and cytotoxic CD8+ T-Lymphocytes. Recombinant pDCs would represent additional factories for interferon production in case further viral self-camouflaging processes occur, whilst recombinant NK cells and T-Lymphocytes would function in Type II Interferon production, as well as the detection and lysis of infected cells respectively. Furthermore, T-Lymphocytes could be treated with a low dosage of Type I and Type III IFNs in order to have their immunity protected and perhaps their immune functions optimised, particularly in the case of HIV infection, which is known to target helper CD4+ and cytotoxic CD8+ Lymphocytes. In such a case, T-Lymphocytes could undergo a gradual process of transformation into "super-lymphocytes", given that an increased immune state of such immune cells could constitute the development of "a proportionate evolutionary punch of self-defence" against evolved microbes like the HIV retrovirus. It is interesting to note that immunity exists within immunity, which suggests that the terrain used by microbes to gain "power" and "intelligence" may itself be improved in order to make it harder for such viruses to evolve in such a manner. If such microbes are given more difficult terrain to operate upon, then their evolutionary processes may be slowed down. Perhaps it will only be then when the research community will be able to make substantial progress with regards to a natural acceleration of human immunological evolution, and such an exchange of evolutionary changes would reflect two laws in physics, the law regarding potential and kinetic energy, as well as Newton's Second Law of Motion regarding the swinging of a pendulum, given that physics represents the foundation of all material sciences. It is also interesting to note that microbes may exist within microbes, as it is not only microorganisms that may act as pathogenic agents, but also proteins as well, given that aggregated proteins like alpha-synuclein and beta-amyloid, act as pathogenic agents, causing a neurodegenerative disease known as Alzheimer's Disease. Likewise, human immunity and microbes both may operate in a multi-dimensional fashion, demonstrating the fact that physics, via relativity, represents the foundation of biology, and implicitly, of evolution, and it may be the apprehension of

such events that will help the research communities continue their discovery process of therapeutic solutions proportionate with the current context of microbial evolution. Albeit there are dozens of prophylactic and early therapeutic options implicating various degrees of stimulating the interferon system to become more sensitised to microbial infection, such as a healthy lifestyle, as well as the administration of natural compounds that include ascorbic acid (Vitamin C), cholecalciferol (Vitamin D3), Zinc and its ionophores (including Quercetin), Vitamins B3, B5, B9 and B12, curcumin (a substance found in turmeric), methylene blue and melatonin, research scientists have been investigating prophylactic and therapeutic candidate approaches that would involve a more direct stimulation of “trained immunity”, which would most likely be possible if the very elements of it are used as stimulatory agents, given the fact that the elements of the interferon system undergo not only paracrine, but also autocrine signalling (Shakoor H. et al., 2021).

Furthermore, such innate immunity-based therapies may be applied into proteinopathies, such as Alzheimer’s Disease, which is caused by the aggregation of the alpha-synuclein and beta-amyloid neuronal proteins, and Retinitis Pigmentosa, which is caused by the aggregation of the rhodopsin retinal protein. For example, the nasal administration of a low dose of Type I and Type III Interferons, alongside the solution of protollin, may simultaneously optimise and catalyse the process of T-Lymphocyte recruitment to the central nervous system area where the proteinopathy is in the process of onset or early development, thereby increasing the effect of delaying the onset or development of the disease. In other words, through a natural immune-based optimisation and catalysis of adaptive immune activation, there will be an increasing number of clinical cases of neurodegeneration and blindness in which such processes of pathophysiological induction will be substantially delayed. It is widely known that recombinant interferons act as powerful vaccine adjuvants. Nonetheless, given the fact that natural immunity contains its own “specific memory” and that adaptive immunity contains its own traits lacking specificity, it is becoming increasingly possible that Type I and Type III Interferons also represent elements with immunisation traits. Likewise, there may be an existing probability that interferon glycoproteins also contain traits of immunising agents for diseases causing neurodegeneration and blindness. Nonetheless, interferon glycoproteins display “double-edged sword”-like properties, as they contribute to serious pathophysiology if they are secreted in an excessive manner and in latter stages of infectious and oncological diseases, also causing collateral bodily damages that are not immune in nature, such as neurological illnesses. Likewise, it is essential to analyse the risks and the benefits in an equally thorough manner, to ensure that no harm is ever performed, through the reach of mismatching clinical and health background-related contexts. The overall approach that could include an update in human and animal vaccinology would involve the creation and application of a concept known as “United Immune System” into clinical practice, by updating the bridge between the interferon system and the lymphocyte system (Carp T., 2024).

Given that a higher quality of interferon system activation is statistically associated in a rather significant manner with decreased rates of oxidative stress, demands for metabolic energy consumption and overall speed of cellular and tissular ageing, it could be that an administration of human recombinant interferon glycoproteins of classes I and III in people of a younger age, with little to no underlying health conditions, will help prolong the average human lifespan with a number of years ranging from 10 to 20 in the second half of the 21st century, provided that such an approach will be offered worldwide, as a potential prophylactic and early therapeutic approach option of immunisation, against life threatening infectious and oncological diseases. It is not only human recombinant interferon glycoproteins, alongside plasmacytoid dendritic cells as their factories, that would bring such an effect, but also existing plant-derived proteins stimulating a more robust and sharper synthesis of interferons that would significantly play a role, albeit on a longer term basis. Namely, there are existing plants that produce and secrete proteins of such kind, which include: *Silybum marianum*, *Astragalus membranaceus*, *Schisandra chinensis*, *Agaricus blazei*, *Ganoderma lucidum*, *Morinda citrifolia*, *Aloe vera* and *Foeniculum vulgare* (Dacia Plant, 2021). Perhaps, clinical practices of translational medicine may involve the development of drug-like compounds consisting of more abundant concentration of the protein macromolecules particularly involved with the activation of the signal transduction cascade responsible for the activation of interferon-encoding

genes (INGs), given that such plant-derived proteins bring slow effects and require a long-term prophylactic session.

Conclusions

The recent discovery of a dangerous precedent with regards to microbial evolution and adaptation to rapid signalling of the interferon system to the responsible innate and adaptive immune cells has arrived with the recent potential discovery that natural immune components also have traits specific to immunising adaptive immune components. Likewise, in a possible response to a sharp increase in microbial evolution against human and animal immunity, researchers could perform a wider inclusion of natural immunity in the efforts of vaccine development, with the purpose of catalysing the activation of the interferon system, before viruses translate protein products that are responsible with preventing the proper assembly of the bridge to the core of the organism's defence system; the adaptive immunity. Two important clinical approaches directly countering the dilemma of microbial self-camouflaging via the synthesis of NSPs may involve the stimulation of trained immunity-based catalysis, as well as the development of immunotherapies aimed at lysing such NSPs. It may be that the stage of microbial evolution is so advanced that the general course of therapeutic and vaccine-based research requires a visible change of direction, despite the colossal success that previously developed traditional therapeutic and vaccine approaches have shown for centuries throughout the world. Namely, it may be that Universal therapies and vaccines also need to be developed to avoid bringing an excessive amount of specificity into the equation, given the highly diverse phylogenetic backgrounds of pathological microbes. It is possible that such a case especially involves polymorphic pathogenic agents. A combination of the candidate medical approaches to prevent or attenuate the effects of future epidemic and pandemic diseases would probably constitute the best efforts to preserve public health, with an existing focus of ensuring that the gaps created by polymorphic microbes in the first-line and second-line immune defences are filled in as thoroughly as humanly possible. The overall objective would be to ensure that little to no points of physical, chronological or "intelligence"-related weakness exist in either immune department, so that microbes do not find host terrain that encourage their gain of evolutionary advantage.

Key Scientific Abbreviations

ACE2 - Angiotensin-Convertase Enzyme 2
RBD - Receptor-Binding Domain
PRR - Pattern Recognition Receptor
TLR - Toll-Like Receptor
RLR - RIG-I-Like Receptor
MDA5 - Melanoma Differentiation-Associated Protein 5
PAMP - Pathogen-Associated Molecular Pattern
DAMP - Damage-Associated Molecular Pattern
NSP - Non-Structural Protein
SAM - S-Adenosyl-L-Methionine
SAH - S-Adenosyl-Homocysteine
ExoN - N-terminal 3'-5' Exoribonuclease (NSP10/14 enzyme complex)
N7-MTase - C-terminal N7-Methyltransferase (NSP14 enzyme)
2'-O-MTase - 2'-O-Methyltransferase (NSP10/16 enzyme complex)
cGAS - Cyclic GMP-AMP Synthase
STING - Stimulator of Interferon-Encoding Genes
IRF - Interferon-Regulatory Factor
NF-κB - Nuclear Factor kappa-light-chain enhancer of activated B-Lymphocytes
IFN - Interferon
IFNAR - Interferon-Alpha Receptor
IFNLR - Interferon-Lambda Receptor
IL10R - Interleukin-10 Receptor

JAK - Janus Kinase
 STAT - Signal Transducer and Activator of Transcription
 ISG - Interferon-Stimulated Gene
 pDC - plasmacytoid Dendritic Cell
 NK cell - Natural Killer cell
 CD - Cluster of Differentiation
 BCR - B-Cell Receptor
 TCR - T-Cell Receptor
 MHC - Major Histocompatibility Complex
 HLA - Human Leukocyte Antigen
 Ig - Immunoglobulin
 Ab - Antibody (synonym of Ig)
 Rho - Rhodopsin protein
 RHO - Rho-encoding gene

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