

Review

# Countering and Tackling Advanced First-Line Immune Evasion Represents the Most Feasible and Precise Approach to Control and Eradicate Rabies

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**Abstract:** Despite being a rare disease worldwide, rabies has the highest morbidity and mortality rates, with roughly 99% of symptomatic cases leading to coma and death. Rabies represents an infectious disease caused by the Rabies virus (RABV), which is part of the Lyssavirus group and the Rhabdoviridae family, and it mainly spreads through the bite and scratch of an infected mammal, but particularly of wild animals, such as bats, foxes, wolves and racoons, and of domestic animals, such as dogs and cats, in rabies-prone areas of the world. Airborne transmission has been deemed as extremely rare, and no clinical case as such has been recorded worldwide yet, except in the enclosed environment, such as research laboratories and caves where infected bats are present. Domestic mammals, such as dogs and ferrets, represent other important reservoirs of disease transmission, and the human cases of Asia and Africa amount approximately 95% of all human cases worldwide. Infected animals most commonly start transmitting the virus once the first symptoms have occurred, and if they experience disease aggravation and death within 10 days, a case of rabies is registered, more easily if the incidence occurred in the urban area and then, any person or animal that had been potentially exposed are strongly recommended to receive the inoculation. It is rare for asymptomatic mammals to transmit the illness. Most First-World and several Second-World countries have recently been declared dog rabies-free by the World Health Organization. The disease can only be treated prophylactically, with three doses of a vaccine containing an inactivated form of RABV, or with five doses of the vaccine and two doses of anti-RABV immunoglobulins within 28 days if the patient is believed to have been exposed to the virus beforehand. It has been projected that, once the viral load reaches elements of the central nervous system, prophylactic approaches are no longer effective, even if symptoms have not begun yet, and this highlights the urgent trait of the medical condition, strongly recommending exposed people to receive the prophylactic doses immediately after the potential exposure to the virus. The pathogen first infects the bodily fluids, before reaching the peripheral nervous system, from where it will gradually move toward the spinal cord or the encephalon, at a speed of movement ranging from 1 to 40 cm per day. It was also found, in extremely rare circumstances, to infect the nasopharyngeal cavity and the lungs. The primary cause of a successful, gradual advance of the viral load toward the point of clinical no-return for the patient - the CNS - is a complex mechanism of induced innate immune evasion, with the interferon system being heavily targeted and silenced by RABV proteins. The 'Milwaukee' protocol is locally believed to decrease the mortality rate of the clinical illness to approximately 80%, although significantly more research is required in this sense. First-line immune evasion represents the central mechanism developed by viruses during their evolutionary process to gain control over human immunity, so it could be the development and adjustment of a counter-offensive to this evolutionary operating system that could address the core elements of the problem. Human recombinant Type I and Type III Interferons were found to be significant vaccine adjuvants and to considerably delay the clinical onset of the disease. Despite their central role in natural immunity-based prophylaxis, vaccine support and, in often cases, vaccination per se, a local administration of IFNs as such may not be enough to tackle the core problem of the endemic disease, and a specific and systemic treatment of potential host cells with IFN I and III, as well as IFN-stimulating proteins, may constitute a major research requirement in the coming years of disease investigation, as the inoculation efforts with the inactivated virus and immunoglobulin administration continue. The administration of a relatively low dosage of somatic Natural Killer cells, gamma-interferon and perhaps, of somatic helper CD4+ and somatic cytotoxic CD8+ T-lymphocytes treated with alpha-, beta- and lambda-interferon could be merged with the administration of a similar dosage of alpha-, beta- and lambda-interferon during the efforts to develop an effective and less costly prophylactic vaccine against rabies. A combination of a nasal substance containing a low dosage of IFN I and III with a reduced concentration of

neutralized RABV copies, and/or with a low dose of anti-RABV IgA antibodies, could also be tested for humans for the purposes of pre- and post-exposure prophylaxis.

**Keywords:** rabies; RABV; PRV; single-stranded RNA; RNA-dependent RNA Polymerase; viral self-camouflaging; glycoprotein; innate immunity; interferon system; natural lymphocytes; adaptive immunity; adaptive lymphocytes; IgA; IgM; IgG; primary dendritic cells; macrophages

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## 1. Introduction

Rabies virus (RABV) represents an enveloped negative-sense, single-stranded ribonucleic acid-based virus that infects mammals, although the degree of transmission varies from species to species. The virus has a length that generally varies from 100 to 300 nm and a diameter of approximately 75 nm in the majority of the cases. It first needs to express RNA-dependent RNA Polymerase before its genome becomes activated for distribution, meaning that, the less sensitive the viral genome is - due to various external factors - the less capable it is to express its activation enzyme. RABV-induced encephalitis was first documented around 2,000 years B.C. and represents one of the most complicated and life threatening illnesses mankind has ever come across. Despite the fact that humans primarily become infected as a result of a direct transmission of the virus from infected dogs, the primary reservoirs of the virus are not in domestic animals, such as dogs and ferrets, but in wild animals, such as bats, foxes and raccoons. The virus is mainly transmitted directly from the saliva of infected animals through bites and deep scratches, transmission of infected saliva through the intact mucosal layer of the host is uncommon and airborne transmission has been deemed as virtually impossible, particularly if the environment is natural and in the open air. As soon as the virus is suspended through micro-drops of infected saliva into the dry air, it quickly becomes neutralized and its structure and genetic sequence are then disintegrated. Once the virus infects a host organism, it then travels toward the encephalon at a median speed of 5-10 cm per day, although it highly varies from case to case. It seems that the speed of the viral migration in the nervous system is proportional with the quality and extent of the innate immune sensitivity, meaning that, generally speaking, the virus migrates faster with age, and likely this also applies with the health background status of the patient. Moreover, the speed of the viral load migration could be proportional with the amount of time it was exposed to environmental factors during the process of transmission. The virus typically survives in fluids and at temperatures ranging from 27 to 37 degrees Celsius. Due to the fact that the virus is enveloped and its ssRNA is negative-sense, it is particularly sensitive to the outside environment. UV radiation was found to lyse the virus within seconds if found on dry material, whilst dry air alone at a temperature outside of the 27-37 degree Celsius range was found to weaken and lyse the virus robustly as well. RABV was found to survive longest on glass and metal surfaces, and this may be due to the longest sustainability of water molecules on surfaces as such. Although airborne transmission is almost taken out of the question of transmission and no cases as such have ever been documented in the open environment, everybody who encountered a potentially rabid animal receives the public health recommendation to receive post-exposure prophylaxis (PEP), which includes a 5-dose course of rabies vaccination and a one or two-dose course of prepared anti-RABV IgM and IgG immunoglobulins. The recommendation is not based upon the rarity of transmission, but upon the virtual certainty of death in case symptoms of the disease develop. Despite the fact that a safe and effective clinical approach exists, there is still a wide extent of evidence to be determined with regards to the duration of prophylactic immunity against the disease. One clinical case of rabies occurred in a patient who had been immunized around 13 years beforehand, raising a few worries with regards to the length of immunity against the disease. Furthermore, there is evidence to suggest that the clinical disease can become unpreventable even with a full course of prophylaxis that is administered several weeks and months before the first symptoms occur, as studies indicate that, once the viral load reaches elements of the central nervous system or even principal pathways of the

peripheral nervous system, no currently available clinical approaches can stop its advance to the encephalon, where it is known to result in the onset of viral encephalitis.

The irreversible progression of the disease to coma and systemic organ failure was found to be due to the uncontrolled inflammation of the encephalon, as the virus quickly spread in the organ. Clinicians would then be strongly encouraged to deduce that the virus would be the primary factor of causing brain death. Nevertheless, it may be important to take into consideration the tremendous ability of the virus to evade important pathways of immune activation and major antimicrobial activity. It is particularly the first-line immune system that is likely targeted by the virus during its irreversible advance from the spinal cord to the encephalon, as the virus was found to heavily hijack the interferon system. However, unlike other major clinical illnesses, where administered recombinant human interferon-alpha, -beta and -lambda play a role as immunizing components, rabies was only found to have its incubation period prolonged following the administration of such a clinical approach. Although this would mean that interferons as such play only a significant role as vaccine adjuvants, this marks the partial tackling of the viral load migration toward the brain. As a result, it may be that seeking further innate immune system stimulating factors in the current research efforts could gradually get the clinical world closer to the point where the migration of the viral load is completely stopped and where the host immune system would be given the necessary tools to detect and lyse the viral copies. In other words, it may be the advanced phenomenon of viral self-camouflaging that is the primary cause of pathogenesis and virtual certainty of disease-induced death. Furthermore, it may be the manner of immune activation in the final stages of viral spread that is inappropriate for the actual context of the disease, as the immune system could be “misled” to fight against a virus that operates completely based on the model of immune activation. In other words, the only solution against the problem is a temporal lack of immune response, as all survivors of the disease were found to become almost fully functional again. RABV could not be targeting the core elements of the central nervous system, but the core elements of immunity that contribute to its discernment. As a result, whilst the ‘Milwaukee’ protocol could be a significant step toward the discovery of the keys of a complete immune conquest against the virus, the temporary inactivation of the central nervous system could actually not be fully matching to the context of immunopathogenesis. A temporary inactivation of the host immune system would probably be at least more matching to the context, and it would require to be as short-term as possible, and to take place in a septic environment.

## 2. Discussion

Microbial evasion of the host immune systems could represent a factor of lethal pathogenesis that is of a primary importance. All microbial agents are known to spread in the host organisms through a mechanism of innate immune evasion, and the diversity of such immune evasion is wide. Some pathogens mainly aim to inhibit the interferon system via hijacking the activity of pattern-recognition receptors (PRRs), such as Toll-Like Receptors (TLRs) 3, 7 and 8, and RIG-I-Like Receptors (RLRs), such as Melanoma-Differentiation Associated protein 5 (MDA5), others target the transcription factors for the expression of Interferon-encoding genes (INGs), others cleave the mRNA molecules that encode Type I and Type III IFNs, others prevent the transport of exocytosed IFNs to Interferon-binding receptors, such as IFNAR1/2 and IFNLR1/IL10R2, whilst others prevent the activation and/or translation of various Interferon-Stimulated Genes (ISGs). Type III Interferons were often particularly found to pronouncedly stimulate the production of antiviral immune responses and reduce the extent of pathogenic inflammatory activation. Some pathogens target exocytosed Interferon-Stimulated Gene products in a direct response against their ability to lyse specific viral proteins, such as non-structural proteins 1 and 2, that evolved in their initial response against first-line immunity, thereby highlighting the core evolutionary battle section, despite the central importance of adaptive immune components, such as primary dendritic cells, monocytes, M1 and M2 macrophages, B- and T-lymphocytes, alongside IgA, IgM and IgG antibodies. Microbial evasion is known to be visibly associated with the development of disrupted ratios of M1 to M2 macrophage activation, often implicating the first as aberrantly activated and the latter as weak. It could be that,

the more advanced level of induced first-line immune escape, the more disrupted the M1/M2 macrophage ratio often is. Specifically, it was recently discovered that RABV induces M1 macrophage polarization and, instead of the initial expectations that there would be the M0 state of neutralization reached, an experimental study showed that several states of M1, M2a and M2c polarization were detected post RABV-infection, with overall a unique macrophage polarization extent, potentially marking the advanced level of virus-induced immune escape. Importantly, multiple viral infective pathways were detected to have significant implications upon the interferon system, which implies that RABV has direct ways of inhibiting major antiviral immune responses. Rather than inhibiting the activation of M1 and M2 macrophages, RABV prevalently agonizes it, resulting in an effect upon the activity of antiviral genes, such as IFIT, OAS, TRIM and APOBEC3A. Hence, this study could indicate the allowance of RABV for delayed immune responses to operate freely, as its load would already be advancing through a new group of cells and silencing their antiviral genes by the time cells that had been infected a longer time beforehand would have their antiviral genes activated after the induced delay (Embregts C. et al, 2023).

It is perhaps interesting to note the poetic traits of human immunity, the foundational role played by its peripheral side, which marks innate immunity (Carp T., 2023). In the determination of a precise resolution of the big image of human immunity, it may also be important to mention the existence of a strong relationship of co-dependence and of interdependence between major innate and adaptive immune components. In the case of RABV, due to the negative-sense nature of the viral ribonucleic acid, the number of expressed viral proteins is restricted. Nevertheless, the viral genome was found to translate glycoproteins for the purpose of inhibiting Type I Interferon-based immune responses, and the therapeutic approach of RNA interference has been taken into consideration to aid host cells in their process of IFN I signaling (Denizot M. et al., 2012). Furthermore, it has been suggested that small drug-like molecular agonists could be developed to stimulate the activity of RLRs, as well as of the Interferon Regulatory Factor 3 (IRF3), which in turn would lead to the production, exocytosis and transmission of Type I IFNs to cells containing various ISGs that are responsible with the production of major antiviral cytokines. IRF3 is known to play a major role in the adequate synthesis of Type I IFNs and produce a broad extent of viral load clearance. Overall, such an approach could result in a tissular activation of innate immune mechanisms responsible for the induction of a sharp decrease of the local viral load, and this could very likely apply to the rabies viral disease (Pattahbi S. et al., 2015). Furthermore, lambda-interferon has been shown to manage RABV infection and restrict encephalic inflammation following the onset of rabies, by promoting the activation of the JAK-STAT pathway, by enhancing the activation and expression of ISGs and by stimulating the expression of the blood-brain barrier (BBB)-bound ZO-1 protein, which is implicated in the maintenance of the integrity of tight junctions and overall, in the restriction of encephalic inflammation. RABV specimens containing IFN-lambda2 and IFN-lambda3-encoding genes were found to reduce the production rate of pro-inflammatory cytokines in infected astrocytes and microglial cells (Li Y. et al., 2020). IFN-lambda was also found to stimulate the recovery of patients from central nervous system-related autoimmune responses (Manivagasam S. et al., 2022). Due to the high extent of viral self-camouflaging, it seems that the only approach that would substantially decrease the mortality rate of the disease would be to develop a counter immune "self-camouflaging" method, which would also be known as "fighting off the disease without fighting at all". This status would, of course, be temporary and, in an accordance as high as possible with the safety of a silent host immunity. The most complicated situation would be in patients with underlying health conditions and/or with family history of immunological, oncological and genetic disease. This scenario would only highlight the stage of immunological evolution mankind is at, where self-defense becomes a necessary method to survive advanced microbial evolution. But there is a slight possibility for a high quality offensive against advanced pathogens during this process of immune "self-camouflage". Due to the fact that nasal immunization with UV-neutralized RABV copies was made possible for the animal species of foxes, there could be a novel research method of combining a low dose of glycosylated alpha-, beta- and lambda-interferons with the neutralized viral copies and/or with anti-RABV and/or PRV IgA immunoglobulins, depending on the viral agent, due to the



proximity of the nasal cavity to the encephalon, as well as to the existence of pores that make connections between the nasal cavity and the encephalic neuronal network more facile.

Given the current level of evidence available on all public health databases, there could be a probability of a significantly effective early therapeutic approach against rabies. The timeline of the approach could include the following; the administration of strong innate immune stimulators and modulators, the administration of low to medium doses of Zinc ionophores, such as quinine or chloroquine, to temporarily inactivate the immune system, the allowance of the viral load to further spread without a significant immune reaction, the administration of human recombinant IFN I, II and III with a glycosylation site on the N- or O-terminus, alongside IFN-treated natural and adaptive lymphocytes, which could be deemed as “super-lymphocytes” due to their increased intelligence against the highly developed methods of first-line immune evasion by RABV, as well as the intravenous administration of high doses of immunostimulatory/modulatory minerals, such as Vitamins B3, 6, 9 and 12, Vitamin C, Vitamin D3 and Zinc, alongside others. Zinc ionophores represent drug-like compounds that enhance the process of ion channel-mediated endocytosis of Zinc, which is known for its major role in immunomodulation and the induction of microbial lysis. Interestingly, chloroquine is an antimalarial drug that is also known as a major immunosuppressant, meaning that, whilst some therapeutic drugs stimulate the production of immune responses whilst increasing the process of clearing the microbial load, other drugs inhibit existing immune responses whilst enhancing microbial clearance, and this highlights the complexity of immunity as a whole. A relatively decreased dosage of corticosteroids could be combined with the chloroquine immunosuppressant drugs to enhance a transient reduction of the immune reactions during important stages of viral encephalitis. Also, a number of antiviral drugs have been tested for both Rabies and Pseudorabies viruses (RABV and PRV), and some studies suggest that certain broad-spectrum antiviral drugs, such as Umifenovir, Favipiravir, Ribavirin and low-dose Ivermectin play a considerable role in the prevention of the disease by means of inducing viral clearance in major areas of the peripheral and central nervous system. One study suggested that Favipiravir could play a role in viral clearance as major as anti-RABV immunoglobulins. Furthermore, surgery could become a viable option if the virus causes uncontrollable harm in the encephalon, whether directly or indirectly, as a direct method of treatment with UVB and UVC radiation on the surface of the encephalon would become necessary to destroy the viral load and stimulate host immunity to restrict and cease its damaging reaction against vital components of the central nervous system, which is known to coordinate all bodily functions, thereby to have substantial implications on the general integrity and functioning of the human body. It could be possible to project that an immunomodulatory process as such would decrease the mortality rate of the disease, from 99%, all the way to 10% or less, provided that the methods of neuronal surgery are precise up to date in relation to the current state of medical progress. The method of targeting the virus using its own physical frequency, based on the models developed by Dr. Rife, could be researched further, as the high mortality rate of the disease may be raising a bioethical urgency to develop safe methods of precise biophysical targeting of the microbe.

### 3. Conclusion

Whilst rabies is certainly situated among the most complicated and long-sustained infectious diseases that mankind has witnessed, the current state of scientific and medical progress, as well as the recent shift of attention toward the hidden “gem” of first-line immune pathways, it has now become possible that clinicians develop pharmaceutical approaches to considerably decrease the mortality rate of the disease whilst maintaining risks of drug-induced adverse events toward zero, via a specific inclusion of prophylactic and early therapeutic innate immune stimulation, to simultaneously stimulate and modulate the produced adaptive immune responses. The development of anti-rabies vaccines by Dr. Louis Pasteur certainly represents a milestone in the highly complex and often energy-draining process of microbiological research, as the discipline of vaccinology was discovered and implemented in human civilization during the midst of the modern era. As with all other mainstream processes that human life comprises, the discipline of vaccinology requires a

continuous development to become up to date with the fresh demands of evolved microbial illnesses that locally threaten the integrity and wellbeing of human inhabitants. The administration of recombinant innate immune components, as well as adaptive lymphocytes with advanced innate immunity themselves could be combined with the administration of small drug-like agonist compounds that stimulate the activity of PRRs implicated in the detection of RABV copies, as well as the activation of the cGAS-STING pathway to ultimately stimulate a more systemic production of antiviral and anti-inflammatory cytokines. The advanced level of immune evasion displayed by the virus may imply that the areas of the immune system localized around the encephalon remain incapable of detecting the virus in cells where it induced the transient inhibition of their interferon system and the fact that the aberrant immune responses also remain behind the actual state of tissue infection during 99% of the cases may imply that the immune system at that stage does not have any control over the virus, despite the high intensity of its developed activity. As a result, the latter treatment method involving a restart of the immune system may be among the most feasible methods, potentially exceeding the 'Milwaukee' protocol substantially. Overall, it is likely that the research community needs to thoroughly apprehend the extent of complexity that human and mammal immunity displays, directly and subtly, before developing a "brainstorm" approach to control and possibly eradicate rabies in the end.

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