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Prions and virus pathogen gain-of-function

Eric Almeida Xavier *

Department of Microbiology, Experimental Oncology Unit, Immunology and Parasitology, Federal University of São Paulo, São Paulo, SP, Brazil.

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Abstract

There are many rumors and mutual accusations between belligerent nations of carrying out studies of gain of function of pathogens with the intention of using such pathogens as weapons of hybrid war. Thus the reported of A neurotropic H5N1 avian influenza A virus (IAV) strain named IAV/WSN /33 (H1N1) that induced the conversion of PrPC into PrPSc and the formation of infectious prions bring out the danger of a type of virus as potential risk for development of such weapons to warfare of fourth and fifth generation.

Keywords: Virus; Prions; Biochemical Weapons; Pandemic

1. Introduction

Prion are unprecedented infectious pathogens that cause fatal neurodegenerative diseases thus they are transmissible particles that are devoid of nucleic acid. So, a new neurotropic H5N1 avian influenza A virus (IAV) strain named IAV/WSN /33 (H1N1) induced not only the conversion of PrPC into PrPSc (Figure-1) but also the formation of infectious prions in cultured mouse neuroblastoma (N2aC24) cells, investigated by Hara et al [1,2,3].

Furthermore, *in vitro* PrPSc amplification techniques such as protein misfolding cyclic amplification (PMCA) have shown that RNA and lipid molecules function as a cofactor for the conversion of PrPC into PrPSc and the propagation of infectious prions [4]. Thus, is possible that IAV/WSN-derived RNA or lipid molecules might play a role as a cofactor in the conversion of PrPC into PrPSc in IAV/WSN-infected N2aC24 cells (Figure 1)[3].

In addition, there are theories arguing that viral RNA molecules might be able to function as a cofactor for the conversion of PrPC into PrPSc in PMCA [3]. So, protein sequence analysis of eukaryotic viruses has identified many prion-like domains in various viral proteins [5].

Due to their singular characteristics a virus that induces prion disease can be a stealth advantage for the attacker if he has an effective vaccine. A fact that contributes to the efficiency of a vaccine is that PrPC has a protective role against lethal infection of IAV/WSN infection in mouse through the octapeptide repeat (OR) region [6]. So, theoretically the OR region is also required for viral induce conversion of PrPC into PrPSc [6].

* Corresponding author: Eric Almeida Xavier
Department of Microbiology, Experimental Oncology Unit, Immunology and Parasitology, Federal University of São Paulo, São Paulo, SP, Brazil.

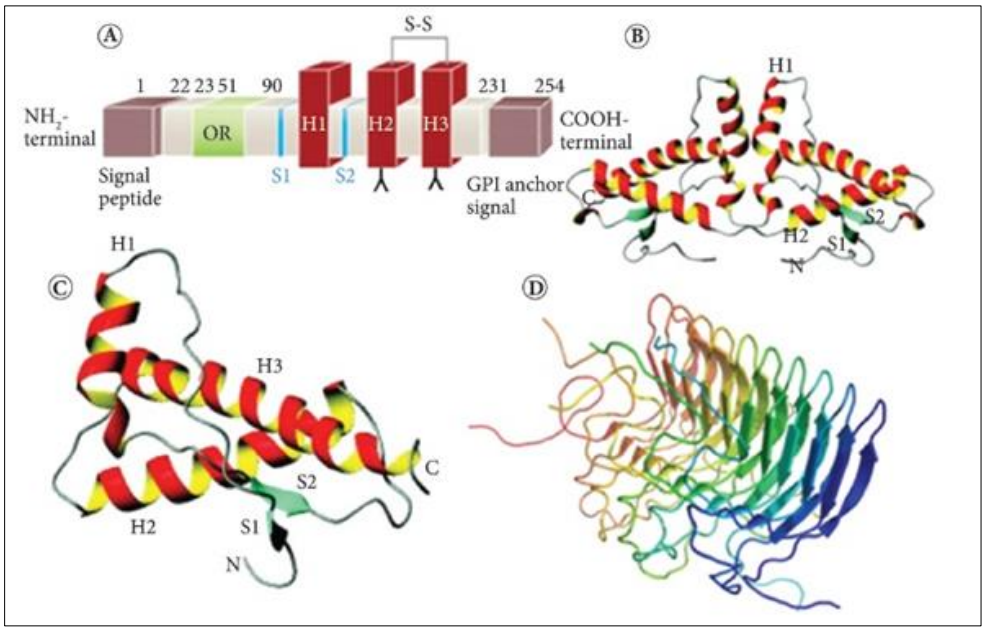

Figure 1 (A) Illustration of the normal structure of human prion protein gene (PRNP). PrPc is synthesized from a 254 amino acid precursor. The nascent peptide is cleaved at both the N-and C-terminal in the Endoplasmic Reticulum (ER). A glycosylphosphatidylinositol anchor (GPI) (purple) is attached to the C-terminus at position 231 of PrPc that helps link it to the extracellular membrane (lipid bilayer).In the Golgi, PrPc is N-glycoslyated at positions 181 and 197. Mature PrPc consists of the amino acid residues 23-231 and is expressed as a membrane glycoprotein anchored to the cell surface by a GPI moiety. (H) and (S) indicate α-helix and β-strandregions, respectively. (S-S) and (Y) "inverted" indicate a disulfide bond and N-glycosylation sites, respectively. (OR) specific octapeptide repeat. (B) Mature PrPc dimer. Under native conditions, bovine PrPc exists as a monomer-dimer. It is theorized from this dimeric structure that the dimerization is the first step in amyloid formation and the presence of these dimers could possibly speed up the aggregation of PrPSc. (C) The mature human PrPc protein. (B and C) NH2-terminal (letter N in Figure), COOH-terminal (letter C in Figure), α-helix (H1-H3) and β-strand (S1 and S2 in Figure). (D) A model for fibrils of fungal HET-s prion forming domain. Since no structural data for PrPSc have been reported to date, this is shown for comparison. The organization of this fibril is a left-handed β-solenoid with dense, parallel β-sheet packing. (A) Courtesy of Cayman Chemical Company. Ann Arbor, Michigan. USA. (B-C) Adapted From: Sekijima. M et al., (2003) (DOI:https://doi.org/10.1016/S0006-3495(03)74553-6). (D) Adapted From: Wasmer, C. et al ., (2008) (DOI: 10.1126/science.1151839). With permission.

At times the warfare involves biological and economic attacks, if the attacking force has the medicine or the population vaccinated before the attack, it will inflict crippling damage on the enemy force. So, the gain-of-function (GOF) experiments result in an increase in the transmission and pathogenicity of potential pandemic pathogens (PPPs) with the risk of using as biological weapons and recombinant prions as biochemical weapons, [7,8].

Recently the media has been publicizing reports of GOF research laboratories just like biological and biochemical; and intelligence agencies of North America and Russian, has been mutually accusing the intended of use weapons, such as, poison, radioactive and GOFs, against their political enemies in attacks stealthy and frightening.

Therefore, we refer to a hypothetical virus that contains a protein apparatus capable of inducing the formation of prions [8].

Furthermore, hypothetically, if a GOF virus inducing of prion were used as a biological weapon, they could damage humans, animals and economy of countries as described by *Xavie* [7,8].

1.1. Viral mechanism of action

Is possible that IAV/WSN infection might induce the conversion of PrPC into an IAV/WSN-specific form of PrPSc, thereby conferring new pathogenic properties on prions in an IAV/WSN-specific way [3]. So, in theory the, nucleic acid molecules have been suggested to be a factor contributing to strain-specific properties of prions [9].

Is possible that virus infections might increase the conversion rate of PrPC into PrPSc, by increasing the accessibility of PrPC to PrPSc through enhancing the cell surface binding of PrPSc molecules and stimulating their internalization to lysosomal compartments, where PrPSc convert PrPC into PrPSc, and increasing the release of PrPSc from prion-infected cells to prion-uninfected cells [3].

Therefore the propagation of prions uses the innate defense system by pH dependent endosome-like organelles or lysosomes with acidic environments. So professional antigen presenting cells (APCs) like dendritic cells (DCs) are plausible locations for viral propagation of PrPSc, [10,11].

If a virus is caught by APCs can triggered the convertion of PrPc into PrPSc by drop of pH in endocytosis and promoting the conformational convertion of PrPc into PrPSc by interaction of virus proteins with PrPc. So, phagocytic cells may propagate the disease if a particle reaching the central nervous system by immune system or sympathetic and parasympathetic nervous from tissues (Figure-2) [12,13,14,15].

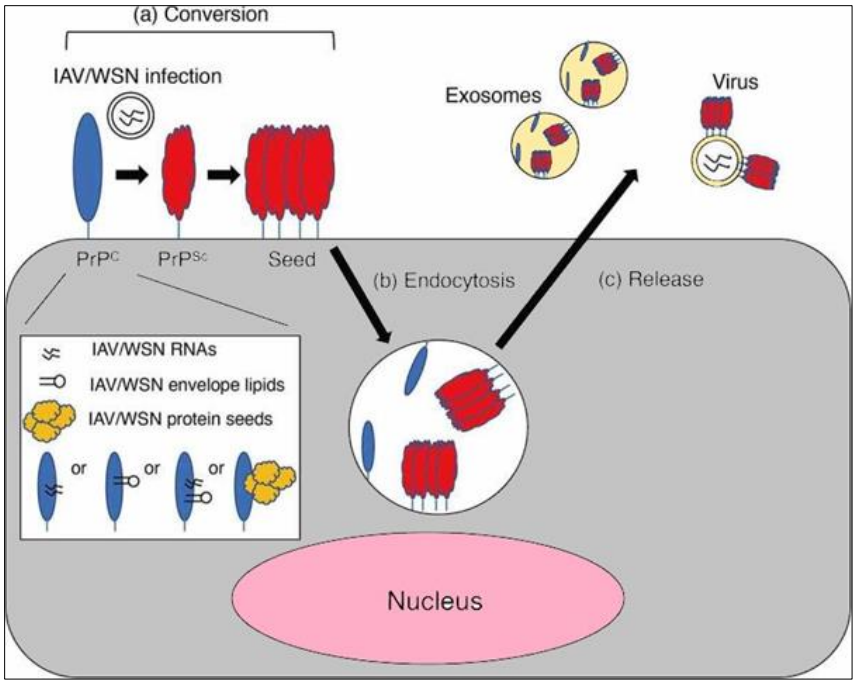

Figure 2 Possible steps of PrPSc propagation. (a) IAV/WSN infection induces the conversion of PrPC into PrPSc, subsequently forming PrPSc seeds. IAV/WSN-derived RNA or lipid molecules or the protein seeds of IAV/WSN-derived proteins, might convert PrPC into PrPSc. (b) Infection stimulates intracellular internalization of PrPSc seeds. (c) The incorporation of PrPSc into virus particles or exosomes, to increasing and release of PrPSc scrapie prion in cells. Adapted From: Sakaguchi. S and Hara. H (2022). under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided by the original work: (https://doi.org/10.1080%2F19336896.2021.2015224)

So, an obvious advantage of using a virus over a pure prion weapon [7] would be the fact that a vaccine could protect the population of the attacking country through opsonizing antibodies, which would prevent the virus crossing the epithelial barriers of the innate immune system [8].

For example important experimental trials have shown that infectious recombinant prions can be dispersed by aerosol, see (Figure-3 A-B) [16,17,18].

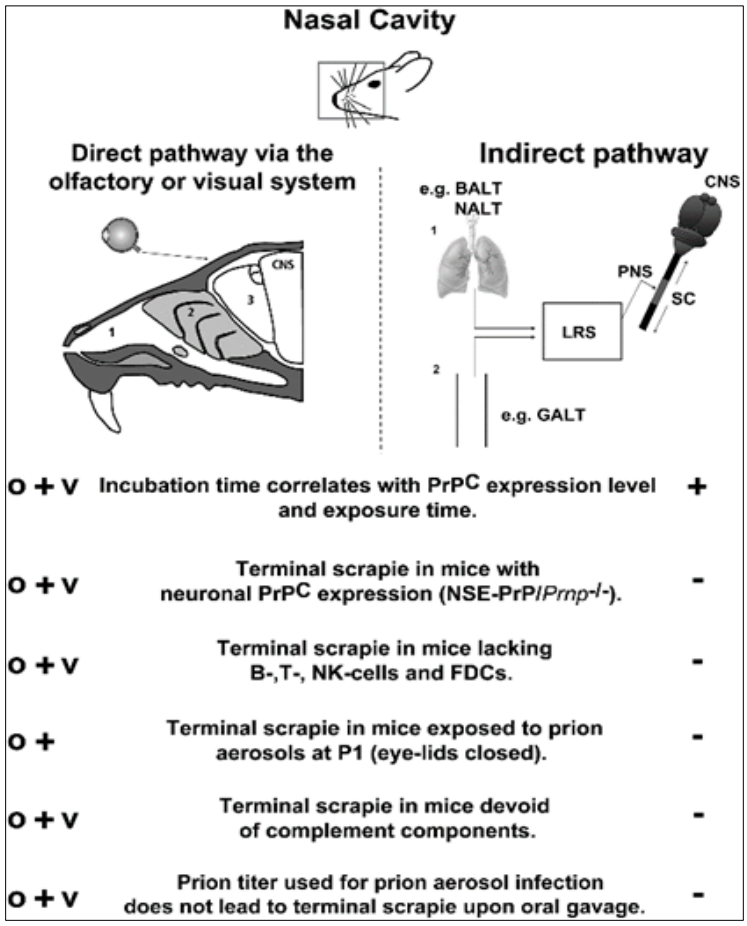

Figure 3 Model of the possible pathways of aerogenic prion transmission. (left) Prion aerosols entering the nasal cavity (1) may directly migrate through the nasal epithelium towards olfactory nerve terminals (2). Subsequently, prions reach olfactory bulb neurons and colonize the limbic system and other regions of the brain (3). Prions may be taken up by the eyes and transported via the visual system (e.g. optic nerves) to the central nervous system (CNS). O: olfactory system; V: visual system. Alternatively (right) prions may be taken up by immune cells residing in (1) the nasal cavity, lung, or (2) the gastrointestinal tract, from where they may be transferred to lymphoreticular system (LRS) components such as bronchial lymph nodes (BALT), nasal associated lymphoid tissue (NALT), gastrointestinal lymphoid tissue (GALT), mesenteric lymph nodes, or spleen for further amplification. Subsequently, prions traffic towards peripheral nerve terminals (PNS), from where they invade the central nervous system (CNS). SC: spinal cord. Arrows indicate possible migration directions of prions once they have invaded the spinal cord. Courtesy of Haybaeck. J *et al*., (2011), available at (https://doi.org/10.1371/journal.ppat.1001257.g008)

In addition, experiments have shown that prions can remain in the environment for a long time and decontamination of the environment can be a problem [19]. If GOF virus or PrPSc is made in laboratories with this purpose and dispersed in the air could kill a large number of people, since the sole as water can be the reservoir of infectious prions [19, 20, 21, 22, 23].

Thus, a nation can develop and refine through gain-of-function experiments a virus that causes prion disease in relatively simple laboratories using animals such as rats, mice, and monkeys [24,25,26,27].

As a general feature, prion diseases have a sinister characteristic, which is the long incubation time [28, 29, 30, 31, 32, 33, 34]; but the quantitative viral load of the primary infection and chronic contact with viral particles or PrPSc could also be taken into account in development of acute or chronic type of illness.

An example of the application of this type of biochemical weapon is ricin already used as a weapon, in the case that caught attention of media described by Papaloucas *et al* [35] about a political dissident that was killed by an alleged Russian secret service assassin using an umbrella as a weapon.

Consequently, prion/virus can be delivered by simple objects without giving the target any chance to receive a treatment. Some political enemies must be eliminated and prion/virus can be a possible alternative to the use of venoms, precisely because prions do not kill instantly and make the investigation process very difficult to trace the assassin agent. Another class of venom that have been used before and can be substituted by prions are the radioactive venom [36] because prions can cause the same horror effect with the advantage of no detectable by anti-gama; so, is a more stealthy element for the weapon operator agent willing to use it.

We cannot underestimate the immense adaptability of viruses, as well as their ability to adapt and transfect different species [37]. Because peptides are part of a fantastic universe thus for example their broad of specificity can be exposed until antitumor agents to pathological bioagents [38, 39, 40, 41].

2. Conclusion

Attacks with diseases and toxic agents are records since the Peloponnesian War, Punic Wars, Opium War and Spanish Invasion of the Americas. History repeats itself; these means have already been used efficiently and there is a great risk of being used again.

The last generation warfare has used stealth means of attack, aiming the impossibility to identify the aggressor agent. A country that develops new pathogens will be able to vaccinate your own population previously, through a government program, where vaccine could be administered along with others, to ensure little collateral damage in population of the aggressor country.

With the intensification of conflicts, many prisoners of war could be used to test and improve the efficiency of vaccines. So, the coronavirus pandemic has raised serious suspicions of a biological attack aimed deaths in the enemy population and economic damage.

Finally, is easy for closed regimes to make up and manipulate numbers of deaths, and simulate that they have been affected too.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

The authors declare that there is no conflict of interest. We authorize the full disclosure of the manuscript text and data.

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