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Rabies Pathogenicity

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Abstract:

Rabies is a zoonotic disease capable of affecting a plethora of mammalian hosts including humans. The most significant hosts are dogs which cause 90% of all human rabies cases, and haematophagous bats which serve as prime reservoirs of Lyssavirus spp.

Rabies may be manifested as the relatively uncommon paralytic rabies (20% of all cases) or the more well-known furious rabies (80% of all cases). Humans have known about furious rabies and recorded its occurrence since the very first evidence of written records.

'Rabies' originates from the Latin 'rabere' meaning rage, and thus, the genus of rabies-causing viruses, Lyssavirus, is named after Lyssa, the Greek goddess of rage and fury.

RABV - Rabies Lyssavirus:

RABV, the prototype of Genus Lyssavirus, has a characteristic bullet shaped structure with an unsegmented negative-sense single-stranded RNA genome indirectly coding for five viral proteins in a conserved sequence:

1. Matrix (M) proteins: the structural proteins encasing the virus, on top of which the phospholipid bilayer envelope is formed. Recent studies (Yuan et al., 2024) indicate their role in autophagosome formation for intracellular transport.

2. Phosphoproteins (P): the major pathogenic proteins which help in dissemination and immune evasion. Their role in rabies infection will be discussed in detail in the further sections.

3. Nucleoproteins (N): the ribonucleoprotein complex forming proteins that stabilise the genomic RNA as a result. As RNA is inherently susceptible to chemical damage, this ribonucleoprotein complex protects the viral genome outside the host cell.

4. Glycoproteins (G): the surface spike proteins capable of recognising Nicotinic Acetylcholine Receptors (nAChR) on neuronal surface and triggering endocytosis. It is also the primary immunogen of the RABV.

5. Polymerase (L) protein: the Virion-associated RNA-dependent RNA-polymerase required to form a positive-sense mRNA from the negative-sense vRNA and vice versa.

Pathogenicity:

1. Entry:

RABV enters deep into muscular tissue at the site of the bite from a rabid animal. The virus then infects neuronal synapses by endocytosis triggered by biocompatible articulation of the viral G protein with the nerve nAChR the neuromuscular junction.

Even though the virus has entered the neurons, it is vital for its reproduction to reach the neuronal cell body, which houses the nucleus. However, the sheer length of axons, sometimes reaching up to a whole metre, serve as an obstacle not only in viral transport, but also for the host cells' cargos.

To overcome this challenge, the neurons have a vast network of microtubules spanning the entire length of the axons. These practically function as "intracellular highways" on which Dynein and Kinesin locomotor complexes transport the cellular cargo packaged inside transport vesicles in retrograde and anteretrograde directions respectively.

RABV-P proteins hijack this transport system by docking onto the Dynein locomotor complex by mimicking the endosomal proteins of the transport vesicles. Dynein locomotor transports the viral body to the neuronal nucleus, where it utilises the host cell machinery for reproduction.

2. Replication and Reproduction:

The structural proteins dissociate and the viral body disintegrates, liberating the negative sense vRNAonce inside the cell body. L protein synthesises positive sense mRNA from the vRNA by RNA-dependent RNA-polymerase activity, which is then translated to produce their respective viral proteins.

Progeny viruses are formed and packaged, and are prepared for further infection. Unlike most viruses, daughter viruses are released at the synaptic junction by exocytosis as opposed to host cell lysis. This is a key immune evasion strategy whereby the infecting Lyssavirus prevents the triggering of Damage-associated Molecular Patterns (DAMPs).

DAMPsare endogenous molecules of self-origin which can be detected to recognise uncontrolled and unanticipated cell death or damage, which is usually caused by pathogenic tissue invasion. Under normal and controlled conditions, DAMPs are not permitted to enter the bloodstream or the interstitial space, thus, their presence indicates infection or a potential site for one, triggering inflammation as a protective and preventive measure.

Alongside DAMPs, PAMPs (Pathogen-associated Molecular Patterns) are vital in the antiviral immune defence of our body. PAMPs are exogenous molecules of foreign origin, specifically that of the invading pathogens. Most civilian cells of the body house Pattern Recognition Receptors (PRRs) which can detect PAMPs and trigger the release of interferon molecules, particularly IF-α and IF-β.

These signaling molecules direct selective overexpression of certain proteins that play a pivotal role in antiviral defences while simultaneously downregulating the general expression of proteins in neighbouring civilian cells. Viruses, being facultative intracellular parasites which require the host ribosome-dependent translation machinery to reproduce, are thus unable to survive in these cells despite being capable of infecting them.

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Furthermore, the judicious production of proteins like Ribonuclease L, which catalyses indiscriminate degradation of cytoplasmic RNA molecules, including the vRNA and viral mRNA, and overproduction of Class 1 Major Histocompatibility (MHC1) protein molecules act as innate antiviral measures.

MHC1molecules are expressed in all nucleated cells of the body including neurons. Random samples of polypeptides synthesised in the cells are complexed with MHC1 molecules and presented on the cell surface, where they can be recognised by TC cells. This generates cellular transparency and allows the invigilation and monitoring of the proteins synthesised by the cell. If, perchance, an exogenous polypeptide, that of viral origin, were to be sampled and coupled with the MHC1 molecule of an infected cell, these can be recognised by TC cells inducing apoptosis of the infected cell.

Lyssavirus gets around this by simply blocking the production of interferons. These traits of blocking interferons and avoiding host cell lysis practically makes Lyssavirus invisible to the immune system as, in dissemination, the virus travels through neurons, strictly avoiding entering the bloodstream, as it is not immune to recognition by the B cells and the ensuing antibodies produced.

3. Dissemination:

From the bite location, Lyssavirus slowly creeps up the neurons, infecting, and reproducing in each subsequent neuron, ultimately infecting the brainstem. Therefore, the incubation period of rabies can range from a week to up to a few years depending on the location of the bite and the inoculum size.

4. Symptoms and Illness:

Finally, Lyssavirus reaches and colonises the brainstem, and starts reproducing rapidly. This causes encephalitis, manifesting as headache, fatigue, and hypersensitivity, the first clinical symptom of rabies. Even in the brainstem, Lyssavirus avoids brain cell lysis and any behavioural and physiological symptoms of rabies arise due to the virus altering the release of neurotransmitters, the exact mechanism of which is still unexplored.

The virus then reverses the direction of travel to colonise other tissues, like the salivary glands. The specific symptoms of furious rabies include hyperactivity, restlessness, aggression, loss of coordination, hypersalivation, and hydrophobia. Although human-to-human transmission of rabies hasn't been recorded yet, all the aforementioned symptoms aggravate the patient and nudges them to transmit the disease.

Vaccine:

As mentioned before, Lyssavirus steers clear of B cells as the anti-G protein antibodies can encounter the viral body at synaptic junctions and immobilise the virus by immunoprecipitation. Thus, artificially introducing the virus into the bloodstream can generate an immune response against the virus.

In 1885, Louis Pasteur and Emile Roux created the first rabies vaccine by progressively attenuating the virus cultured in rabbits. However, modern vaccines contain inactivated viruses with an intact structure. The vaccination program requires a few booster shots at set intervals (3, 7, 14, and 28 days) after the first dosage.

Due to the extensive incubation period, it is possible to be immunised against rabies after getting bit by a rabid animal. Rabies vaccine is given as a precautionary measure for any bite cases as it is difficult and expensive to detect Lyssavirus until the onset of clinical symptoms, after which, the disease has shown to have a 100% mortality rate.

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