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expression in parallel with changes in symptom formation can be explained by the battle being waged between silencing suppression and silencing.

Silencing is autocatalytic and systemic, and hence the silencing of CaMV can also lead to the silencing in trans of transgenes driven by the CaMV 35S promoter. In a special case, herbicide resistance in oilseed rape conferred by expression of a 35S promoter-driven bialaphos tolerance transgene can be silenced due to the host response to CaMV infection.

See also: Caulimoviruses; General Features; Endogenous Retroviruses; Legume Virus Vectors (Gene Expression Systems); Rice Tungro Disease; Viral Suppressors of Gene Silencing; Virus Induced Gene Silencing (VIGS).

Further Reading

Blanc S (2002) Caulimoviruses. Virus–Insect–Plant Interactions. New York: Academic Press.
Covey SN and Al Kaff NS (2000) Plant DNA viruses and gene silencing. Plant Molecular Biology 43(special issue): 307–322.
Goldbach R and Hohn T (1996) Plant viruses as gene vectors. In: Bryant JA (ed.) Methods in Plant Biochemistry 10b: Molecular Biology, pp. 103–120. San Diego: Academic Press.
pose formidable barriers to the entry or dissemination of viruses within the nervous system. Yet, the multitude of dense dendritic connections among neurons provide a unique environment for cell-to-cell spread of pathogens. Furthermore, neurons are unique cells with high metabolic rates, intense membrane specialization, and no regenerative capacity. The same barriers that exclude viruses also limit access of immunocompetent cells and antibodies, and the nervous system lacks an intrinsic lymphatic system and has a paucity of phagocytic cells. Thus, the barriers that inhibit virus invasion also deter viral clearance. Therefore, many persistent infections involve the CNS.

The blood–brain barrier was originally conceptualized from the observation that dyes, such as Trypan Blue, stain all tissues except the brain and spinal cord after injection into the systemic circulation. The barrier at the cerebral capillary level consists of tight junctions between the capillary endothelial cells (beyond which most dyes do not pass), a dense basement membrane around the cells and tightly opposed astrocytic footplates. In the choroid plexus, the blood–CSF barrier is structurally different. The capillaries of the plexus are fenestrated, lack a basement membrane, and are surrounded by a loose stroma. Dyes and particles readily pass into the choroid plexus but are prevented from entering the CSF by tight junctions located at the apices of the secretory epithelial cells of the choroid plexus. Tight junctions between the arachnoid cell over the surface of the brain complete the barrier.

There is no comparable barrier between the brain and the spinal fluid. The ependymal cells are not joined by tight junctions and, therefore, there is a free exchange between the extracellular space of the brain and the CSF. However, the intracellular gap between neural cells measures only 10–15 nm, less than the diameter of even the smallest virus, so that free movement of virus particles or inflammatory cells within the extracellular space is relatively restricted.

Neurons have specialized membranes for the transmission and receipt of specific messages; they also have axonal extensions to carry signals to and from distant neuronal populations, motor endplates, and sensory endings. In humans these cytoplasmic extensions may exceed a meter in length. These features are important in viral infections, since different subpopulations of neurons have different receptors usurped by viruses to permit entry into cells. Furthermore, viruses in some cases can be carried by axoplasmic transport systems either into the nervous system or within the nervous system where axonal processes link functionally related neurons.

Antibodies found in the normal CNS are derived entirely from the serum. Antibody levels of immunoglobulin G (IgG) are approximately 0.4% of the serum levels. Since diffusion of macromolecules across the barrier is largely size-dependent, immunoglobulin M (IgM) is present in even lower levels. Complement is largely excluded. There is also no lymphatic system in the usual sense and few phagocytic cells. When inflammation disrupts the blood–brain barrier, antibody molecules leak into the nervous system along with other serum proteins. When a mononuclear inflammatory response is mounted against infection, T lymphocytes usually enter the nervous system first followed by macrophages and B lymphocytes. These B cells from the peripheral circulation move into the perivascular space and can generate immunoglobulins intrathecally.

The postmitotic nature of neurons is one of the most important features when considering viral infections of the nervous system. Unlike most organ systems, the fundamental component of the nervous system lacks the ability to regenerate. Thus, by definition, infections that cause cell death (directly or indirectly via the elicited immune response) create irreversible damage. In this setting, neurons have developed various strategies for suppressing viral replication, clearing virus infections, and for creating environments suitable for latent infections.

**Pathways of the CNS Invasion**

Viruses have been shown to enter the nervous system both along nerves and from the blood. The first experimental studies of viral invasion employed rabies, herpes simplex, or polioviruses, all of which, under experimental circumstances, can penetrate the nervous system along peripheral nerves. The precise mechanisms of neural spread remained a mystery for many years, since it was thought that the axoplasm slowly oozed in an anterograde direction. It was proposed that virus might move in perivascular lymphatics, by ascending infection of the supportive cells within the peripheral nerve, or even by replication in axons, a speculation that is now untenable because of the observed lack of ribosomes or protein synthesis within axons. In the 1960s active anterograde and retrograde axon transport systems were found. Viruses or other particles can be taken up in vesicles at the nerve terminals and transported to the cell body of the sensory or motor neuron (Figure 1). This neural route of entry is important in primary viral infections such as rabies and possibly poliomyelitis. Retrograde transport also moves herpes simplex and varicella-zoster viruses from mucous membranes or skin into sensory ganglia at the time of primary infection. Subsequently, anterograde transport carries the reactivated virus from the ganglia to the periphery during exacerbations. Anterograde transport of herpes simplex virus by nerves innervating the dura from the trigeminal ganglia may explain the unique temporal lobe localization of herpes simplex virus encephalitis.

The olfactory spread of virus is a variation of neural spread. In the olfactory mucosa, neural fibers provide a
unique pathway; the apical processes of receptor cells extend beyond the free surface of the epithelium as olfactory rods and the central processes synapse in the olfactory bulb. These are the only nerve cells with processes that link the CNS and ambient environment. Indeed, some colloidal particles placed on the olfactory mucosa can be found in the olfactory bulbs within 1 h. Experimental studies show that viruses can enter through this route, and this may occur in some aerosol infections in humans such as laboratory accidents or rabies virus infections in bat-infested caves. Also, the olfactory pathway has been postulated as a possible route of herpes simplex virus entry into the nervous system as an alternative explanation for the orbital–frontal and medial–temporal lobe localization of herpetic encephalitis. Nevertheless, despite the apparent ease of spread along this route, it appears to be a rare route of natural infection.

In most experimental and natural infections, viruses invade the brain from the blood. Historically, the blood–brain barrier was believed to be impervious to viruses. This belief was based in part on the fact that viruses experimentally inoculated directly into brain cause disease after a brief inoculation period, whereas the incubation period after intravenous inoculation is longer and comparable to that following cutaneous or peritoneal inoculation. The reason for this delay in infection is that virus in the blood is rapidly removed by the reticuloendothelial system; therefore, intravenous inoculation is, in fact, an inoculation primarily of the Kupffer cells of the liver and other reticuloendothelial cells. Therefore, virus must establish a nidus of peripheral replication that can effectively seed a viremia of sufficient magnitude and duration to allow invasion across the blood–brain barrier (Figure 2). Thus, some viruses grow in lymphatics and seed into the blood directly via the thoracic duct, others grow in vascular epithelial cells, and others replicate in highly vascular tissue such as muscle.

A persistent viremia can be achieved by several mechanisms. Rate of clearance is dependent upon particle size; small particles such as togaviruses and flaviviruses can maintain high-titer plasma viremias with sufficient rapid replication in peripheral tissue. Other viruses adsorb to red blood cells and thus evade clearance. Many large viruses such as measles and herpes viruses infect white blood cells thus evading clearance and replicating at the same time.

Some viruses enter the nervous system either across the capillary endothelium and others across the choroid plexus. Some viruses infect the capillary endothelial cells and simply grow into the brain while others are able to transit across endothelial cells despite their paucity of endopinocytotic vesicles. Entry in infected leukocytes is a theoretical possibility but leukocyte traffic into the nervous system is limited, although trauma or inflammation due to other causes may predispose the nervous system to infection with viruses that infect white blood cells. Although there are areas of increased blood–brain barrier permeability, no viral infection has been shown to infect these areas selectively. Other viruses, such as mumps
virus, grow in choroid plexus epithelium and seed into CSF. Thus, the clearance of particles by the reticuloendothelial system, barriers of nonsusceptible extraneural cells, production of interferon and other nonspecific inhibitors, and the physical barriers of the nervous system itself probably explain why viral infections of the brain are rare, even though systemic infections with the potential pathogens are very common.
Infections of Neural Cells

Once a virus has penetrated into the nervous system it must contact a susceptible cell and spread through the compact neuropil which is a theoretical problem. The fact that some viruses can be neutralized by extracellular antibody even after CNS invasion shows that viruses such as togaviruses and flaviviruses do spread in extracellular space, but this is not true of larger viruses. Conversely, the compact neuropil may facilitate the contiguous cell-to-cell spread of viruses. For example, in subacute sclerosing panencephalitis, a chronic brain infection of humans with measles, extracellular enveloped virus is never seen, and there are enormous titers of extracellular antibody. Apparently, the fusion protein allows measles virus to move from cell to cell through the brain.

Cell-to-cell spread may also involve axoplasmic flow causing infection of functionally linked cells; for example, in poliovirus infections the virus is rapidly spread through the motor system. Some viruses infect only neuronal populations such as rabies, polioviruses, and the arthropod-borne viruses (arboviruses), and some infect selective neuron populations. Other viruses such as herpes simplex virus appear to infect neurons and glial populations with little selectivity.

Infection limited to vascular endothelial cells is found with rickettsial infections but is not recognized in any viral infection of the nervous system. Infection limited to choroid plexus and meningeal cells appears to occur with those viruses that cause benign meningitis. In experimental studies with a number of viruses, widespread lytic infection of ependymal cells can lead to closure or stenosis of the aqueduct of Sylvius and resultant hydrocephalus. Similar aqueductal stenosis and hydrocephalus have been described in children after mumps virus meningitis.

The selective infection of oligodendrocytes has been recognized in nature in the disease progressive multifocal leukoencephalopathy caused in humans by the JC virus and in monkeys by SV-40 virus. In the course of immuno-suppression, now seen most frequently with acquired immune deficiency syndrome (AIDS), a selective lytic infection of oligodendrocytes causes multifocal areas of demyelination in the brain. This usually fatal condition has also been seen in patients treated with immunomodulating medical regimens that included natalizumab (a monoclonal antibody against alpha 4 integrin). This drug causes a release of lymphocytes from lymph nodes and prevents the trafficking of lymphocytes across the blood–brain barrier. Thus, this medication may have interfered with the normal immune surveillance of the CNS, leading to the unabated emergence of JC virus within the brain.

With changes in age, the specificity of infection and vulnerability of neural cells may change. For example, bluetongue virus infection of fetal sheep destroys the precursors of neurons and glia of the subependymal plate which leads to hydrancephaly or porencephaly dependent on the age of fetal development, whereas the virus fails to infect the mature postmigratory cells in the late gestational or postnatal animal. Similarly, the external granular cells of the cerebellum in fetal or newborn animals are selectively infected by paroviruses, and destruction of these mitotic cells leads to the granulopriival cerebellar degeneration seen in both natural and experimental animal infections. Alphaviruses which cause encephalomyelitis have more profound effects in young hosts including mice and humans.

Mechanisms of Cell Damage

Lytic infections of neural cells cause regional destruction of brain or lysis of specific cell populations. Noncytopathic infections of neural cells also occur and lead to persistent infection with no disease or disorders without obvious histological changes. For example, neuroblastoma cells in culture infected with noncytopathic viruses such as rabbies can show normal morphology growth rates and protein synthesis, but reduced synthesis of specific neurotransmitters or receptors. These have been termed ‘luxury functions’, although in vivo the ability of neurons to synthesize transmitters or receptors would hardly be considered a luxury. Analogous noncytopathic infection has been demonstrated in mice congenitally infected with lymphocytic choriomeningitis virus. Congenitally infected mice are usually ‘runts’, but recent studies have shown selective infection of cells of the anterior pituitary which normally generates growth hormone. The animals are actually pituitary dwarfs responsive to growth hormone therapy.

Alternatively, the infected cell may not be damaged by virus replication but destroyed by the immune responses, as seen in adult mice infected with lymphocytic choriomeningitis virus. Indirect cell damage can occur in viral infections that leads to sensitization of the host to neural antigens. This has recently been demonstrated in rats infected with coronaviruses, where the infection of neural cells leads to a cell-mediated autoimmune response to myelin proteins and to subsequent demyelination. In postmeasles encephalomyelitis of humans, autoimmune demyelination appears to occur in the absence of infection of neural cells. Infection of lymphoid tissue leads to disruption of normal immune regulation, and about 1 per 1000 persons develop a symptomatic autoimmune reaction to myelin basic protein.

Other indirect mechanisms of neural cell damage have been postulated to explain the diverse neurological diseases seen in the course of human immunodeficiency virus (HIV) infection. The virus does not appear to cause significant or readily documented infections of
neuronal or glial cells. The primary cells that are infected are macrophages and the microglia of the brain derived from macrophage populations. Possibly viral proteins produced by these cells or cytokines released by these cells interfere with neuronal function or are toxic to neurons or glial cells. For example, tumor necrosis factor, a lymphokine often increased in brains of neurologically affected AIDS patients has been shown in vitro to induce demyelination.

**Clinical Features**

**Acute Infections**

The varied clinical features of viral infections of the nervous system can be explained in large part by the factors discussed above. Thus, a virus may infect only meningeal or ependymal cells, and cause a clinical syndrome known as viral meningitis or acute aseptic meningitis. This clinical syndrome is characterized by fever, headache, and nuchal rigidity secondary to meningeal irritation but without clinical signs suggesting parenchymal disease. The commonest causes of acutely viral meningitis are enteroviruses and mumps virus.

Encephalitis is a clinical syndrome in which in addition to fever, headache, and stiff neck, there is paralysis, altered mental status, seizures, or other evidence of parenchymal disease of the brain. The commonest causes of severe encephalitis in man are herpes simplex virus and the arboviruses. The former infects neurons and glia and causes diffuse necrotizing encephalitis in the newborn but focal encephalitis in the immune adult presumably because diffuse virus spread is contained by immune responses. Focal signs, hallucinations, behavioral abnormalities, and aphasia are more common with herpes encephalitis because of the localization to temporal lobes. Arboviruses have a propensity to infect neurons, and some flaviviruses tend to infect basal ganglia and brainstem neurons causing movement disorders and sudden respiratory failure. If signs of spinal cord involvement accompanies encephalitis, the term encephalomyelitis is often used. However, the term encephalomyelitis is also used to distinguish an acute postinfectious demyelinating disease of assumed autoimmune origin from acute viral encephalitis. Postinfectious encephalomyelitis (or acute disseminated encephalomyelitis) usually occurs 3–14 days after exanthems (measles, varicella, or rubella) or respiratory infections (mumps, influenza, and others) and clinically is characterized by the abrupt onset of fever, obtundation, seizures, and multifocal neurological signs.

The clinical syndromes of rabies and poliomyelitis are the most distinctive of viral infections because of the selective infection of specific populations of neurons. Polioviruses selectively infect motor neurons which lead to flaccid paralysis. Rabies causes early infection of the limbic system neurons with a relative sparing of cortical neurons which leads to behavioral abnormalities. Rabies infections represent a diabolical adaptation of virus to animal host, causing the animal to remain alert but to lose timidity and develop aggressive behavior to transmit the virus. The advantage of this selectivity is evident considering that strains of rabies that cause the so-called ‘dumb’ or passive rabies are seldom transmitted in nature.

**Slow Infections**

Slow infections are characterized by long incubation periods of months to years followed by an afebrile progressive disease. The term was originally coined in veterinary medicine to describe several transmissible diseases in sheep. The prototype slow infections are scrapie, a chronic noninflammatory spongiform encephalopathy due to a transmissible agent in which no nucleic acid has been identified (a prion), and visna, a chronic inflammatory encephalomyelitis caused by a lentivirus. The first slow infection identified in man was ‘kuru’, a progressive ataxia of a tribal group in New Guinea where the agent, resembling the agent of scrapie, was apparently transmitted by ritual cannibalism. Creutzfeldt–Jakob disease, a subacute dementia with myoclonus, is a worldwide disease due to prion agents. In some cases, transmission is genetic, in others, transmission is by transplants or administration of contaminated growth hormone, but in the vast majority the means of transmission is unknown. In both of these human spongiform encephalopathies, the clinical disease progresses irrevocably to death in about 6 months, but without fever or other clinical or histological findings to suggest infection.

Dementia, a chronic deterioration of cognitive function, can also be caused by several conventional viruses. Subacute sclerosing panencephalitis is a chronic dementing illness caused by measles virus. One per million otherwise healthy children develop this chronic illness at an average of 7 or 8 years after uncomplicated measles. Dementia evolves slowly, associated with myoclonic movements and massive levels of measles antibody in serum and CSF. Children usually die a year or less after infection, but survival may vary from 6 weeks to 6 years. The disease is due to a subacute, slowly progressive diffuse infection of neurons and glial cells. Another viral cause of dementia, HIV, has become a common problem as patients are surviving longer while on highly active antiretroviral therapy.

Clinical symptoms associated with HIV are very diverse (Figure 2). This virus now represents the commonest viral infection of the nervous system. From prospective studies of CSF changes, it appears that the majority of people infected with the virus have early invasion of the nervous system, that is, the virus is highly neuroinvasive. However, early during this infection
neurological disease is rare. A presumed autoimmune disorder occasionally causes a demyelinating peripheral neuropathy (Guillian–Barre syndrome); acute meningitis is occasionally seen at the time of seroconversion or during early asymptomatic infection. An asymptomatic pleocytosis is often found. Therefore, the virus is, at this stage, not highly neurovirulent. However, after the onset of immunodeficiency the infection is neurovirulent; at least 50% of the patients develop progressive dementia with cerebral involvement, myelopathies, or painful sensory neuropathies. The pathogenesis of these complications is unknown, but they are thought to be due to some viral protein or lymphokine incited by the virus because of the relative paucity of the virus in the nervous system and its localization to the microglial and macrophage populations.

Tropical spastic paraparesis complicating human T-cell leukemia virus type 1 infections is a recently recognized slow nervous system infection. Less than 1% of the patients infected with this virus develop either acute T-cell leukemia or neurological disease. Since many of those infected are infected by breast milk and the onset of tropical spastic paraparesis is usually in the fourth or fifth decade of life, the incubation period is extraordinarily long. A subacute disease develops with progressive paralysis of the lower extremities associated with impotence, incontinence, and sensory symptoms, but usually minimal sensory findings. Disease progresses slowly until the patients are wheelchair bound, but the disorder remains primarily at the level of the thoracic spinal cord. The involvement of the upper extremities is minimal with hyperreflexia but usually good function, and there is usually little, if any, indication of cerebral involvement. Early pathology found in a biopsy of the spinal cord in a single case showed vasculitis. In late cases, hyalinization of vessels with necrosis and demyelination of spinal cord is found, and findings are most prominent in the thoracic cord. Whether virus replicates in any cells other than T lymphocytes is unknown. These observations lead to the questions of why less than 1:100 who are infected develop disease; why the incubation period is as long as 40 years; why the disease localizes to the thoracic spinal cord; and why over years the disease becomes relatively quiescent despite the fact that there is ongoing high levels of intrathecal antibody synthesis, suggesting that there is still antigenic stimulation by virus within the nervous system.

Identification of viruses or virus-like agents (prions) in a variety of chronic neurological diseases has led to speculation of a viral etiology for multiple sclerosis, Parkinson’s disease, amyotrophic lateral sclerosis, Alzheimer’s disease, schizophrenia, and other illnesses. Experimental evidence for viruses in these chronic diseases is still tenuous.

See also: Herpesviruses: Latency; Measles Virus; Mumps Virus; Persistent and Latent Viral Infection; Rabies Virus; Viral Receptors; Visna-Maedi Viruses.

Further Reading

Johnson RT (1982) Viral Infections of the Nervous System. New York: Raven Press.

Cereal Viruses: Maize/Corn

P A Signoret, Montpellier SupAgro, Montpellier, France

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Introduction

Maize is the main cereal crop in the world regarding total yield; it is grown on about 120 Mha. Maize has been grown for millennia in Central America. From a plant mainly used as human food, maize is now a main component for feeding animals but is still a major staple food crop in sub-Saharan Africa and America.

Viruses can cause important diseases of maize worldwide. While some viruses are widespread, others are localized. Some maize viruses can be sporadic and devastating causing severe yield losses, others may occur each year but losses are relatively minor. The average yield of maize in several African countries is only about a third of the world’s average, and some viral diseases of maize are one of the major factors responsible for this low productivity. When available, resistant or tolerant hybrids provide the most effective means to control maize viruses. A pathogen-derived resistance strategy was developed for some viruses such as maize dwarf mosaic virus (MDMV) and maize streak virus (MSV). The major viruses affecting maize are transmitted by leaf- or planthoppers (16) but four viruses have aphids, two have mites, and one has beetles as vector. Populations of leafhopper and