Poliovirus

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Introduction

The family *Picornaviridae* includes many human and animal pathogens, such as poliovirus, hepatitis A virus, foot-and-mouth disease virus, and rhinovirus. All picornaviruses are small, non-enveloped viruses with a single-stranded RNA genome of positive polarity, properties that are reflected in the name of the virus family: pico, a small unit of measurement [10^{-12}], and the nucleic acid of the viral genome, RNA. This chapter will focus on the biology and pathogenesis of poliovirus, the best studied picornavirus that causes disease of the nervous system. There are three serotypes of poliovirus which are classified in the species *Enterovirus C* within the genus *Enterovirus*. See "Measles Virus and Subacute Sclerosing Panencephalitis" chapter for a discussion of other neurotropic picornaviruses.

Virus Structure

Poliovirus particles consist of a 30 nm protein shell surrounding the naked RNA genome. The virus particles lack a lipid envelope, and consequently their infectivity is insensitive to organic solvents. These viruses pass through the stomach to gain access to the intestine and therefore must be resistant to low pH.

The capsids of polioviruses are built with 60 copies each of four structural proteins, VP1, VP2, VP3, and VP4, arranged into an icosahedral lattice (Fig. 1) (Rueckert et al. 1969). The basic building block of the poliovirus capsid is the pro-

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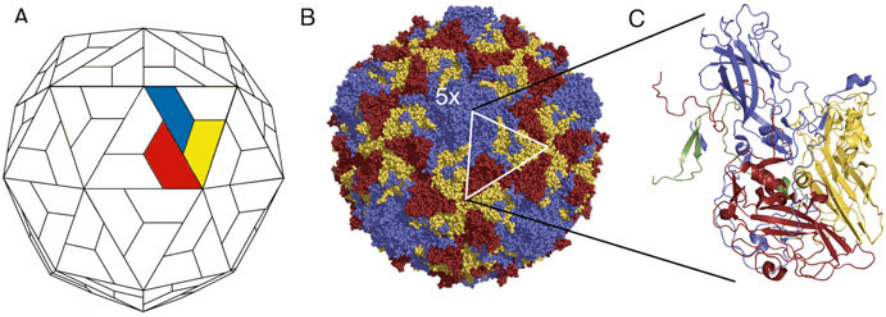

Fig. 1 Structure of poliovirus. (**a**) Schematic of the viral capsid, showing the packing arrangement of VP1 (*blue*), VP2 (*yellow*), and VP3 (*red*). VP4 is on the interior of the capsid. (**b**) Model of poliovirus type-1, Mahoney strain, based on the X-ray crystallographic structure determined at 2.9 Å (Hogle et al. 1985). At the fivefold axis (labeled) is a star-shaped mesa surrounded by the canyon, which is the receptor-binding site. (**c**) A single protomer is shown as a ribbon diagram, showing the locations of capsid proteins VP1, VP2, VP3 and VP4

tomer, which contains one copy of each capsid protein. The shell is formed by VP1, VP2, and VP3, while VP4 lies on its inner surface. VP1, VP2, and VP3 have no sequence homology, yet all three proteins form a wedge-shaped, eight-stranded antiparallel β-barrel. The wedge shape facilitates the packing of structural units to form a dense, rigid protein shell. The main structural differences among VP1, VP2, and VP3 lie in the loops that connect the β-strands and the N- and C-terminal sequences that extend from the β-barrel domain.

Resolution of the atomic structure of poliovirus revealed that the surface of the capsid has a corrugated topography; there is a prominent star-shaped plateau (mesa) at the fivefold axis of symmetry, surrounded by a deep depression (canyon) and another protrusion at the threefold axis (Hogle et al. 1985) (Fig. 1). It was originally proposed that the canyon is the receptor-binding site, and this hypothesis has been proved for poliovirus and other picornaviruses (Belnap et al. 2000; He et al. 2000).

The Viral Genome

The genome of poliovirus, a single positive-stranded RNA molecule, is infectious because it is translated upon entry into the cell to produce all the viral proteins required for replication. The genome is 7.4 kb in length and is covalently linked at the 5′ end to VPg protein (Virion Protein, genome linked) (Flanegan et al. 1977; Lee et al. 1977), which serves as a primer for viral RNA synthesis (Nomoto et al. 1977; Pettersson et al. 1978). The long (~742 nucleotide) and structured 5′-noncoding region contains sequences that control genome replication and translation. The 5′-noncoding region contains the internal ribosome entry site (IRES) that directs translation of the mRNA by internal ribosome binding. Following the 5′-noncoding region is a single open reading frame on the viral RNA that is translated into a polyprotein that is processed to form individual viral proteins. The polyprotein is cleaved

during translation by virus-encoded proteinases, so that the full-length product is not normally observed. At the 3′-end of the poliovirus genome is the 3′-noncoding region (~70 nucleotides) which has been implicated in controlling viral RNA synthesis (Jacobson et al. 1993), and a 3′ stretch of poly(A) (Yogo and Wimmer 1972) that is required for viral infectivity (Spector and Baltimore 1974).

Viral Replication

Virus Entry into Cells

Poliovirus replication begins with attachment of virus particles to a cell surface receptor; for all three serotypes this molecule is CD155, a glycoprotein that is a member of the immunoglobulin superfamily of proteins (Mendelsohn et al. 1989). CD155 is composed of three extracellular immunoglobulin-like domains: a membrane-distal V-type domain that binds poliovirus, followed by two C2-type domains. The first Ig-like domain contains the site that binds poliovirus (Koike et al. 1991a; Morrison and Racaniello 1992; Selinka et al. 1991, 1992; Aoki et al. 1994; Bernhardt et al. 1994; Morrison et al. 1994; Belnap et al. 2000; He et al. 2000; Xing et al. 2000). Alternative splicing of mRNA leads to the synthesis of two membrane-bound isoforms, CD155a and CD155d, and two isoforms that lack transmembrane domains and are secreted from the cell (Mendelsohn et al. 1989; Koike et al. 1990). The function of the secreted isoforms is unknown. The membrane-bound isoforms are adhesion molecules, participating in the formation of adherens junctions by interacting with nectin-3, an immunoglobulin-like protein related to CD155 (Mueller and Wimmer 2003). CD155 is also a recognition molecule for natural killer (NK) cells, and interacts with CD226 and CD96 on NK cells to stimulate their cytotoxic activity (Bottino et al. 2003; Fuchs et al. 2004). Cytomegalovirus evades NK cell-mediated killing because the viral UL141 protein blocks the surface expression of CD155 (Tomasec et al. 2005).

After attachment to a cellular receptor, the poliovirus capsid dissociates, releasing the RNA genome, which then enters the cytoplasm, the site of replication. Interaction of poliovirus with domain 1 of CD155 causes a conformational change in the capsid leading to release of the genome. These particles, called altered (A) particles, contain the viral RNA but lack the internal capsid protein VP4. The N-terminus of VP1, which is normally on the interior of the capsid, is on the surface of the A particle (Fricks and Hogle 1990). The exposed lipophilic N-terminus of VP1 inserts into the cell membrane, forming a pore through which the viral RNA can travel to the cytoplasm (Bubeck et al. 2005a, b).

Uncoating of the poliovirus genome probably occurs either at the plasma membrane or from within endosomes. Drugs that block acidification of endosomes do not inhibit poliovirus infection (Perez and Carrasco 1993), and arrest of the clathrin-dependent endocytic pathway using dynamin mutants that prevent clathrin-coated pit budding have no effect on poliovirus replication (DeTulleo and Kirchhausen

1998). Endocytosis alone is not sufficient to trigger poliovirus uncoating, because antibody-coated poliovirus particles cannot effectively infect cells expressing Fc receptors, which are efficiently endocytosed (Arita et al. 1999; Mason et al. 1993). CD155-mediated conformational changes in poliovirus are clearly important for the uncoating process.

Translation and Proteolytic Processing

After positive-strand polioviral RNA enters the cytoplasm, it is translated to provide viral proteins essential for genome replication and the production of new virus particles. The viral genome lacks a 5′-terminal cap structure, and cannot be translated by 5′-end dependent mechanisms. The 5′-untranslated region of poliovirus RNA harbors an internal ribosome entry site (IRES) that promotes internal binding of the 40S ribosomal subunit and allows 5′-end independent translation (Fig. 2). The poliovirus IRES contains extensive regions of RNA secondary structure that is crucial for ribosome binding. Translation initiation mediated by the IRES of poliovirus involves binding of the 40S ribosomal subunit to the IRES and scanning of the subunit to the AUG initiation codon. The 40S ribosomal subunit is recruited to the IRES through interaction with eIF3 bound to the C-terminal domain of the translation initiation protein eIF4G, which binds directly to the IRES.

Ribosome binding to the poliovirus IRES requires cell proteins other than the canonical translation proteins. Such proteins have been identified by their ability to bind the IRES and restore internal initiation in reticulocyte lysates, in which

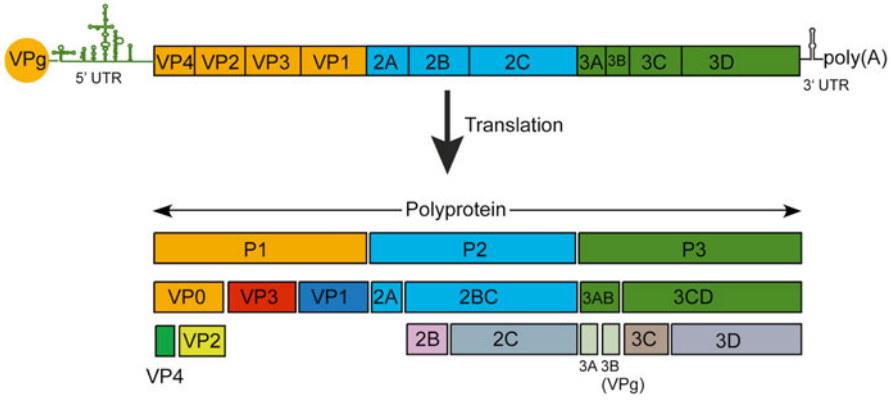

Fig. 2 Schematic of the poliovirus genome. At *top* is shown a diagram of the viral RNA with coding regions labeled. RNA structural elements include an enterovirus IRES within the 5′ untranslated region and the pseudoknot within the 3′ untranslated region. *Below* is the processing pattern of poliovirus polyprotein. The coding region is divided into P1, P2, and P3, which are separated by nascent cleavage by viral proteinases. Intermediate and final cleavage products are shown

IRES-mediated translation is inefficient. Cell proteins required for IRES-mediated initiation include the La protein, which binds to the 3′-end of the poliovirus IRES and stimulates its activity (Meerovitch et al. 1993; Kim and Jang 1999). Other proteins include polypyrimidine tract-binding protein, a regulator of pre-mRNA splicing (Hellen et al. 1993; Kaminski et al. 1995); unr, a RNA-binding protein with five cold-shock domains (Hunt et al. 1999); and ribosome-associated poly r(C)-binding proteins (Blyn et al. 1996, 1997; Gamarnik and Andino 1997). A common property of cellular proteins needed for IRES activity is that they are RNA-binding proteins that can form multimers with the potential to contact the IRES at multiple points. This observation has led to the hypothesis that these cell proteins may act as RNA chaperones and maintain the structure of the IRES in a configuration that allows direct binding to the translational machinery (Jackson et al. 1995).

Poliovirus proteins are produced by the translation of the single open reading frame encoded by the viral positive-stranded RNA genome, followed by cleavage of the polyprotein by virus-encoded proteinases. The polyprotein is processed cotranslationally by intramolecular reactions (in *cis*), followed by secondary processing in *cis* or in *trans* (intermolecular). The poliovirus genome encodes two proteinases: $2A^{pro}$, and $3C^{pro}/3CD^{pro}$, which carry out cleavage of the polyprotein (Fig. 2).

RNA Synthesis

Poliovirus RNA synthesis is carried out by the virus-encoded RNA-dependent RNA polymerase, $3D^{pol}$, a primer- and template-dependent enzyme that specifically copies viral RNA and not cellular RNAs. The RNA polymerase $3D^{pol}$ is produced by cleavage of a precursor protein, $3CD^{pro}$, which is active as a proteinase but has no RNA polymerase activity. The primer for viral RNA synthesis is VPg, the small protein linked to the 5′-end of viral RNA. VPg is first uridylylated to form VPg-U-U, a reaction that is carried out by $3D^{pol}$ using as a template either the 3′-poly(A), or a short RNA hairpin structure (50–100 nt), the cis-acting replication element, *cre*, located in the coding region of the poliovirus genome (Paul et al. 2000; Rieder et al. 2000; Yin et al. 2003).

The first step in genome replication is copying of the positive-stranded RNA to form a negative-stranded intermediate. The template for this reaction appears to be a circular molecule formed by interaction of a 5′-cloverleaf structure in the viral RNA with the 3′-poly(A) tail. Circularization of the viral RNA is meditated by the interaction of $3CD^{pro}$ with cellular poly(A) binding protein (PABP). These proteins also interact with the viral RNA: $3CD^{pro}$ with the 5′-cloverleaf structure, and PABP with the 3′ poly(A) of the viral genome (Herold and Andino 2001). The viral polymerase, $3D^{pol}$, initiates RNA synthesis at the 3′-poly(A) tail and produces a complete (−) strand copy of the viral genome. The product is a double-stranded RNA intermediate, which is believed to serve as a template for the synthesis of (+) strand viral RNA. Synthesis of (+) strand viral RNA also requires uridylylated VPg (Morasco et al. 2003; Murray and Barton 2003).

Poliovirus RNA synthesis takes place on the cytoplasmic surfaces of membranous structures that are induced by viral infection (Bienz et al. 1987; Cho et al. 1994; Egger et al. 2000). Early in infection these include vesicles and tubular structures, while later in infection double-membrane vesicles predominate. It is thought that the replication complex is recruited to these vesicles by the interaction of 3AB, which is inserted into the membrane via a hydrophobic domain, with $3D^{pol}$ and $3CD^{pro}$. Membrane remodeling is induced by several virus proteins, including 2BC, 2C, and 3A, and involves the COPI and COPII secretory pathways, lipid kinases, and autophagy (Jackson 2014).

Once the pool of capsid proteins is sufficiently large, encapsidation of the viral RNA begins. Coat protein precursor P1 is cleaved to produce an immature protomer, which then assembles into pentamers. Newly synthesized, positive-stranded RNA associates with pentamers, which then form the provirion, a particle that contains the viral genome, VP1, VP3, and VP0. Cleavage of VP0 to VP4 + VP2 stabilizes the capsid and creates the infectious virion (Basavappa et al. 1994). VP0 is probably cleaved by an autocatalytic mechanism mediated by the viral RNA (Arnold et al. 1987).

The time required for a single replication cycle ranges from 5 to 10 h, depending on many variables, including the cell type, temperature, pH, host cell, and multiplicity of infection. The primary mechanism of poliovirus release from cells is by lysis, but non-lytic mechanisms have also been observed (Jackson et al. 2005; Bird and Kirkegaard 2015). Multiple viral particles appear to be packaged within phosphatidylserine lipid-enriched vesicles, and these are released without lysis from cells (Chen et al. 2015).

Pathogenesis of Poliomyelitis

General Features

Near the beginning of the twentieth century epidemics of poliomyelitis, a previously rare disease, began to occur in the United States and Europe. The etiologic agent of this disease, poliomyelitis virus (derived from *polios* and *myelos*, Greek for grey and matter) was isolated in 1908 (Landsteiner and Popper 1908). At its peak in industrialized countries, poliomyelitis leads to paralysis of thousands of children each year. Research on the virus over the next 40 years leads to the development of two effective vaccines in the 1950s and 1960s. Recognition of poliomyelitis as a problem in developing countries did not take place until the 1970s. The Global Polio Eradication program began in 1988, when over 1000 children developed poliomyelitis each day. Eradication of polio now seems within grasp, although lingering pockets of disease confound this goal (Wassilak et al. 2014).

Infection with poliovirus begins when the virus is ingested and multiplies in the oropharyngeal and intestinal mucosa (Fig. 3) (Bodian and Horstmann 1965; Sabin 1956). Virus shed in the feces of infected individuals is largely responsible for transmission of infection. From the primary sites of multiplication in the

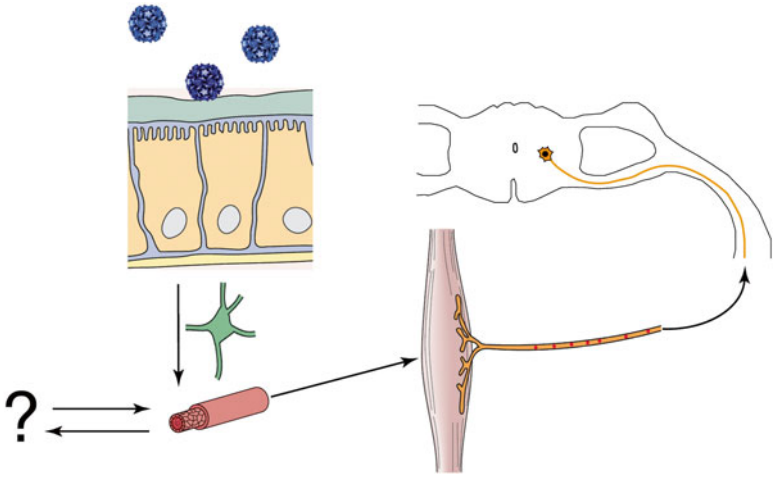

Fig. 3 Pathways of poliovirus spread in humans. Virus enters at the oropharyngeal and intestinal mucosa, replicates, and spreads to the blood through the lymph nodes, leading to viremia. Entry of virus into the central nervous system may occur either directly from the blood, or by retrograde axonal transport when virus is brought to the muscle via the blood stream. Invasion of the brain or spinal cord is preceded by viral multiplication in extraneural tissues (labeled, possibly skeletal muscle and brown fat), which produces a sustained viremia. Virus replication in the alimentary tract mucosa leads to virus shedding in feces and transmission of infection to other human hosts

mucosa, virus drains into cervical and mesenteric lymph nodes and then to the blood, causing a transient viremia (Bodian and Horstmann 1965). Most natural infections end at this stage with no symptoms or a minor disease consisting of nonspecific symptoms such as sore throat, fever, and malaise, followed by complete recovery. Replication at extraneural sites is believed to maintain viremia beyond the first stage and increase the likelihood of virus entry into the central nervous system. These extraneural sites might include brown fat, reticuloendothelial tissues, and muscle (Bodian 1955; Wenner and Kamitsuka 1957; Ren and Racaniello 1992a). In 1–2 % of infected individuals, the virus enters the central nervous system and replicates in motor neurons within the spinal cord, brain stem, or motor cortex. Viral replication in motor neurons within the spinal cord leads to the characteristic muscle paralysis. In spinal poliomyelitis, paralysis is limited to muscles supplied by motor neurons in the spinal cord. The legs are affected more frequently than the arms. In bulbar poliomyelitis, the cranial nerve nuclei or medullary centers are affected; this form is often fatal due to respiratory or cardiac failure.

Because only 1–2 % of poliovirus infections lead to poliomyelitis, the neurological phase of infection can be viewed as an accidental diversion of the enteric stage. Transmission of poliovirus within the population, and maintenance of the virus, depends only on viral multiplication in the alimentary tract. It is not known why poliovirus only rarely invades the central nervous system. One hypothesis comes from the observation of a genetic bottleneck in poliovirus spread from peripheral

sites to the brain in mice (Pfeiffer and Kirkegaard 2006). When a mixture of genetically marked viruses is inoculated peripherally into mice, only a subset can be detected in the brain. Two mechanisms were proposed to explain the bottleneck. The pathway the virus must travel from the periphery to the brain might be difficult, and each virus has a low probability of reaching the brain. Alternatively, those viruses that initially reach the brain might induce an innate antiviral state that prevents entry and spread of other viruses. Such a bottleneck could explain the stochastic nature of poliomyelitis during outbreaks of the disease.

Host Range

Humans are the only known natural hosts of poliovirus; chimpanzees and old world monkeys such as rhesus, cynomolgous, and African green monkeys can be experimentally infected. The resistance of mice and other species to infection by poliovirus is likely due to the absence of a suitable cell receptor. Cultured mouse cells are not susceptible to poliovirus infection, but they are permissive, e.g., they produce infectious virus after transfection with viral RNA (Holland et al. 1959a, b). The synthesis of CD155 in mouse L cells or in transgenic mice confers susceptibility to infection (Mendelsohn et al. 1989; Ren et al. 1990; Koike et al. 1991b). Orthologs of the *CD155* gene are present in the genomes of a number of mammals, including those that are not susceptible to poliovirus infection (Ida-Hosonuma et al. 2003). The amino acid sequence of domain 1 of CD155, which contains the binding site for poliovirus, varies extensively among the nonsusceptible mammals, especially in the regions known to contact poliovirus. The absence of a poliovirus binding site on these CD155 molecules explains why poliovirus infection is restricted to simians.

Some strains of poliovirus can infect mice that do not produce human CD155. The poliovirus strains P2/Lansing, P1/Lsb, and a variant of P3/Leon, were selected for replication in mice by a serial passage of viruses in non-primate hosts (Armstrong 1939; Li and Schaeffer 1953). Other poliovirus strains are naturally virulent in mice (Moss and Racaniello 1991). When mice are inoculated intracerebrally with P2/Lansing, they develop a disease with clinical, histopathological, and age-dependent features that resembles human poliomyelitis (Jubelt et al. 1980a, b). The murine cell receptor that allows entry of these strains into mouse cells has not been identified. Substitution of a six amino acid sequence of the P1/Mahoney strain with the corresponding sequence from P2/Lansing confers mouse neurovirulence to the recombinant virus (Murray et al. 1988). This six amino acid sequence is part of capsid protein VP1, on the surface of the virion at the fivefold axis of symmetry (Lentz et al. 1997), near the binding site for CD155 (Belnap et al. 2000; He et al. 2000; Xing et al. 2000). These observations suggest that these six amino acids in the P2/Lansing capsid regulate the interaction with a mouse cell receptor, possibly by direct contact.

Entry into the Host

Whether epithelial or lymphoid cells are the primary sites of poliovirus replication in the oropharyngeal and intestinal mucosa has been a matter of debate for many years. Virus has been detected in tonsillopharyngeal tissue and Peyer's patches of chimpanzees that had been orally infected with poliovirus (Bodian and Horstmann 1965). Poliovirus has been isolated from human tonsillopharyngeal tissue, the wall of the ileum, and mesenteric lymph nodes (Sabin and Ward 1941). However, removal of tonsils or adenoids does not reduce the level of poliovirus multiplication in the throats of humans (Sabin 1956). Consequently, it is not known if poliovirus replicates in lymphoid tissues or is absorbed into lymph nodes after replication in epithelial cells.

Examination of CD155 expression in cells of the alimentary tract has provided information on which cell types might be susceptible to infection. Human epithelial cells produce high levels of CD155 RNA, suggesting that these cells might be primary sites of poliovirus replication (Ren and Racaniello 1992a). In humans, CD155 protein is present on the intestinal epithelium, M cells of Peyer's patches, and in germinal centers within the Peyer's patches (Iwasaki et al. 2002). In rhesus macaques, which are not susceptible to oral poliovirus infection, CD155 levels are reduced in follicle-associated epithelium and the protein is not present in germinal centers. These results have been interpreted to suggest that poliovirus replication in the gut depends on the presence of CD155 in follicle-associated epithelium, including M cells, and on cells of the Peyer's patches (Iwasaki et al. 2002).

CD155 transgenic mice are not susceptible to oral infection with poliovirus (Ren et al. 1990; Koike et al. 1991b). CD155 protein is present at very low levels in the intestinal epithelium of these mice, and absent in the Peyer's patches (Zhang and Racaniello 1997; Iwasaki et al. 2002). Overproduction of CD155 in the intestinal epithelium of transgenic mice by the use of a fatty acid-binding protein promoter did not lead to oral susceptibility to poliovirus (Zhang and Racaniello 1997). However, disruption of the type-I interferon gene in CD155 transgenic mice leads oral susceptibility to infection (Ohka et al. 2007). After oral infection, virus replication takes place in many tissues, including esophagus, nasopharynx-associated lymphoid tissue, small intestine, and spinal cord.

The susceptibility to oral poliovirus infection of CD155 transgenic IFNAR$^{-/-}$ mice has lead to an examination of the role of the intestinal microbiota in replication (Robinson et al. 2014; Kuss et al. 2011). Treatment of mice with antibiotics to reduce the intestinal microbiota leads to reduced susceptibility to poliovirus infection by the oral route, and lower viral replication in the intestine. Viral infectivity is enhanced by incubation with gut bacteria or surface polysaccharides such as lipopolysaccharide and peptidoglycan. These results demonstrate that poliovirus has evolved to benefit from the gut microbiota which enhances viral replication and transmission.

Although poliovirus is believed to be transmitted by fecal–oral contamination, in countries with high standards of hygiene, virus may be transmitted by the respiratory route. The source of virus for this mode of transmission is the tonsils and pharynx.

Replication at these sites usually occurs after virus replication in the intestine and spread by viremia. It is not known if virus spread by the respiratory route replicates in the nasopharynx, or is ingested and replicates in the intestine.

Spread in the Host

After replication at primary sites in the mucosal epithelium, poliovirus drains into deep cervical and mesenteric lymph nodes and then to the blood, causing a transient viremia (Bodian and Horstmann 1965). Viral replication in extraneural tissues is thought to maintain viremia beyond the primary stage, and is required for viral invasion of the central nervous system (Bodian and Horstmann 1965). However, the sites at which viral replication occurs in humans is not known. In experimentally infected chimpanzees, high concentrations of virus are detected in brown fat (Nathanson and Bodian 1961), and in lymph nodes, axillary fat, adrenal glands, and muscle of monkeys (Wenner and Kamitsuka 1957). There is also evidence that virus may replicate in cells of the reticuloendothelial system and in the vascular endothelium of monkeys (Blinzinger et al. 1969; Kanamitsu et al. 1967). Poliovirus replication has been observed in skeletal muscle, brown adipose tissues, and nasal mucosa (Ren and Racaniello 1992a).

There is evidence that poliovirus may enter the central nervous system in two ways: from the blood, or by entering a peripheral nerve and being carried to the central nervous system by axonal transport (Fig. 3). It has been established that viremia preceding paralytic infection is necessary for virus entry into the central nervous system. In addition, the presence of antiviral antibodies in the blood prevent invasion of the brain and spinal cord (Bodian and Horstmann 1965). The results of experiments in CD155 transgenic mice have provided additional support for the hypothesis that virus enters the brain and spinal cord from the blood. In one study of the fate of poliovirus inoculated into the tail vein of mice, it was observed that poliovirus is delivered to the brain at higher levels than would be expected based on the vascular volume of the organ (Yang et al. 1997). Furthermore, the distribution of poliovirus in the brain of transgenic and non-transgenic mice is similar, indicating that CD155 does not play a role in delivering circulating poliovirus to the central nervous system. The authors conclude that in mice, polioviruses permeate the blood–brain barrier at a high rate, independent of CD155 or virus strain. The molecular mechanism of poliovirus entry by this route is unknown.

Poliovirus infections in humans and monkeys have provided evidence for neural pathways of poliovirus dissemination. When poliovirus is inoculated into the sciatic nerve of monkeys, virus spreads along nerve fibers in both peripheral nerves and the spinal cord (Hurst 1936). After intramuscular inoculation of monkeys with poliovirus, the inoculated limb is usually the first to become paralyzed, and freezing the sciatic nerve blocks virus spread to the spinal cord (Nathanson and Bodian 1961). Children who received incompletely inactivated poliovaccine in 1954 (the Cutter incident) developed a high frequency of initial paralysis in the inoculated limb

(Nathanson and Langmuir 1963). Evidence for neuronal spread of poliovirus has also been obtained from experiments in CD155 transgenic mice. After intramuscular inoculation, the first limb paralyzed is the limb that is inoculated; poliovirus is first detected in the lower spinal cord, and sciatic nerve transection blocks infection of the spinal cord (Ren and Racaniello 1992b; Ohka et al. 1998). The rate of poliovirus transport along the sciatic nerve was determined to be >12 cm per day, independent of virus replication (Ohka et al. 1998). This rate is consistent with fast retrograde axonal transport of the virus.

Skeletal muscle injury is known to be a predisposing factor for poliomyelitis, a phenomenon known as "provocation poliomyelitis." For example, in Oman, intramuscular injections have been linked to cases of vaccine-associated poliomyelitis (Sutter et al. 1992). Provocation poliomyelitis has been reproduced in CD155 transgenic mice (Gromeier and Wimmer 1998). In mice, skeletal muscle injury stimulates retrograde axonal transport of poliovirus to the spinal cord (Kuss et al. 2008).

The observation that the cytoplasmic domain of CD155 interacts with Tctex-1, the light chain of the retrograde motor complex dynein (Mueller et al. 2002; Ohka et al. 2004) suggests a hypothesis for the mechanism of axonal transport of poliovirus (Fig. 4). At the interface of muscle and motor neuron, the neuromuscular junction, poliovirus binds CD155 and enters the neuron by endocytosis. The endocytic vesicles containing poliovirus are linked to Tctex-1 by the cytoplasmic domain of CD155, which remains on the exterior of the endocytic vesicle. Virus-containing vesicles are transported to the motor neuron cell body, where the viral RNA is

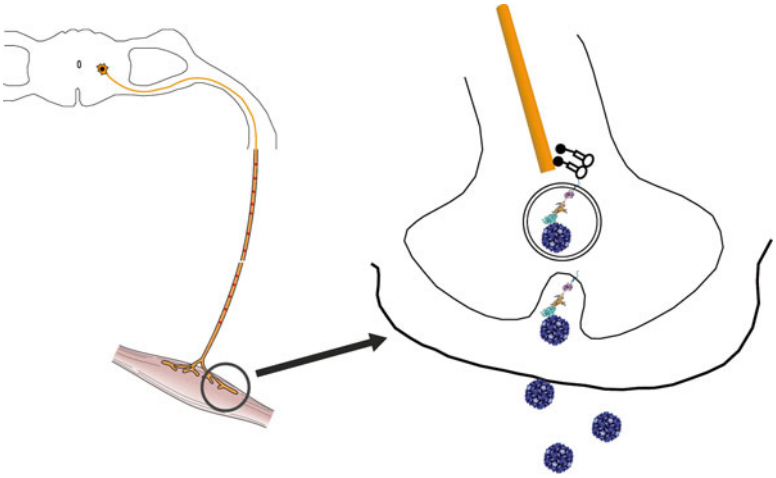

Fig. 4 Hypothetical mechanism of poliovirus axonal transport. Virus particles are transported to the muscle via the blood. At the neuromuscular junction, virus binds to its receptor, CD155, at the presynaptic membrane and is taken into the cell by endocytosis. The cytoplasmic domain of CD155 interacts with Tctex-1, a component of the dynein motor, allowing transport of the endocytic vesicle containing poliovirus to the cell body of the neuron. Viral RNA is released in the cytoplasm of the neuron cell body, initiating the viral replication cycle

released into the cytoplasm and virus replication begins. In support of this hypothesis, CD155 has been detected at the neuromuscular junction of human muscle (Leon-Monzon et al. 1995), and it has been shown that poliovirus-containing vesicles are brought to the spinal cord by axonal transport dependent upon Tctex-1 (Ohka et al. 2004). Poliovirus appears to be transported in axonal endosomes as an infectious, 160S particle. This hypothetical scheme contrasts with virus entry in HeLa cells, where interaction of poliovirus with CD155 leads to conversion of the virus to A particles, which are believed to be intermediates in uncoating (Fricks and Hogle 1990). Viral uncoating in axons may be inhibited to avoid degradation of viral RNA before it reaches the neuron cell body. The proposed uptake of poliovirus at the neuromuscular junction would also differ from the process in HeLa cells, where infection does not require dynamin and is unlikely to involve the clathrin-mediated endocytic pathway (DeTulleo and Kirchhausen 1998).

Tropism

Poliovirus replicates only in specific cells and tissues in primates, even though the virus reaches many organs during the viremic phase (Bodian 1955; Sabin 1956). The proposition that poliovirus tropism is determined by the cellular receptor was supported by the finding that virus-binding activity in tissue homogenates correlated with susceptibility to poliovirus infection (Holland 1961). The identification of the poliovirus receptor allowed more extensive study of the role of this molecule in tropism. In humans, CD155 RNA and protein are expressed in many tissues, but not all are sites of poliovirus infection (Mendelsohn et al. 1989; Freistadt et al. 1990; Koike et al. 1990). CD155 RNA and protein expression are also observed in many tissues of CD155 transgenic mice, including those where poliovirus does not replicate (Ren and Racaniello 1992a; Koike et al. 1994). These findings indicate that CD155 is required for susceptibility to poliovirus infection, but tropism is determined at a later stage of infection.

It has also been suggested that poliovirus tropism is controlled by cell type-specific differences in IRES-mediated translation (Ohka and Nomoto 2001; Gromeier et al. 1996; Yanagiya et al. 2003; Borman et al. 1997). Organ-specific synthesis, localization, or modification of cell proteins needed for IRES-mediated translation could control viral replication. When recombinant adenoviruses were used to express bicistronic mRNAs in murine organs, the IRES of poliovirus was found to mediate translation in many organs, including those that are not sites of poliovirus replication (Kauder and Racaniello 2004). These results indicate that poliovirus tropism is not determined by internal ribosome entry, but at a later stage in replication.

The interferon (IFN) response appears to be an important determinant of poliovirus tissue tropism. IFN is part of the innate immune system, which can respond to the presence of virus within hours and has a major influence on the outcome of infection. The tropism of diverse viruses is regulated by alpha/beta IFN (IFNα/β) (Garcia-Sastre et al. 1998; Ryman et al. 2000). Poliovirus infection of CD155

transgenic mice lacking the receptor for IFNα/β leads to viral replication in liver, spleen, and pancreas, in addition to the central nervous system (Ida-Hosonuma et al. 2005). CD155 is produced in all of these tissues, but poliovirus only replicates in the brain and spinal cord of CD155 transgenic mice that synthesize the IFNα/β receptor. In CD155 transgenic mice, poliovirus infection leads to a rapid and robust expression of IFN-stimulated genes (ISGs) (oligoadenylate synthetase, PKR, IFNβ, RIG-I, MDA-5, and IRF-7) in extraneural tissues that are not normally sites of poliovirus replication. In the brain and spinal cord, ISG expression was only moderately increased after infection. These results indicate that IFNα/β functions as an important determinant of poliovirus tissue tropism in CD155 transgenic mice by protecting extraneural organs from infection.

The ability of IFNα/β to determine poliovirus tissue tropism suggests that this cytokine might play a role in determining whether or not the virus invades the central nervous system. As discussed earlier, poliovirus replication at the entry portal leads to viremia, which allows virus to reach an unidentified extraneural site. Replication at this site appears to be required for virus entry into the central nervous system. In 99 % of infections, the IFNα/β response may limit poliovirus replication in extraneural tissues, thereby preventing invasion of the central nervous system. In the 1–2 % of individuals in which paralytic disease occurs, the IFN response may be defective, allowing unchecked virus replication in non-neural sites followed by invasion into the central nervous system.

Histopathology of Poliomyelitis

In experimentally infected primates, lesions in the central nervous system consist of neuronal changes and inflammation. Viral replication leads to destruction of neurons and the inflammatory process follows as a secondary response (Bodian and Horstmann 1965). There is little evidence for viral replication in other cell types in the central nervous system. The relative contributions of polovirus-induced cell lysis and immunopathology to neuronal damage have not been determined. It is widely assumed that because poliovirus leads to lysis of most cells in culture, then it must also have the same effect on neurons in vivo. However, it would be informative to determine the outcome of infection of CD155 transgenic mice lacking specific components of the immune system, such as B-cells and/or T-cells.

Two factors determine the characteristic pattern of poliomyelitis lesions: the susceptibility of nervous centers to infection, and restricted movement of the virus along nerve fiber pathways (Bodian and Horstmann 1965). The motor neurons in the anterior horns of the cervical and lumbar regions are most sensitive to infection, followed by neurons in motor nuclei of cranial nerves in the brainstem. Lesions in the spinal cord are largely restricted to the anterior horns, but may also be observed in the intermediate, intermediolateral, and posterior gray areas (Bodian and Horstmann 1965; Bodian 1959) and may extend to the sensory spinal ganglia. Lesions in the brain are mainly in the brain stem, from the spinal cord to

the anterior hypothalamus, while those in the forebrain are generally mild and limited to the motor cortex, the thalamus, and the globus pallidus. More severe lesions may be found in the cerebellar vermis and the deep cerebellar nuclei (Bodian and Horstmann 1965).

In CD155 transgenic mice, the sites of poliovirus replication in the central nervous system are parallel to those observed in primates (Koike et al. 1991b; Ren et al. 1990; Ren and Racaniello 1992a). Motor neurons of the ventral horns of the cervical and lumbar regions are most sensitive to infection. A difference is that poliovirus replicates in the hippocampus of CD155 transgenic mice and causes damage to that area. Viral replication has been observed in neurons in the ventral and dorsal horns of the spinal cord of CD155 transgenic mice (Ren and Racaniello 1992a). However, neuronal degradation and inflammation is localized to the ventral horns. Histopathology is observed in the posterior horn (analogous to the dorsal horn of mice) in the spinal cord of humans and monkeys, but less frequently than in the anterior horn (Bodian 1959).

Post-poliomyelitis Syndrome

Survivors of poliomyelitis may develop muscle weakness, atrophy, and fatigue many years after poliovirus infection. These late consequences of infection, also observed in non-paralytic infections, were collectively called post-polio syndrome (PPS) and accepted in the 1980s as a new medical condition (Halstead 2011). Post-polio syndrome may develop in 20–75 % of infected patients 15 to over 60 years after the original infection, even in non-paralytic cases (Nee et al. 1995). With an estimated 15–20 million polio survivors throughout the world, the disease is the most common to affect anterior horn neurons. No specific and effective therapy for the syndrome is available.

The cause of post-polio syndrome is unknown. It has been suggested that a small number of PPS patients harbor fragments of the poliovirus genome, but infectious virus has not been recovered and the sequences of these genomes are not known (Baj et al. 2015). Another hypothesis for the etiology of PPS is that the loss of neurons during previous viral infections renders the patients susceptible to muscle weakness as age-related loss of neurons takes place. Alternatively, the large motor neuron units that form after recovery from poliomyelitis might degenerate, consistent with disintegration of these units in patients (Baj et al. 2015). The lack of an animal model of PPS has hindered an understanding of the mechanism of this syndrome.

Vaccines

Two highly effective vaccines to prevent poliomyelitis were developed during the 1950s. Inactivated poliovaccine (IPV), developed by Jonas Salk, consists of wild-type poliovirus strains that are treated with formalin to destroy infectivity without

altering the antigenic properties of the capsid. This vaccine was licensed in 1955 in the US and reduced the number of cases of paralytic disease from about 20,000 per year to ~2000. Despite this success, it was debated whether the use of a non-replicating vaccine such as IPV could eradicate the disease. Consequently, the infectious, attenuated oral poliovaccine, OPV, developed by Albert Sabin was licensed in the 1960s (Sabin et al. 1954). OPV has been shown to interrupt epidemics and break transmission of the virus, leading to elimination of the virus from entire continents by the 1980s. Therefore, these vaccine strains were selected by the World Health Organization for the campaign to eradicate global poliomyelitis by 2000 (Organization WH 1993). When the eradication initiative began, wild-type poliovirus was endemic in over 125 countries, and over 350,000 cases of polio were reported annually. In mid 2015, polio was endemic in only three countries: Nigeria, Pakistan, and Afghanistan, and no cases of polio have been reported in Nigeria so far in 2015. Political instabilities, armed conflicts, and other complex social challenges impede immunization initiatives in these countries. As discussed below, circulating vaccine-derived polioviruses have further confounded the eradication effort.

The Sabin vaccine strains were empirically selected to be able to infect the alimentary tract and produce immunity to infection without inducing poliomyelitis. Genetic analysis has shown that a point mutation within the IRES of each of the three poliovirus vaccine strains is a determinant of the attenuation phenotype (Kawamura et al. 1989; Evans et al. 1985; Ren et al. 1991). For example, a mutation from C to U at nucleotide 472 in the IRES of poliovirus type-3 attenuates neurovirulence in primate and murine models (Evans et al. 1985; Westrop et al. 1989; La Monica et al. 1987). This mutation has been shown to cause a translation defect in vitro and in cultured cells of neuronal origin (Gutierrez-Escolano et al. 1997; Svitkin et al. 1990; Haller et al. 1996). A hypothesis for how the C472U mutation leads to reduced neurovirulence is that it causes a translation defect that is specific to the brain and spinal cord, leading to lower viral replication in these organs (Ohka and Nomoto 2001; Gutierrez-Escolano et al. 1997; La Monica and Racaniello 1989). This hypothesis was tested by examining IRES-mediated translation in mouse organs and cells. The results show that the C472U mutation leads to translation defects in neuronal and non-neuronal cells and tissues (Kauder and Racaniello 2004) and therefore cannot attenuate neurovirulence by specifically reducing translation in neuronal cells. Furthermore, polioviruses with the C472U mutation are attenuated in adult CD155 transgenic mice but cause paralytic disease in newborn mice (Kauder and Racaniello 2004). These observations lead to the conclusion that the C472U mutation does not eliminate viral replication in the brain. Alternatively, the C472U mutation could reduce viral replication in the alimentary tract enough to prevent spread to the central nervous system without impairing immunogenicity of the vaccine. Because they replicate more poorly than wild-type virus, the vaccine strains may be more effectively limited by the IFNα/β response.

Immunization with the Sabin vaccine strains is associated with a low rate of vaccine-associated poliomyelitis, either in vaccine recipients or their immediate contacts. The rate of vaccine-associated paralysis in primary vaccines is approximately 1 per 750,000 recipients (Nkowane et al. 1987). Vaccine-associated poliomyelitis occurs

due to reversion of the mutations in the viral genome that confers the attenuation phenotype. For example, a reversion from U to C at nucleotide 472 is observed in virus isolated from cases of vaccine-associated poliomyelitis caused by Sabin type-3 (Evans et al. 1985). Because the Sabin strains undergo reversion in the gastrointestinal tract of nearly all recipients (Martinez et al. 2004), it is surprising that the frequency of vaccine-associated paralysis is so low. Perhaps replication of the Sabin strains is sufficiently delayed to allow containment by the immune response. The individuals who contract vaccine-associated poliomyelitis might have a defective IFNα/β response that allows revertant viruses to replicate to high levels in extraneural tissues, invade the central nervous system, and cause paralytic disease. Determination of patient genome sequences should be done to determine whether mutations in innate immune genes are associated with vaccine-associated poliomyelitis.

Circulating vaccine-derived polioviruses (cVDPV) pose a challenge to the eradication effort because they are capable of spreading from person to person and causing poliomyelitis. The first outbreak caused by cVDPV was in Hispaniola in 2001, where 22 cases of poliomyelitis were identified (Kew et al. 2002). The responsible strain was a type-1 cVDPV strain that had been circulating undetected for 2 years. Subsequent outbreaks of poliomyelitis caused by cVDPVs occurred in the Phillipines (2001), Madagascar (2002 abd 2005), China (2004), and Indonesia (2005) (Kew et al. 2004; Katz 2006). It has also been reported that all cases of poliomyelitis occurring in Egypt between 1988 and 1993 were caused by vaccine-derived strains (Yang et al. 2003). These outbreaks call into question the WHO plan to stop immunization after polio eradication is achieved. In the post-immunization world, cVDPV strains will continue to circulate, posing a threat to the increasingly non-immune population.

One reason why polio was believed to be an eradicable disease was the belief that there are no chronic human carriers or non-human reservoirs of the virus. This notion was dispelled by the discovery of prolonged excretion of VDPV strains from individuals with defects in humoral immunity (Abo et al. 1979). To date, 21 such cases have been identified globally with shedding of VDPV for months to years. In one remarkable case, the patient shed virus for over 20 years but remained healthy, although the excreted virus was shown to be neurovirulent in animals (Minor 2001). In contrast, individuals with normal immune systems shed vaccine viruses for approximately 4 weeks. The incidence of long-term poliovirus shedding among patients with immunodeficiencies is unknown, but their existence is another obstacle to the eradication program. As long as these individuals shed VDPVs, it will be difficult to stop immunization against poliomyelitis.

Since 1988, when the World Health Organization announced the polio eradication plan, it had relied exclusively on the use of OPV. The polio eradication and endgame strategic plan announced in 2014 includes at least one dose of IPV (Organization 2014). The rationale for including a dose of IPV was to avoid outbreaks of vaccine-derived type-2 poliovirus. This serotype had been eradicated in 1999 and had consequently been removed from OPV. However, IPV, which is injected intramuscularly and induces highly protective humoral immunity, is less effective in producing intestinal immunity than OPV. This property was underscored by the finding that wild poliovirus circulated in Israel during 2013, a country which

had high coverage with IPV. Furthermore, in countries that use only IPV, over 90 % of immunized children shed poliovirus after oral challenge. This shortcoming of IPV is problematic, in view of the recommendation of the World Health Organization to gradually shift from OPV to IPV. Even if the shift to IPV occurs after eradication of wild-type polioviruses, vaccine-derived polioviruses will continue to circulate because they cannot be eradicated by IPV. These concerns are mitigated by new results from a study in India which indicate that IPV can boost intestinal immunity in individuals who have already received OPV. This study shows that a dose of IPV is more effective than OPV at boosting intestinal immunity in children who have previously been immunized with OPV. Both IPV and OPV should be used together in the polio eradication program.

As of this writing, all cases of polio caused by wild-type virus are serotype-1; type-2 has been declared eradicated and type-3 will soon be as well.

Antiviral Drugs

Antiviral compounds have not played a role in control of poliovirus infections; none have been licensed for use in humans. However, one class of antiviral drugs has been useful in elucidating mechanisms of virus entry into cells. These are the WIN compounds, originally produced by Sterling-Winthrop (Smith et al. 1986), and similar molecules produced by Schering-Plough (Kenilworth, NJ) and Janssen Pharmaceuticals (Titusville, NJ) (Andries et al. 1990; Cox et al. 1996). The compounds bind tightly in a hydrophobic tunnel that is located within the core of VP1, just beneath the canyon floor of many picornaviruses. In poliovirus type-1 and -3, the pocket appears to contain sphingosine (Filman et al. 1989). These hydrophobic, sausage-shaped compounds displace the lipid by binding tightly in the hydrophobic tunnel. When a WIN compound is bound to the poliovirus capsid, the virus can bind to cells, but the interaction with CD155 does not lead to the production of A particles (Fox et al. 1986; Zeichhardt et al. 1987). WIN compounds block poliovirus infectivity by preventing CD155-mediated conformational alterations needed for uncoating. Poliovirus mutants have been isolated that are not infectious unless WIN compounds are present (Mosser and Rueckert 1993). Such WIN-dependent mutants spontaneously convert into altered particles at 37 °C, probably because there is no lipid in the hydrophobic pocket to stabilize the particles. It is believed that docking of CD155 onto the poliovirus capsid just above the hydrophobic pocket initiates structural changes in the virion that lead to the release of the lipid.

Some of these drugs have been evaluated in clinical trials, such as Pleconaril for treatment of common colds caused by rhinoviruses (Pevear et al. 2005). One problem that has prevented licensing of these compounds is the problem of resistance: picornaviruses that are not inhibited by the drugs are readily isolated. This problem could in theory be partially addressed by using three antiviral drugs in combination, the approach that has been successful in controlling infections with human immunodeficiency virus (Chen et al. 2007). Because picornavirus infections are

generally short-lived, and the virus must be identified by laboratory diagnosis, by the time an appropriate antiviral could be prescribed, it would have little effect on the outcome. Recently a committee appointed by the National Research Council of the US recommended that anti-poliovirus drugs should be developed in the event of a post-eradication outbreak. Assuming multiple drugs could be administered to overcome the problem of resistance, the use of antiviral therapy might be effective to prevent spread of the virus during an outbreak.

A novel approach to antiviral therapy is based on the observation that mutations in the region of the poliovirus genome encoding the capsid proteins, VPg, $2A^{pro}$, and the RNA polymerase result in dominant negative phenotypes (Crowder and Kirkegaard 2005; Tanner et al. 2014). If antiviral drugs could be identified that produce dominant negative proteins, then the replication of drug-resistant genomes should be inhibited by the drug-sensitive genomes. For example, when cells were coinfected with wild-type and WIN-resistant polioviruses, the yield of WIN-resistant virus was reduced to 3–7 % the yield of a single infection. The results suggest that inhibition of virus yields occurs because chimeric capsids consisting of subunits from wild-type and WIN-resistant genomes are sensitive to the drug. Hence, in the presence of WIN compound, the wild-type capsid subunits display a dominant negative phenotype.

The polio eradication effort has lead to a renewed effort to discover anti-poliovirus compounds that could be useful for limiting outbreaks in a post-vaccine era. Examples include the capsid inhibitor pocapavir (McKinlay et al. 2014), and itraconazole, an anti-fungal agent that blocks poliovirus replication (Strating et al. 2015).

Perspectives

If the eradication of poliomyelitis succeeds, shortly afterwards it will be necessary to halt work with virulent strains of poliovirus, a step that will severely curtail research on the pathogenesis of poliomyelitis. There are many unanswered questions about poliomyelitis, and all the necessary experimental tools are available, but it is not clear whether there will be sufficient time to carry out this work. Fundamental problems include the identity of cells that are infected by poliovirus in the alimentary tract, and precisely how the gut microbiota assists in poliovirus replication. The mechanism of poliovirus axonal transport remains to be elucidated: how is the virus maintained as a 160S particle in the endosome, and subsequently uncoated in the neuron cell body? Although it is clear that the IFNα/β response determines poliovirus tropism, it is not known why ISG expression is limited in the central nervous system. Why is viral replication in mice regulated by IFNα/β when the virus inhibits many important cellular processes, including translation, transcription, and protein secretion? How are neurons destroyed during infection, by the virus, or the immune response, or both?

Poliovirus has been studied for over 100 years, first as the etiologic agent of a significant human disease, then as a model for RNA virus infections of the central nervous system. Once research on poliovirus ceases, attention will likely turn to understanding how other picornaviruses infect the central nervous system. Because of a lack of research focus, nearly nothing is known about the pathogenesis of neurological disease caused by cardioviruses and enteroviruses—there is no understanding of initial replication sites, mechanisms of transport to the central nervous system, or the role of specific viral proteins in neurotropism. Mouse models of infection are available for unraveling many of these fundamental problems. Which picornavirus will emerge to replace poliovirus as a model system?

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