Carol Shoshkes Reiss *Editor*

Neurotropic Viral Infections

Volume 1: Neurotropic RNA Viruses

Second Edition

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Preface

This is one of two books that comprise a total of 29 cutting-edge review articles written by leaders in the basic or clinical and translational fields working on viruses that infect the central nervous system (CNS). Book 1 focuses on those pathogens with an RNA genome. Book 2 includes chapters on retroviruses, DNA viruses, prions, immunity, transmission, and beneficial uses of neurotropic viruses.

In this first volume are 14 chapters on neurotropic or neuroinvasive RNA viruses that are human pathogens. Viruses capable of infecting the cells within the brain can be spread to people by many routes including ingestion (for instance, polio, chapter "Poliovirus"), the respiratory route (one example is measles, chapter "Measles Virus and Subacute Sclerosing Panencephalitis"), and insect (Japanese encephalitis virus is spread by mosquitoes, chapter "Japanese Encephalitis Virus: Molecular Biology to Pathology") or animal (bats can transmit rabies, chapter "Measles Virus and Subacute Sclerosing Panencephalitis") bites.

Some viruses cause CNS disease in a small subset of people infected, and this may be due to many factors including variants in host genes, underlying chronic health conditions, or mutations in the virus (West Nile virus is one example, chapter "Neurotropic Flaviviruses"). To become successful pathogens, many neurotropic viruses have become masters of evasion of host innate or adaptive immune responses.

Viral infections can be prevented by avoiding exposure or by some excellent vaccines. For instance, in 2015, aggressive and deliberate use of the vaccine enabled Nigeria to eradicate endemic poliovirus infections (chapter "Poliovirus"). A new equine vaccine has been developed against the *Hendra* virus, and therefore people who care for horses are protected (chapter "Henipaviruses").

This book is restricted to RNA viruses. RNA viruses range from small, extremely simple agents in the picornavirus family that have a capsid and are relatively resistant to environmental conditions (chapter "Poliovirus") to more complex viruses with cell-derived membranes around the nucleic acid that can be easily disrupted by drying or soap and water (chapters "Measles Virus and Subacute Sclerosing Panencephalitis" to "Borna Disease Virus"). All these viruses can cause acute infections; some are capable of persisting in chronic infections (for instance, bornavirus in chapter "Borna Disease Virus").

This second edition of *Neurotropic Viral Infections* builds upon the highly successful first edition published in 2008 by Cambridge University Press (ISBN-13: 978-0521869645). I would like to acknowledge the generosity of Cambridge University Press in permitting us to move *Neurotropic Viral Infections* to Springer Scientific Publishers for the second edition. Arthur Smilios convinced me to undertake this volume. When he left Springer, Rita Beck ably succeeded him with the project. The book would not have reached the final stage without the fantastic production assistance by Portia Formento Wong.

New York, NY, USA Carol Shoshkes Reiss
February 19, 2016

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Poliovirus

Vincent Racaniello

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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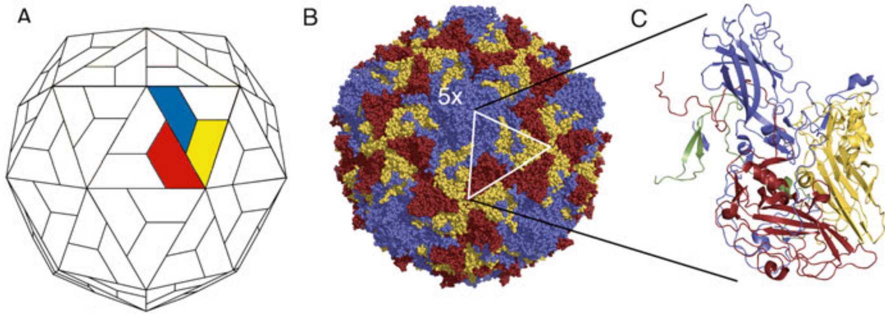

Fig. 1 Structure of poliovirus. (**a**) Schematic of the viral capsid, showing the packing arrangement of VP1 (*blue*), VP2 (*yellow*), and VP3 (*red*). VP4 is on the interior of the capsid. (**b**) Model of poliovirus type-1, Mahoney strain, based on the X-ray crystallographic structure determined at 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

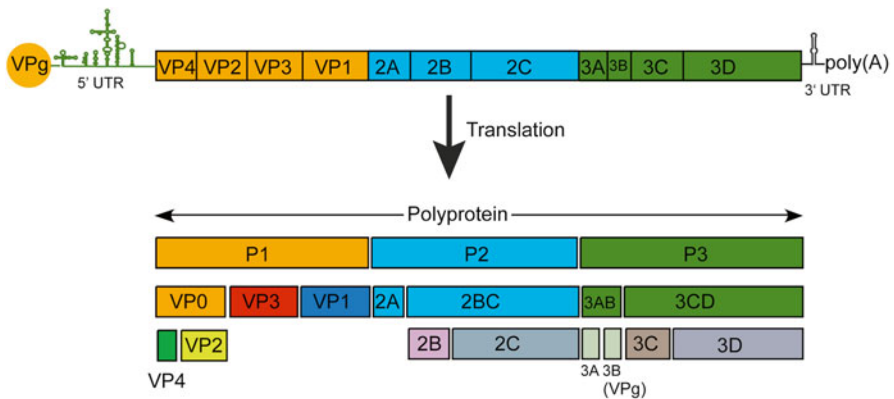

Fig. 2 Schematic of the poliovirus genome. At *top* is shown a diagram of the viral RNA with coding regions labeled. RNA structural elements include an enterovirus IRES within the 5′ untranslated region and the pseudoknot within the 3′ untranslated region. *Below* is the processing pattern of poliovirus 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