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Direct-acting antivirals and host-targeting strategies to combat enterovirus infections

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Enteroviruses (*e.g.*, poliovirus, enterovirus-A71, coxsackievirus, enterovirus-D68, rhinovirus) include many human pathogens causative of various mild and more severe diseases, especially in young children. Unfortunately, antiviral drugs to treat enterovirus infections have not been approved yet. Over the past decades, several direct-acting inhibitors have been developed, including capsid binders, which block virus entry, and inhibitors of viral enzymes required for genome replication. Capsid binders and protease inhibitors have been clinically evaluated, but failed due to limited efficacy or toxicity issues. As an alternative approach, host-targeting inhibitors with potential broad-spectrum activity have been identified. Furthermore, drug repurposing screens have recently uncovered promising new inhibitors with disparate viral and host targets. Together, these findings raise hope for the development of (broad-range) anti-enteroviral drugs.

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Introduction

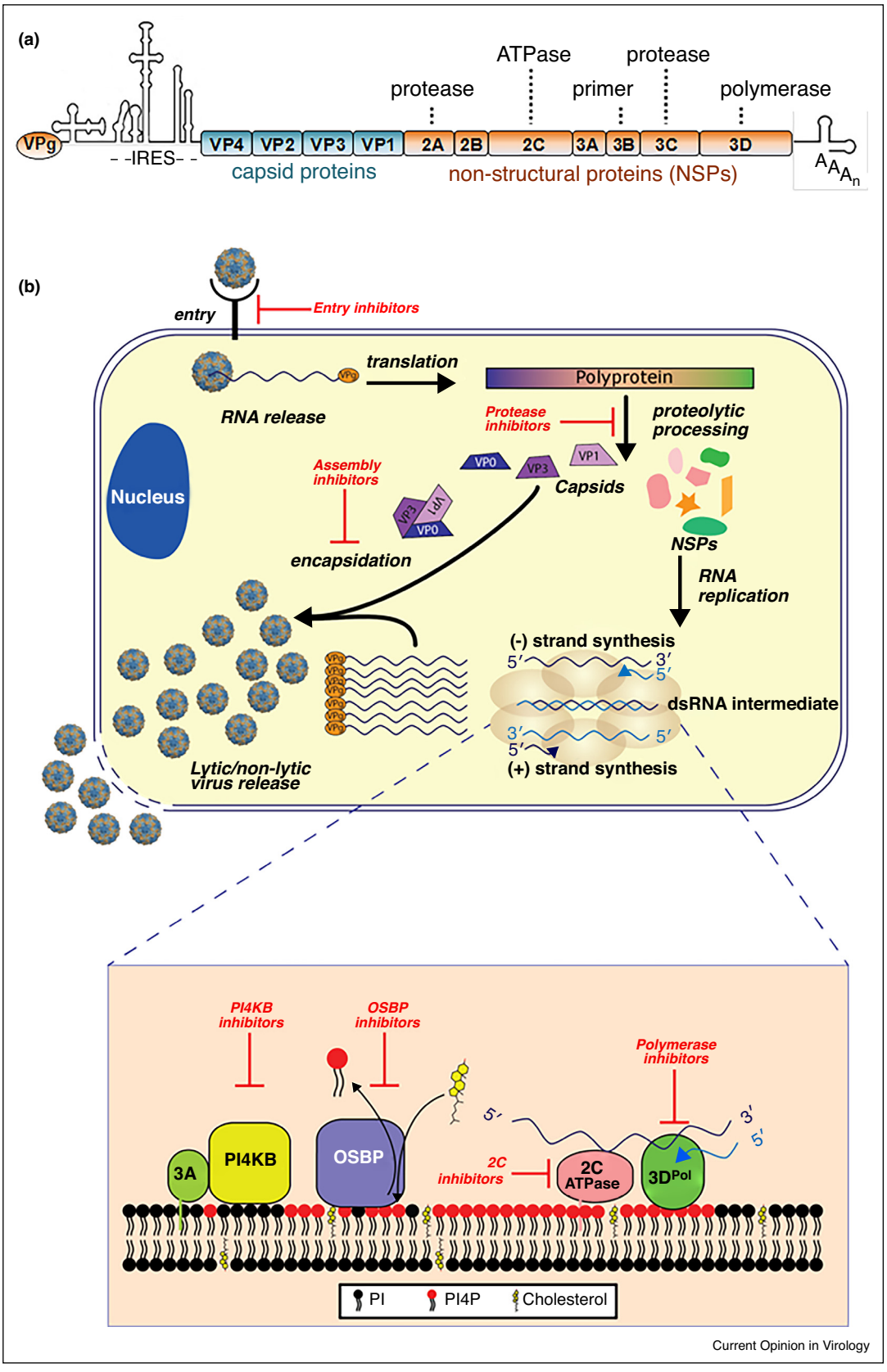
The *Picornaviridae* constitutes a large family of non-enveloped, positive-stranded RNA (+RNA) viruses, currently consisting of 31 genera. The genus *Enterovirus*, which is by far the largest genus, comprises many human pathogens, including poliovirus, coxsackie A and B viruses, echoviruses, numbered enteroviruses (*e.g.*, EV-A71 and EV-D68), and rhinoviruses. Infections with non-polio enteroviruses can result in a wide variety of symptoms, including hand-foot-and-mouth disease, conjunctivitis, aseptic meningitis, severe neonatal sepsis-like disease, and acute flaccid paralysis, whereas infections with rhinoviruses cause the common cold as well as exacerbations of asthma and chronic obstructive pulmonary disease (COPD) (reviewed in Ref. [1]). Vaccines are only available against poliovirus and EV-A71. Development of vaccines against all enteroviruses seems unfeasible, given the large number of (sero)types (*i.e.*, >100 non-polio enteroviruses and >150 rhinoviruses). Hence, there is a great need for (broad-acting) antivirals against enteroviruses. Here, we will review recent efforts to develop direct-acting antivirals as well as host factor-targeting inhibitors to treat enterovirus infections (Table 1).

Direct-acting antivirals

Entry inhibitors

Enterovirus capsids are icosahedral (pseudo $T = 3$) structures composed of 60 copies of each of the four capsid proteins (VP1 to VP4). The enterovirus replication cycle (Figure 1b) is initiated by binding of a virion to its receptor. Most enterovirus receptors are protein receptors that belong to the Ig superfamily or the integrin receptor family (reviewed in Ref. [2]). The receptors usually bind in the 'canyon', a depression in the virion surface around the five-fold axes of symmetry [2]. Receptor-binding induces virion destabilization and release of the 'pocket factor', a fatty acid located in a hydrophobic pocket beneath the canyon, to initiate virion uncoating [2].

So-called 'capsid binders' are the most extensively studied class of anti-enteroviral compounds [3,4]. These compounds replace the pocket factor in the canyon and thereby block virion uncoating. Clinical trials for the capsid binders pleconaril, vapendavir (a.k.a. BTA798), and pocapavir (a.k.a. V-073) are currently in progress or have recently been completed, the status of which has been described last year [5]. Since then, another trial with pleconaril was conducted for the treatment of neonates with enterovirus sepsis, which showed greater survival among pleconaril recipients [6]. A major drawback of capsid binders is the rapid emergence of resistance. Indeed, in a clinical trial for the treatment of rhinovirus infections with pleconaril, compound-resistant viruses were isolated [7]. In addition, naturally occurring pleconaril-resistant viruses (*e.g.*, an echovirus 11 strain) have been reported [8]. These resistance issues may complicate the application of capsid binders in the clinic.



Enterovirus genome, replication cycle, and antiviral targets. **(a)** The enterovirus genome encodes four structural proteins (VP1-VP4) and seven non-structural proteins (2A, 2B, 2C, 3A, 3B, 3C, and 3D). IRES: internal ribosome entry site. **(b)** The enterovirus life cycle begins with the attachment of the virus particle to a cellular receptor followed by the internalization of the particle into the host cell. The genome is released and directly