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Review

Poliovirus Receptor: More than a simple viral receptor

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ABSTRACT

The human poliovirus receptor (PVR) is a cell surface protein with a multitude of functions in human biology. PVR was initially identified as the receptor for the human poliovirus and recent discoveries have given a greater insight into both its morphology and its function. Alternative splicing of the PVR gene results in a total of 4 alternatively spliced isoforms. Two of these isoforms lack a complete transmembrane domain and are considered soluble and block viral infection; the remaining two transmembrane isoforms differ only at their extreme C-terminal domains resulting in differential localization in epithelia and polarity of viral infection. In addition to its role as a receptor for the human poliovirus, several native biological functions have also been uncovered. PVR is an important cell adhesion protein and is involved in the transendothelial migration of leukocytes. Through its interactions with CD226 and TIGIT, transmembrane proteins found on leukocytes, PVR is a key regulator of the cell-mediated immune response. As PVR is differentially regulated in a broad spectrum of cancers, it has a strong potential for clinical use as a biomarker. PVR is also a possible target for novel cancer therapies. Utilizing its natural tropism for PVR, a genetically modified form of the live attenuated poliovirus vaccine is currently being tested for its ability to locate and destroy certain tumors. These recent studies emphasize the importance of PVR in human biology and demonstrate its utility beyond being a viral receptor protein.

1. Introduction

The objective of this review is to summarize both historical and contemporary research on poliovirus and its receptor, PVR. The human poliovirus receptor (PVR) has a plethora of names due to disagreements in naming conventions between different fields of research and multiple independent discoveries of both the protein and its corresponding gene. Names include Cluster of Differentiation 155 (CD155), Poliovirus Sensitivity gene (PVS), Herpesvirus entry mediator D (HVED), Nectin-like molecule 5 (NECL5 or Necl-5), and Tumor-Associated Glycoprotein E4 (TAGE4), however, the human poliovirus receptor (PVR) remains dominant in the literature and will be used throughout the review (Baury et al., 2001; Masson et al., 2001; Nixdorf et al., 1999; Siddique et al., 1988; Takai et al., 2008). PVR was found to be an integral membrane protein at a period when the polio vaccine was still in its infancy and initial research focused on its role in poliovirus infection. (Holland and Mc, 1961). However, as poliomyelitis gradually transitioned from global pandemic to the verge of eradication, interest in human poliovirus and its eponymous receptor protein waned. The actual identity of the PVR protein was elucidated in 1989 by Mendelsohn et al. and enormous strides have since been made concerning its many native functions (Mendelsohn et al., 1989). Recent research has demonstrated PVR to be broadly relevant to cell adhesion and migration, adaptive immunity, and cancer.

1.1. Poliomyelitis

Poliomyelitis is a devastating neurologic disease that has greatly impacted humanity for millennia (Falconer and Bollenbach, 2000; Paul, 1971). It is propagated by the human poliovirus, a positive sense single stranded RNA virus (Ryan and Ray, 2014). Because this virus is transmitted primarily by the fecal-oral route, it has historically been widespread in regions with high population densities and subpar sanitation systems (Kew et al., 2005). Poliovirus infection progresses to poliomyelitis when the virus invades the central nervous system. By attacking the motor functions of the spinal cord, the disease begins weakening muscle function, which can lead to widespread muscle paralysis and even death, usually due to loss of respiratory muscle function. Often this paralysis is irreversible, permanently disabling survivors of poliomyelitis (Mueller et al., 2005). Since major vaccination campaigns began in the 1950's, the incidence rate of poliomyelitis has dramatically decreased. In 2015, there were fewer than 100 reported cases of poliomyelitis with only two countries, Afghanistan and Pakistan, reporting endemic transmission (Cochi et al., 2016). Although political instability has limited full vaccination efforts, it is a strong possibility that wild-type poliovirus transmission could be eradicated

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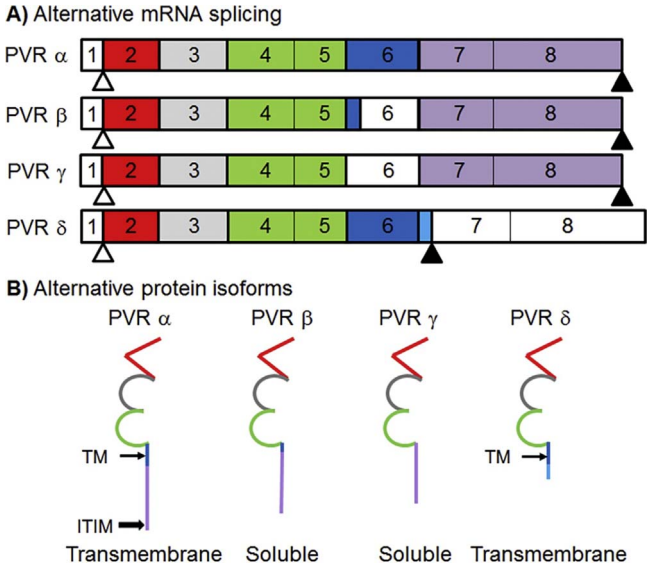

Fig. 1. Schematic of exon map for PVR A) RNA spliceforms and B) protein isoforms. Unshaded exons are not expressed in the protein. Exons are color coded to match the portions of the protein that they encode: red = Ig-like domain 1, grey = Ig-like domain 2, green = Ig-like domain 3, dark blue = transmembrane domain (thin arrow/TM), light blue = unique sequence in δ isoform, and purple = C-terminal domain. Start codons appear as white triangles and stop codons appear as shaded triangles. Compared to the canonical isoform PVRα, soluble isoforms PVRβ and γ contain splicing events in exon 6 which result in partial (β) or complete (γ) loss of exon 6. There is an alternative splicing event between transmembrane isoforms PVRα and PVRδ in which an additional eight residues and a stop codon are incorporated at the end of exon 6, resulting in exons 7 and 8 not being translated in PVRδ. The immunoreceptor tyrosine-based inhibitory motif (ITIM) of PVRα is indicated (block arrow).

within the next decade (Cochi et al., 2016; Kennedy et al., 2015).

1.2. PVR: an overview

While poliomyelitis is no longer a highly prevalent medical condition, there has been a substantial volume of research published on the poliovirus in the past 20 years. Particular interest has been given to the cell surface protein that functions as the primary receptor for human poliovirus. PVR is a cell adhesion protein that facilitates the binding and entry of poliovirus into susceptible cells (Koike et al., 1991; Oda et al., 2004; Strauss et al., 2015). Like many cell surface proteins, and viral receptors such as the Coxsackievirus and Adenovirus Receptor (CAR) and CD46, PVR undergoes alternative splicing, generating 4 unique splice forms (Fig. 1, Table 1) (Excoffon et al., 2014; Koike et al., 1990). Two of these splice forms lack a complete transmembrane domain, rendering them as secreted or soluble isoforms (Baury et al., 2003). The other two splice forms have a complete transmembrane domain and are often referenced as the transmembrane isoforms (Koike et al., 1990). Although PVR was originally described as a viral receptor, recent literature has focused primarily on its endogenous functions in host biology. PVR has been shown to function as a cell adhesion protein as well as a facilitator of transendothelial migration (TEM) (Oda et al., 2004; Sullivan et al., 2013). PVR also has a vital role in regulating the cell mediated response of the immune system (Stanietsky et al., 2009; Tahara-Hanaoka et al., 2005). Finally, PVR is often differentially regulated in neoplastic and cancerous cells (Brown et al., 2014; Gong et al., 2014). Studies have demonstrated the efficacy of using a genetically modified strain of the human poliovirus to target PVR positive cancerous cells (Brown et al., 2014; Brown and Gromeier, 2015; Dobrikova et al., 2008; Gromeier et al., 2000). As many of PVR's newly discovered functions have direct clinical applications, it is critical that we have a deeper understanding of PVR and its unique role in human biology.

2. Morphology and splice form diversity of PVR

PVR is a transmembrane glycoprotein in the immunoglobulin superfamily. Located on human chromosome 19 (NC_000019.10), the PVR gene is transcribed into a 20 kb mRNA sequence composed of 8 different exons (Koike et al., 1990; Mendelsohn et al., 1989; Siddique et al., 1986; Speir et al., 2016) (Fig. 1). Exon 1 codes for the 5′ UTR and a signal peptide domain that functions as a leader sequence. Exon 2 is translated into the first of three immunoglobulin-like domains. The first immunoglobulin-like domain is a V domain while the second and third immunoglobulin-like domains are C2 domains, encoded by exon 3 or exons 4 and exon 5, respectively (Baury et al., 2003; Koike et al., 1990; Koike et al., 1991). Exon 6 and exon 7 become the transmembrane domain and the cytoplasmic domain, respectively. Finally exon 8 is translated into the C-terminus region and the 3′UTR. In total, PVR is 417 amino acids when all 8 exons are translated in full.

2.1. Soluble PVR

PVR expresses as two soluble isoforms, PVRβ and PVRγ, both of which lack all or part of the transmembrane region encoded by exon 6, causing them to be secreted from cells. Exons 1–5 as well as 7–8 on both soluble isoforms are identical to the canonical PVRα. PVRβ, the longer and more common of the two soluble splice forms, contains a small, truncated, fragment of the first part of exon 6; PVRγ lacks exon 6 in its entirety (Baury et al., 2003). Soluble and transmembrane isoforms of PVR can be found in tissues that are susceptible to poliovirus infection, such as the organs of the gastrointestinal tract and nervous tissue, as well as in tissues that are not, including the kidney, lung, liver, and testes. Soluble PVR (sPVR) isoforms can be found in a variety of bodily fluids, including: blood serum, cerebrospinal fluid, and urine (Baury et al., 2003; Iguchi-Manaka et al., 2016). As the extracellular domains of the sPVR isoforms are identical to the extracellular domain of transmembrane PVR, they can compete with transmembrane PVR for the canyon-like receptor binding site of poliovirus (Baury et al., 2003). Therefore when sPVR is overexpressed in poliovirus susceptible HeLa cells, it significantly reduces viral entry and viral infectivity (Baury et al., 2003).

Recent studies have established a relationship between sPVR expression and cancer progression. In animals, fibrosarcoma cells transduced with the ECD of mouse PVR were implanted into Balb/c mice, and the amount of sPVR produced by resulting tumors had a strong positive correlation with tumor size (Iguchi-Manaka et al., 2016). In humans, sPVR is found in higher serum concentrations compared to

Table 1
Protein isoforms of PVR.

Isoform	Exons encoding protein sequence Baury et al. (2003)	Soluble or Transmembrane Baury et al. (2003)	Location in polarized cells Ohka et al. (2001)	Interaction with Poliovirus Baury et al. (2003); Koike et al. (1991)
PVRα	1–8	Transmembrane	Normally basolateral, tissue dependent	Binds to poliovirus, promotes viral entry
PVRβ	1–5, partial 6, 7–8	Soluble	Secreted	Binds to poliovirus, decreases viral entry
PVRγ	1–5, 7–8	Soluble	secreted	Binds to poliovirus, decreases viral entry
PVRδ	1–6, alternative C-terminus	Transmembrane	Non-specific localization, found at both apical and basolateral surface	Binds to poliovirus, promotes viral entry