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Review

Phosphatidylserine receptors: Enhancers of enveloped virus entry and infection

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Integrin αvβ5
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ABSTRACT

A variety of both RNA and DNA viruses envelop their capsids in a lipid bilayer. One of the more recently appreciated benefits this envelope is incorporation of phosphatidylserine (PtdSer). Surface exposure of PtdSer disguises viruses as apoptotic bodies; tricking cells into engulfing virions. This mechanism is termed apoptotic mimicry. Several PtdSer receptors have been identified to enhance virus entry and we have termed this group of proteins PtdSer-mediated virus entry enhancing receptors or PVEERs. These receptors enhance entry of a range of enveloped viruses. Internalization of virions by PVEERs provides a broad mechanism of entry with little investment by the virus itself. PVEERs may allow some viruses to attach to cells, thereby making viral glycoprotein/cellular receptor interactions more probable. Alternatively, other viruses may rely entirely on PVEERs for internalization into endosomes. This review provides an overview of PtdSer receptors that serve as PVEERs and the biology behind virion/PVEER interaction.

Contents

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Introduction

A variety of both RNA and DNA viruses envelop their capsids in a lipid bilayer. This outer membrane is obtained during virus budding from either plasma or organelle membranes. While reliance on an envelope sensitizes viruses to desiccation, detergents, and heat, these envelopes provide a number of benefits for the virus, including protection of viral structural proteins from immune recognition and neutralizing antibodies, a platform for displaying viral proteins, a barrier to enclose viral and cellular proteins necessary for early steps during infection, and a mechanism for virus egress without lysing infected cells. In addition, a more recently appreciated benefit is the incorporation of phospholipids into viral envelopes. Presentation of phosphatidylserine (PtdSer) on the outer leaflet of these membranes disguises viruses as apoptotic bodies, thereby conning cells into engulfing virions through cell clearance mechanisms. This mechanism of enhanced virus entry is termed apoptotic mimicry.

Over the past three years, receptors and receptor complexes have recently been identified that enhance entry of a diverse range of enveloped viruses. This group of viral receptors shares the ability to bind to PtdSer present on the viral envelope and, consequently, we have termed them PtdSer-mediated virus entry enhancing receptors or PVEERs. The broad expression of these receptors and their ability to interact with PtdSer on a wide array of enveloped viruses has huge potential implications for virus infection. Most importantly, PVEERs enhance virus binding to cells and facilitate internalization. These receptors also contribute to immune evasion through both anti-inflammatory signaling and a mechanism of entry that does not require extracellular exposure of key receptor-binding domain and fusion epitopes. In this review we summarize what is known about the identified PVEERs and their role in virus entry and identify important gaps in current knowledge.

History of PVEER discovery

Apoptotic mimicry was first hypothesized to be used by hepatitis B virus (Vanlandschoot and Leroux-Roels, 2003), but was experimentally confirmed with vaccinia virus (Mercer and Helenius, 2008). Inactivation of vaccinia virus by NP-40-mediated lipid depletion could be rescued by incubation with PtdSer liposomes (Oie, 1985). However, the contribution of PtdSer to infection was not understood. Mercer et al. furthered these studies and determined that not only PtdSer is present on the surface of some vaccinia infectious particles, but Annexin V (AnxV), a PtdSer-binding protein, can bind to PtdSer on viral envelopes and inhibit vaccinia infection (Mercer and Helenius, 2008). These results were confirmed by another study that found substitution with a non-biologically relevant isomer of PtdSer restored infectivity (Laliberte and Moss, 2009). In addition, a role for viral envelope PtdSer during infection was demonstrated for Pichinde virus and HIV-1 (Soares et al., 2008; Callahan et al., 2003).

A protein complex composed of growth-arrest-specific 6 (Gas6) and the tyrosine kinase receptor, Axl, was the first set of cellular proteins to be implicated in PtdSer-binding enhancement of viral entry (Morizono et al., 2011). It was shown that the soluble protein Gas6 binds to PtdSer on the virion surface and bridges virus to the cell surface via interaction with the tyrosine kinase receptor, Axl and formation of this complex is necessary for enhancement of virus entry. This study found in addition to vaccinia virus, the Gas6/Axl complex enhances binding and entry of lentiviruses pseudotyped with Ross River GP, baculovirus GP64, or Sindbis env, demonstrating for the first time that PtdSer binding can enhance entry of viral particles bearing a variety of different viral glycoproteins. More recently, a variety of additional PVEERs were identified, including T-cell immunoglobulin and mucin domain 1 and 4 (TIM-1 and 4) proteins and MFG-E8/integrin αvβ3 or αvβ5 complexes (Meertens et al., 2012; Jemielity et al., 2013; Moller-Tank et al., 2013; Morizono and Chen, 2014). The details of virion interactions with different PVEERs are highlighted below.

Several recent studies have expanded our understanding of PVEERs. The group of viruses whose entry is enhanced by PVEERs now include members of the flavivirus, filovirus, New World arenavirus, baculovirus, and alphavirus families (Meertens et al., 2012; Jemielity et al., 2013; Moller-Tank et al., 2013; Morizono and Chen, 2014). Between viruses within these families, the extent to which PVEERs enhance virus entry varies, but generally viruses do not appear to utilize one PVEER effectively and not another. This suggests that virion uptake mediated by the different PVEERs is mechanistically similar. Despite the strong evidence that PVEERs interact with virion associated PtdSer, the utilization of PVEER-dependent virus entry is influenced by the viral glycoprotein presence on the virion. For instance, entry of viruses bearing the envelope proteins of Old World arenaviruses, coronaviruses, influenza A virus, vesicular stomatitis virus, or herpes simplex virus 1 is not enhanced by PVEER expression (Morizono et al., 2011; Meertens et al., 2012; Jemielity et al., 2013; Moller-Tank et al., 2013; Kondratowicz et al., 2011). Thus, while PVEERs do not enhance entry all enveloped viruses, they do represent a potentially important class of receptors for a large and diverse collection of important human pathogenic viruses.

Characterization of identified PVEERs

Six PVEERs have been identified to date: TIM-1, TIM-4, Gas6 or Protein S/Axl, Mer, and Tyro3, and MFG-E8/integrin αvβ3 and αvβ5. A summary of characteristics of these PVEERs is shown in Table 1. The key property that these proteins or complexes utilize to enhance virus entry is their ability to bind PtdSer and a native function of all of these receptors is to bind and clear apoptotic bodies (Ravichandran, 2011). Mutation of residues involved in PtdSer binding or complex formation results in inhibition of PVEER function (Morizono et al., 2011; Meertens et al., 2012; Moller-Tank et al., 2013; Morizono and Chen, 2014). Further, competition with PtdSer liposomes, but not phosphatidylcholine liposomes, inhibits entry enhancement by PVEERs (Jemielity et al., 2013; Moller-Tank et al., 2013). Phosphatidylethanolamine liposomes are also somewhat inhibitory, likely due to sharing similar structure to PtdSer (Jemielity et al., 2013). In some cases, prebinding virus with the PtdSer-binding protein, Annexin V (AnxV), has been shown to inhibit PVEER enhancement of entry (Mercer and Helenius, 2008; Callahan et al., 2003; Meertens et al., 2012), but not in others (Morizono and Chen, 2014). Consistent with the ability of an array of PtdSer receptors to serve as PVEERS, an artificially generated PVEER containing the PtdSer-binding domain from AnxV was highly effective at mediating uptake of vesicular stomatitis virus (VSV) pseudovirions bearing a filovirus, alphavirus or baculovirus glycoprotein (Moller-Tank et al., 2014).

Table 1
PtdSer receptors: distribution and efficacy as a viral receptor.

Protein name (s)	PtdSer binding domain	Tissue/cell type expression	Pseudoviruses for which entry is enhanced (>2 fold)	Pseudoviruses for which entry is unaffected (<2 fold)	Cell lines reported to express PtdSer receptor
TIM-1	IgV(Kobayashi et al., 2007)	**Immune cells:** B cells (Sizing et al., 2007), mast cells (Nakae et al., 2007), T_H2 $CD4^+$ T cells (Meyers et al., 2005; Umetsu et al., 2005; Khademi et al., 2004), and NKT cells (Lee et al., 2010; Kim et al., 2013) **Epithelial cells:** Kidney (Kondratowicz et al., 2011; Ichimura et al., 1998) and airway and eye mucosa (Kondratowicz et al., 2011)	**Filovirus:** Ebola• and Marburg (Jemielity et al., 2013; Moller-Tank et al., 2013; Kondratowicz et al., 2011) **Alphavirus:** Ross River•, Chikungunya, Sindbis•, Eastern Equine Encephalitis (Jemielity et al., 2013; Moller-Tank et al., 2013; Morizono and Chen 2014) **Baculovirus:** Autographa californica multicapsid nucleopolyhedrovirus• (Moller-Tank et al., 2013) **Rhabdovirus:** Vesicular stomatitis virus (Morizono and Chen, 2014) **New World Arenavirus:** Amapari, Tacaribe•, Junín, and Machupo virus (Jemielity et al., 2013) **Flavivirus:** West Nile Virus•, Dengue•, Yellow Fever virus• (Meertens et al., 2012; Jemielity et al., 2013)	**Old World Arenavirus:** Lassa Virus, LCMV (Jemielity et al., 2013; Moller-Tank et al., 2013) **New World Arenavirus:** Oliveros (Jemielity et al., 2013) **Influenza A virus:** H7N1, H1N1• (Jemielity et al., 2013) **Coronavirus:** SARS (Jemielity et al., 2013) **Rhabdovirus:** Vesicular stomatitis virus (Jemielity et al., 2013) **Herpes simplex virus:** HSV-1• (Meertens et al., 2012)	**Human:** Huh-7, ACHN, A498, 786-O, Caco-2, CAKI-1, TK-10, UO-3, Vero, A549, Cos-7 (Meertens et al., 2012; Kondratowicz et al., 2011)
TIM-3	IgV(DeKruyff et al., 2010)	**Immune cells:** T_H1 and T_H17 $CD4^+$ T cells (Khademi et al., 2004; Hastings et al., 2009; Monney et al., 2002; Nakae et al., 2007), mast cells (Nakae et al., 2007), DCs (DeKruyff et al., 2010; Anderson et al., 2007), and monocytes (Anderson et al., 2007) **Epithelial cells:** Bronchial (DeKruyff et al., 2010)	**Flavivirus:** West Nile Virus, Dengue Virus• (Meertens et al., 2012; Jemielity et al., 2013) **New World Arenavirus:** Tacaribe (Jemielity et al., 2013)	**Alphavirus:** Sindbis (Morizono and Chen, 2014) **Filovirus:** Ebola, Marburg (Jemielity et al., 2013) **Old World Arenavirus:** LASV, LCMV (Jemielity et al., 2013) **New World Arenavirus:** Tacaribe, Junín, Machupo, Oliveros (Jemielity et al., 2013) **Influenza A virus:** H7N1 (Jemielity et al., 2013) **Rhabdovirus:** Vesicular stomatitis virus (Jemielity et al., 2013)	**Mouse:** Raw264.7 (DeKruyff et al., 2010) **Human:** PMA stimulated THP-1 cells (DeKruyff et al., 2010)
TIM-4	IgV(Kobayashi et al., 2007; Santiago et al., 2007; Miyanishi et al., 2007)	**Immune cells:** Macrophages and mature DCs (Kobayashi et al., 2007; DeKruyff et al., 2010; Miyanishi et al., 2007; Mizui et al., 2008; Meyers et al., 2005), and B-1 cells (Rodriguez-Manzanet et al., 2010) **Tissues:** Spleen, lymph node, and peritoneum (Miyanishi et al., 2007; Meyers et al., 2005)	**Filovirus:** Ebola, Marburg (Jemielity et al., 2013; Moller-Tank et al., 2013) **Alphavirus:** Sindbis, Ross River (Morizono and Chen, 2014), Eastern Equine Encephalitis (Jemielity et al., 2013) **New World Arenavirus:**	**New World Arenavirus:** Oliveros (Jemielity et al., 2013) **Old World Arenavirus:** LASV, LCMV (Jemielity et al., 2013) **Influenza A virus:**	

Table 1 (*continued*)

Protein name (s)	PtdSer binding domain	Tissue/cell type expression	Pseudoviruses for which entry is enhanced (> 2 fold)	Pseudoviruses for which entry is unaffected (< 2 fold)	Cell lines reported to express PtdSer receptor
			Tacaribe, Junín, Machupo (Jemielity et al., 2013) **Baculovirus:** Autographa californica multicapsid nucleopolyhedrovirus (Morizono and Chen, 2014) **Rhabdovirus:** Vesicular stomatitis virus (Jemielity et al., 2013) **Flavivirus:** West Nile Virus•, Dengue•, Yellow Fever virus• (Meertens et al., 2012; Jemielity et al., 2013)	H7N1 (Jemielity et al., 2013) **Herpes simplex virus:** HSV-1• (Meertens et al., 2012)	
TAM ligand (Protein S or Gas6) / TAM receptor kinases (Tyro3, Mer, or Axl)	Gla(Huang et al., 2003; Rajotte et al., 2008) domain of TAM ligand	**Reviewed here: (**Lemke and Rothlin, 2008**)** **Blood cells:** Platelets (Angelillo-Scherrer et al., 2001) **Immune cells:** Macrophages, NK cells, NKT cells, and DCs (Seitz et al., 2007; Caraux et al., 2006; Behrens et al., 2003) **Connective tissue:** Bone marrow stromal cells (Caraux et al., 2006) **Tissues:** Testes (Lu et al., 1999; Wang et al., 2005), CNS (Stitt et al., 1995; Prieto et al., 2000), retina (Prasad et al., 2006), and foreskin fibroblasts (Brindley et al., 2011)	**Filovirus:** Ebola, Marburg (Jemielity et al., 2013; Shimojima et al., 2006) **Rhabdovirus:** Vesicular stomatitis virus (Morizono and Chen, 2014) **Baculovirus:** Autographa californica multicapsid nucleopolyhedrovirus (Morizono et al., 2011; Morizono and Chen, 2014) **Alphavirus:** Sindbis, Ross River (Morizono et al., 2011; Morizono and Chen, 2014) **Pox virus:** Vaccinia Virus• (Morizono et al., 2011) **New World Arenavirus:** Amapari, Tacaribe, Junín (Jemielity et al., 2013) **Alphavirus:** Chikingunya, Eastern Equine Encephalitis (Jemielity et al., 2013) **Flavivirus:** Dengue• (Meertens et al., 2012)	**Old World Arenavirus:** LASV, LCMV (Jemielity et al., 2013) **New World Arenavirus:** Machupo (Jemielity et al., 2013), Oliveros (Jemielity et al., 2013) **Rhabdovirus:** Vesicular stomatitis virus (Jemielity et al., 2013) **Influenza A virus:** H7N1 (Jemielity et al., 2013) **Herpes simplex virus:** HSV-1• (Meertens et al., 2012)	**Human:** A549, Vero, Cos-7, HeLa, SNB19, and SN12C (Meertens et al., 2012; Shimojima et al., 2006; Brindley et al., 2011)
MFG-E8/ αvβ3-5 integrin	C2 domain (Andersen et al., 2000; Ye et al., 2013)	**Immune cells:** Macrophages (Hanayama et al., 2002; Hanayama et al., 2004; Finnemann and Rodriguez-Boulan, 1999; Antonov et al., 2004), Immature DCs (Miyasaka et al., 2004; Albert et al., 1998) **Tissues:** Mammary glands (Oshima et al., 1999; Stubbs et al., 1990), spleen, lymph node, brain (Hanayama et al., 2004; Garmy-Susini et al., 2007; Uehara and Uehara, 2014), and vascular system (Silvestre et al., 2005; Brooks et al., 1994)	**Alphavirus:** Ross River and Sindbis (Morizono and Chen, 2014) **Baculovirus:** Autographa californica multicapsid nucleopolyhedrovirus (Morizono and Chen, 2014)	**Rhabdovirus:** Vesicular stomatitis virus (Morizono and Chen, 2014)	**Human:** HEC-1A, Ishikawa, HEEC, K562, HL60 (Bocca et al., 2012; Kruger et al., 2000); **Mouse:** COMMA-1D, D1, P388D1(Hanayama et al., 2004; Thery et al., 1999; Oshima et al., 2002)

CD300a	IgV (Simhadri et al., 2012)	**Immune cells:** $CD8^+$ T cells (Xu et al., 2012), $CD4^+$ T cells (Clark et al., 2007; Simhadri et al., 2011; Narayanan et al., 2010), B cells (Silva et al., 2011), and NK cells (Lankry et al., 2010; Cantoni et al., 1999)	**Alphavirus:** Sindbis (Morizono and Chen, 2014)••	**Alphavirus:** Ross River and Sindbis (Morizono and Chen, 2014) **Baculovirus:** Autographa californica multicapsid nucleopolyhedrovirus (Morizono and Chen, 2014) **Rhabdovirus:** Vesicular stomatitis virus (Morizono and Chen, 2014)	**Human:** THP1, U937, REC-1, SUDHL5, 721.221 (Silva et al., 2011; Kim et al., 2012)
BAI1	Type 1 thrombospondin repeats (TSRs) (Park et al., 2007)	**Tissues:** Brain (Shiratsuchi et al., 1997; Sokolowski et al., 2011), muscle(Hochreiter-Hufford et al., 2013), bone marrow, and spleen (Park et al., 2007) **Immune cells:** Macrophages (Park et al., 2007)		**Alphavirus:** Ross River and Sindbis (Morizono and Chen, 2014) **Baculovirus:** Autographa californica multicapsid nucleopolyhedrovirus (Morizono and Chen, 2014) **Rhabdovirus:** Vesicular stomatitis virus (Morizono and Chen, 2014) **Flavivirus:** Dengue• (Meertens et al., 2012)	**Human:** J774 and RAW264.7 (Park et al., 2007)
RAGE	IgV (Friggeri et al., 2011)•••	**Immune cells:** $CD8^+$ and $CD4^+$ T cells (Akirav et al., 2012; Moser et al., 2007), DCs (Dumitriu et al., 2005), macrophages (Zhang et al., 2009; Sunahori et al., 2006), and monocytes (Ohashi et al., 2010) **Tissues:** Smooth muscle (Zhang et al., 2009; Kamioka et al., 2011), cartilidge chondrocytes (Loeser et al., 2005), skin keratinocytes (Zhu et al., 2012), and vascular system (Pollreisz et al., 2010; Liu et al., 2010)		**Old World Arenavirus:** Lassa (Moller-Tank et al., 2013) **Filovirus:** Ebola virus (Moller-Tank et al., 2013)	**Human:** HaCaT (Zhu et al., 2012), A549 (Nakano et al., 2006)
Stabilin-1/-2	Epidermal growth factor-like domain (Park et al., 2009, 2008; Kim et al., 2010)	**Immune cells:** Macrophages (Park et al., 2008, 2009; Martens et al., 2006) **Tissues:** Sinusoidal endothelial cells (Martens et al., 2006; Falkowski et al., 2003), spleen, lymph node, liver, bone marrow, cornea, brain, heart, and kidney (Falkowski et al., 2003; Goerdt et al., 1991)		**Alphavirus:** Ross River and Sindbis (Morizono and Chen, 2014) **Baculovirus:** Autographa californica multicapsid nucleopolyhedrovirus (Morizono and Chen, 2014) **Rhabdovirus:** Vesicular stomatitis virus (Morizono and Chen, 2014)	**Human:** PMA stimulated THP1(Park et al., 2008) **Mouse:** PMA stimulated P388D1 cells (Park et al., 2008)

•Confirmed using infectious virus.
••Enhances binding only, but not infection.
•••Hypothesized but not shown

Recent studies have demonstrated that virus internalization into HEK 293T cells can occur entirely independently of the presence of a viral glycoprotein. This virion internalization is significantly enhanced by PVEER overexpression and is inhibited by competition with PtdSer liposomes (Jemielity et al., 2013; Moller-Tank et al., 2013), providing compelling evidence that virion associated PtdSer/PVEER interactions are responsible for virion uptake, not just virus binding. While the cellular compartment(s) into which PVEERs deliver virions has yet to be identified, indirect evidence indicates that uptake of cargo is into endosomes (Kobayashi et al., 2007; Albacker et al., 2010). Once the virion is internalized, the presence of a viral glycoprotein on the virion is necessary for fusion events with the endosomal membrane. An overview of each group of PVEERs is given below.

TIM-1 and TIM-4

TIM-1 was first implicated in enveloped virus entry as a specific receptor for filoviruses (Kondratowicz et al., 2011). However, it was later discovered that both TIM-1 and family member, TIM-4, enhance virus entry as PVEERs through binding of PtdSer (Meertens et al., 2012; Jemielity et al., 2013; Moller-Tank et al., 2013). The human TIM family members are type I, cell-surface glycoproteins that along with their murine counterparts, share a common structure. Their amino terminal immunoglobulin variable (IgV)-like domain extends from the plasma membrane by a heavily O-linked-glycosylated mucin-like domain (MLD), which is attached to the cell surface by a transmembrane domain followed by a cytoplasmic tail (Fig. 1) (McIntire et al., 2004). TIM-1 signals through phosphorylation of cytoplasmic tail tyrosines (Binne et al., 2007; de Souza et al., 2005, 2008); however, none of the TIM family members require their cytoplasmic domains for PVEER function (Meertens et al., 2012; Moller-Tank et al., 2014).

TIM-1 and TIM-4 are unique among PVEERs as their PtdSer-binding domains are a portion of a transmembrane protein rather than an independent, small protein that binds to a plasma membrane receptor. The PtdSer-binding pocket is located between two loops of the IgV domain (Fig. 2) (Kobayashi et al., 2007; Santiago et al., 2007; DeKruyff et al., 2010; Miyanishi et al., 2007). Conserved aspartate and asparagine residues within the upper loop are involved in coordination of a cation that, in conjunction with residues of the lower loop, form hydrogen bonds with the phosphate and serine groups of PtdSer (Santiago et al., 2007). This PtdSer binding is necessary for the native functions of TIM-1 and TIM-4: apoptotic body clearance and immune cell regulation (Albacker et al., 2010; Miyanishi et al., 2007; Lee et al., 2010; Kim et al., 2013; Ichimura et al., 2008; Rodriguez-Manzanet et al., 2010; Mizui et al., 2008; Wong et al., 2010). Mutation of aspartate and/or asparagine or chelation of free cations with EGTA results in significant loss in PtdSer binding and subsequent PVEER efficacy (Meertens et al., 2012; Moller-Tank et al., 2013). A recent study suggests TIM-4 is more sensitive than TIM-1 or -3 to differences in membrane-PtdSer concentrations due to additional PtdSer-binding residues outside of the pocket (Tietjen et al., 2014). This altered sensitivity may have implications for virus binding.

While all human TIM family members can bind PtdSer and enhance the uptake of apoptotic bodies (Kobayashi et al., 2007; DeKruyff et al., 2010), TIM-3 does not effectively enhance virus entry (<2 fold) (Meertens et al., 2012; Jemielity et al., 2013; Kondratowicz et al., 2011). Though the IgV domain of TIM-3 has reduced affinity for PtdSer (DeKruyff et al., 2010), replacing the TIM-1 or TIM-4 IgV domain with that of TIM-3 results in a functional PVEER (Moller-Tank et al., 2014). Thus, the reduced efficacy is not due to the TIM-3 IgV domain. Rather, the inability of TIM-3 to function effectively as a PVEER is likely due to the short length of the TIM-3 MLD which is ~2.5-fold shorter than that of TIM-1 and -4 (Fig. 1). This is supported by studies showing that deletions within the MLD of TIM-1 reduce PVEER efficacy (Jemielity et al., 2013; Moller-Tank et al., 2014).

Protein S and Gas6/Tyro3, Axl, and Mer

Tyro3, Axl, and Mer (TAM) are members of the TAM family of receptor tyrosine kinases. These highly related proteins contain two N-terminal immunoglobulin-like domains, followed by two fibronectin type III domains, a single transmembrane domain, and a cytoplasmic protein tyrosine kinase (PTK) domain (Fig. 2). TAM N-terminal interaction with Gas6 leads to activation of the TAM receptors and autophosphorylation of tyrosines within the PTK domain (Stitt et al., 1995). Tyro3 and Mer, but not Axl, are similarly activated by binding Protein S (Stitt et al., 1995; Prasad et al., 2006). Both Gas6 and Protein S consist of an N-terminal domain rich in γ-carboxyglutamic acid residues (Gla) that binds to PtdSer (Fig. 1) (Huang et al., 2003; Ishimoto et al., 2000; Rajotte et al., 2008), a loop region, four epidermal growth factor-like repeats, and two C- terminal laminin G-like domains forming a sex

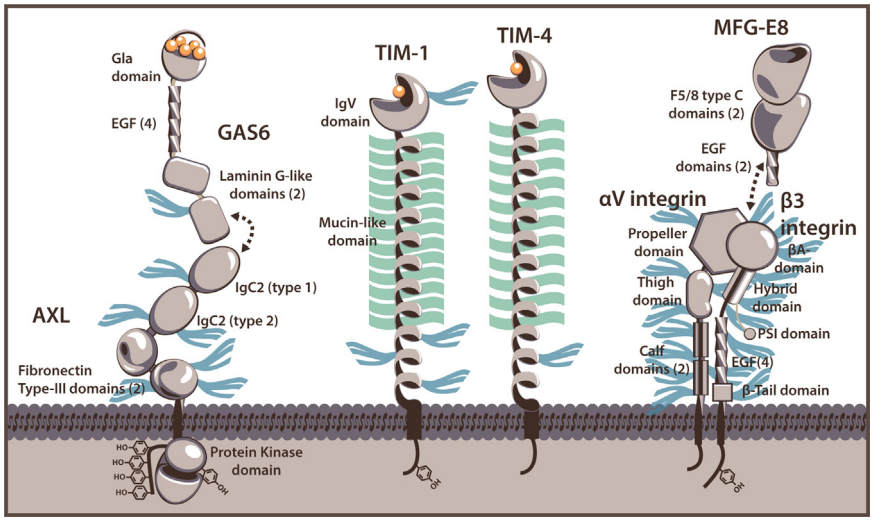

Fig. 1. PtdSer-binding receptors that function as PVEERs. Cartoon representations of Gas 6/Axl (representatives of TAM ligand and receptor kinases), TIM-1, TIM-4, and MFG-E8/ αvβ3 integrin are displayed. Estimations of N-linked glycan sites are represented as blue tridents and O-link glycoslyations (TIM-1 and TIM-4 only) are shown as green lines. Domains for which calcium-binding is necessary for interaction with PtdSer are indicated with calcium ions (orange spheres). Gas6 and Axl interact through their respective laminin G-like and IgC2 domains. MFG-E8 contains an Arg-Gly-Asp (RGD) motif in the second EGF domain that likely binds at the interface of the αvβ3/5 integrin complex (Xiong et al., 2002).

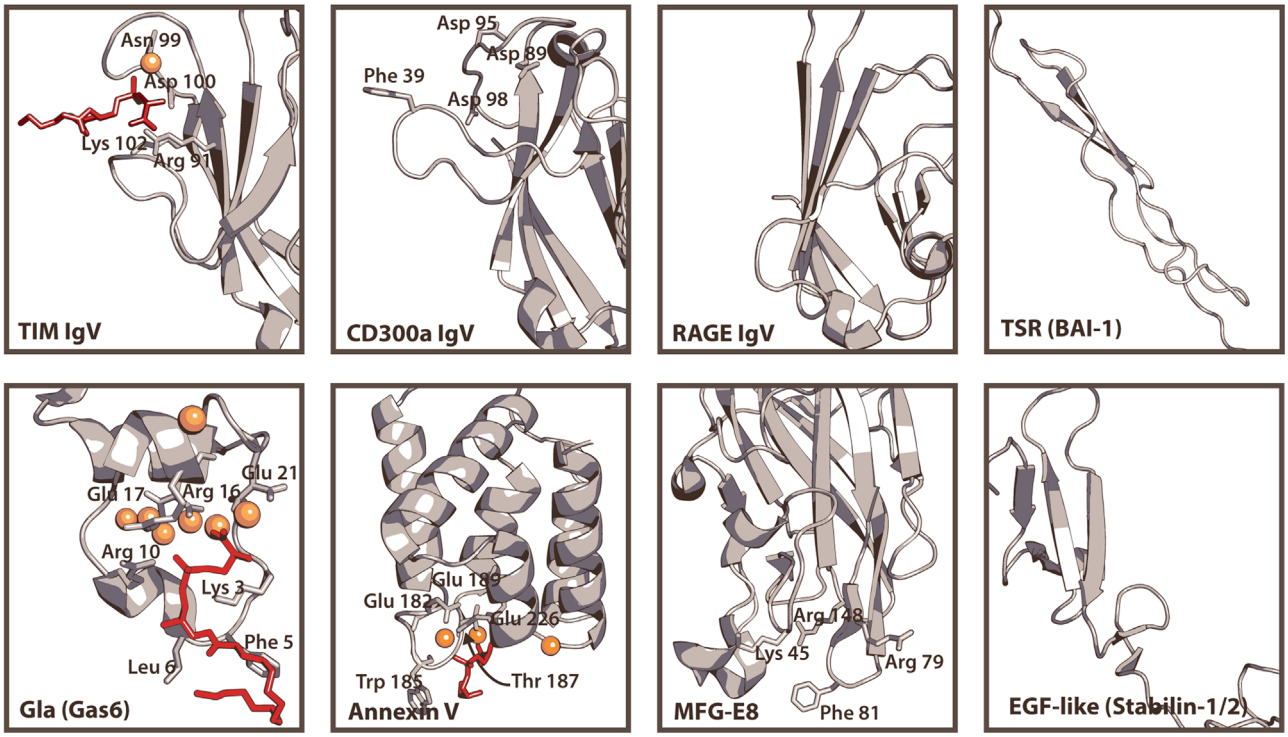

Fig. 2. Structures of PtdSer-binding domains. Representative renders of the PtdSer-binding domains of TIM-1/-3/-4, CD300a, RAGE, BAI-1, Gas6/Protein S, Annexin V, MFG-E8, and Stabilin-1/2 are shown. PtdSer-like ligands (red) and calcium ions (orange) are also displayed for structures with which they were solved. For domains that do not have solved structures, equivalent domains from other proteins are shown. The IgV domain of TIM-1/-3/-4 is represented by the mTIM-4 IgV domain (2OR8) (Santiago et al., 2007). The human CD300a IgV domain crystal structure (Dimasi et al., 2007) is shown with residues hypothesized for interaction (Simhadri et al., 2012). The region of the RAGE IgV domain (3O3U) that corresponds to the binding pockets of CD300a and TIM-1 IgV domains is shown for comparison (Park et al., 2010); however, this domain is only hypothesized to interact with PtdSer and no residues have been implicated (Friggeri et al., 2011). The thrombospondin type-1 repeats (TSRs) of BAI1 are represented by TSR domain 3 of human thrombospondin-1 (3R6B) (Klenotic et al., 2011). Gas6 binds PtdSer via a Gla domain, represented by that of bovine prothrombin (1NL2) with residues identified that interact with PtdSer (red) (Huang et al., 2003). For AnxV, the structure of one annexin repeat domain from rat Anx V is shown (1A8A) with residues identified that interact with PtdSer (red) (Swairjo et al., 1995). The C2 domain of bovine MFG-E8 binds to PtdSer (3BN6) (Shao et al., 2008) and while the structure was not crystallized with PtdSer, key residues involved in interaction have been determined experimentally (Ye et al., 2013). An EGF-like domain of stabilin-1 or -2 is represented by that from human heregulin alpha (1HRE) (Nagata et al., 1994).

hormone-binding globulin-like structure that binds to the Ig-like domains of the TAM receptors (Sasaki et al., 2006, 2002). Dimerization of TAM receptors occurs after binding of their ligands, resulting in a 2:2 complex, and is necessary for signaling (Sasaki et al., 2006).

All TAM receptors in combination with their Gas6 or Protein S ligand have been shown to effectively enhance virus entry, although studies suggest that the relative effectiveness of the three TAM members as PVEERs varies (Morizono et al., 2011; Meertens et al., 2012; Jemielity et al., 2013; Bhattacharyya et al., 2013). This may be due to differences in binding affinities between the TAM receptors and their ligands (Nagata et al., 1996) or relative expression. As the PtdSer-binding activity of PVEERs is essential for efficacy, in the case of the TAM receptors, this occurs through the Gla domain of Gas6/Protein S and removal of this domain eliminates PVEER function of the TAMs (Morizono et al., 2011; Meertens et al., 2012). Similarly mutation of the Gas6 binding residues of Axl inhibits virus uptake by the complex (Meertens et al., 2012). Thus, the PVEER efficacy of the TAM ligand/receptor complexes requires both efficient binding of PtdSer by ligand and binding of ligand by receptor.

Contrary to the TIM family PVEERs where cytoplasmic tail signaling is not required for enhancing virus entry into cells (Moller-Tank et al., 2014), signaling through the PTK domain of TAM receptors is essential for enhancement of viral infection (Meertens et al., 2012; Bhattacharyya et al., 2013). While the Gas6/Axl complex is still able to enhance WNV binding and internalization without kinase activity, subsequent infection is significantly impaired compared to infection of cells expressing WT Axl. This kinase activity is important in vivo for TAM-receptor-inhibition of DC activation and inflammation (Rothlin et al., 2007; Tibrewal et al., 2008). Ligand binding by the receptors and assocation with the type I interferon receptor leads to activation of STAT1 and induction of suppressor of cytokine signaling (SOCS) proteins (Rothlin et al., 2007). Viruses appear to utilize this anti-inflammatory signaling pathway to dampen the immune response and promote replication (Bhattacharyya et al., 2013). While TAM signaling is triggered by interaction with ligand alone, signaling is significantly enhanced by the presence of virus which helps to facilitate the interaction of TAM ligands with their receptors (Bhattacharyya et al., 2013). Thus, the TAM receptors enhance virus infection through PVEER functions by enhancing virus binding and internalization and non-PVEER functions by inhibiting innate immunity, both of which require binding to PtdSer on the virion surface and likely contribute to enhancing in vivo virus loads.

MFG-E8/integrin αvβ3 and αvβ5

Milk fat globule-EGF factor 8 (MFG-E8), the most recently identified PVEER, is a secreted protein that contains two N-terminal EGF repeats followed by a C1 and C2 domain, of which the latter binds to PtdSer (Andersen et al., 2000; Ye et al., 2013). Several key positively charged residues within the C2 domain are responsible for interacting with the phosphate and serine groups, while hydrophobic residues of the domain stabilize the positioning of PtdSer (Fig. 1) (Ye et al., 2013). Like the Gas6, MFG-E8 bridges PtdSer containing membranes to cells through interaction with a membrane bound protein, either integrin αvβ3 or αvβ5 (Andersen et al., 2000; Hanayama et al., 2002). This occurs through an Arg-Gly-Asp (RGD) motif present in the second EGF

repeat of MFGE-8 and mutation of this motif inhibits PVEER efficacy (Morizono and Chen, 2014).

Several aspects of MFG-E8 biology may contribute to infection. Similar to the Gas6/Axl complex, MFG-E8/integrin complexes have been shown to induce production of anti-inflammatory cytokines such as IL-10 (Aziz et al., 2009; Jinushi et al., 2009), some of which are initiated by activation of STAT-3 (Brissette et al., 2012; Jinushi et al., 2011). Interestingly, STAT-3 has also been identified as an upstream regulator of TIM-1 expression (Ajay et al., 2014). However, currently MFG-E8 induced signaling activity has not yet been associated with enhancement of virus entry.

Expression of PVEERs and implications for tropism

The presence of PVEERs in various tissues permissive to infection may contribute to the tropism of some viruses, particularly for flaviviruses and filoviruses, whose entries are most enhanced by PVEER expression. PVEERs are expressed in a variety of tissues and cell types (summarized in Table 1) that are key targets of infection by enveloped viruses. TIM-1, TIM-4, and Axl (Li et al., 2013; Dorfman et al., 2010; Bauer et al., 2012) may enhance uptake of Dengue virus into Langerhans dendritic cells (DCs), one of the first targets during flavivirus infection (Wu et al., 2000; Marovich et al., 2001). TIM-1 is also present on the mucosal epithelia of the airway and eye (Kondratowicz et al., 2011), both of which may be routes of infection for filoviruses (Jaax et al., 1996). Early during infection, flaviviruses and filoviruses replicate in antigen-presenting cell (APC) populations: DCs and macrophages (Geisbert et al., 2003a, 2003b; Jessie et al., 2004). Similarly, alphaviruses infect DCs (Labadie et al., 2010; Gardner et al., 2000; Nishimoto et al., 2007; Shabman et al., 2007) and establish persistent infections in macrophages (Labadie et al., 2010; Linn et al., 1996). Interestingly, these APCs express a variety of PVEERs including TIM-4 (Kobayashi et al., 2007; Rodriguez-Manzanet et al., 2010; Mizui et al., 2008; Meyers et al., 2005; Baghdadi et al., 2013), TAM receptors (Seitz et al., 2007; Caraux et al., 2006; Behrens et al., 2003), and MFG-E8/integrin αvβ3 or αvβ5 (Hanayama et al., 2004; Miyasaka et al., 2004; Albert et al., 1998; Finnemann and Rodriguez-Boulan, 1999; Antonov et al., 2004). However, little is known about whether these PVEERs play critical roles in entry of virus into APC populations. Knock out of TAM receptors from bone marrow-derived DCs significantly reduces infection by West Nile virus or lentiviruses pseudotyped with Ebola, Marburg, vesicular stomatitis, or murine leukemia virus entry proteins (Bhattacharyya et al., 2013). In addition, PtdSer liposomes compete for uptake of EBOV virus-like particles (VLPs) in mouse peritoneal macrophages (Jemielity et al., 2013). These data suggest these receptors are relevant for uptake into early infection targets.

PVEERs are also expressed in tissues that are later targets of virus spread. After infection by flaviviruses, Langerhans cells traffic to the lymph nodes (Johnston et al., 2000). Once there, flaviviruses infect lymph node DCs (Balsitis et al., 2009; Kyle et al., 2007), which have been shown to express TIM-4 (Kobayashi et al., 2007; Meyers et al., 2005). The alphavirus, Chikungunya virus, and filoviruses also replicate in lymph nodes (Geisbert et al., 2003a, 2003b; Labadie et al., 2010), where TIM-4, in conjunction with MFG-E8/integrin αvβ3 and αvβ5 (Hanayama et al., 2004; Garmy-Susini et al., 2007), may mediate infection. Infected APCs also traffic flaviviruses and filoviruses to the liver and spleen, two major sites of replication (Geisbert et al., 2003a; Jessie et al., 2004; Balsitis et al., 2009; Baskerville et al., 1985; Bhoopat et al., 1996). Expression of MFG-E8/integrin αvβ5 and TIM-4 has been detected in spleen (Meyers et al., 2005; Hanayama et al., 2004; Uehara and Uehara, 2014). In particular, TIM-4 is expressed on splenic macrophages (Kobayashi et al., 2007; Wong et al., 2010), a target of flaviviruses (Balsitis et al., 2009). TIM-1 and integrin αvβ5 have been detected on hepatocellular, Huh7-derived cell lines (Meertens et al., 2012; Kondratowicz et al., 2011) and Kupffer cells (Wheeler et al., 2001), respectively, and may contribute to flavivirus and filovirus infection of the liver (Geisbert et al., 2003b; Balsitis et al., 2009; Couvelard et al., 1999; Hall et al., 1991; Xiao et al., 2001; Ryabchikova et al., 1999). Flaviviruses also infect bone marrow myeloid cells (Jessie et al., 2004; Balsitis et al., 2009), which were recently shown to express TIM-4 after stimulation (Baghdadi et al., 2013).

PVEER expression does not appear to affect the tropism of every virus for which they enhance entry. For instance, Ross River, Chikungunya, and Sindbis virus infect muscle cells, which do not express any currently identified PVEERs (Morrison et al., 2006; Johnson, 1965; Ozden et al., 2007), suggesting that either other unidentified PVEERs exist or virus entry into muscle cells is independent of PVEER expression. Interestingly, the PtdSer-binding receptor BAI1 has been shown to be important for myoblast fusion (Hochreiter-Hufford et al., 2013). Although BAI1 does not effectively enhance virus entry in vitro (Meertens et al., 2012), it may contribute to virus entry in vivo in its native cell type and environment. This may also be the case for other PtdSer receptors that do not function as PVEERs in cell culture as the efficacy of these receptors was assessed after exogenous expression in cell types in which they are not endogenously expressed. Interestingly, PVEERs may also not function effectively in every cell population in which they are endogenously expressed as TIM-1 is present on some populations of T-cells (Meyers et al., 2005; Umetsu et al., 2005; Khademi et al., 2004), but, T cells are refractory to EBOV infection (Wool-Lewis and Bates, 1998). However, this may also be due to defects in virion internalization machinery or subsequent steps in the viral life cycle and not PVEER activity. Vaccinia virus does infect activated T-cells (Chahroudi et al., 2005) and in this case TIM-1 may contribute to entry. Nonetheless, the effect of PtdSer binding protein expression on virus tropism has not been thoroughly explored in tissue culture and, as discussed below, has yet to be assessed in vivo.

PtdSer-binding proteins without PVEER function

While some PtdSer-binding receptors function effectively as PVEERs, this is not true for all. Receptor for advanced glycation end-products (RAGE), brain-specific angiogensis inhibitor 1 (BAI1), CD300a, Stabilin-1 and -2, and TIM-3 have all been shown to bind to phosphatidylserine and enhance engulfment of apoptotic cells (Fig. 3) (DeKruyff et al., 2010; Hochreiter-Hufford et al., 2013; Park et al., 2007; He et al., 2011; Friggeri et al., 2011; Nakahashi-Oda et al., 2012; Simhadri et al., 2012; Park et al., 2008, 2009). However, expression of these proteins does not enhance virus entry (Meertens et al., 2012; Moller-Tank et al., 2013; Morizono and Chen, 2014). Of these proteins, only the mechanism responsible for reduced PVEER efficacy of TIM-3 has been studied. The inability of TIM-3 to serve as a PVEER is due to the absence of a MLD stalk of sufficient length (Moller-Tank et al., 2014). However, this may also explain the reduced efficacy of CD300a that, like TIM-3, binds PtdSer using an N-terminal IgV-like domain (Simhadri et al., 2012) and has a short stalk region between its IgV domain and the transmembrane domain.

Stabilin-1/-2 and BAI1 bind PtdSer through epidermal growth factor-like (EGF) domain repeats (Park et al., 2009; Kim et al., 2010; Park et al., 2008) and type 1 thrombospondin repeats (TSRs), respectively (Park et al., 2007) (Fig. 2), although the residues within these domains mediating PtdSer binding have yet to be identified. While it is unknown why these motifs are able to bind apoptotic cells, but not virions, none of the PtdSer binding receptors that function as PVEERs bind PtdSer using repeat regions. One explanation may be that the repeats require a larger or flatter surface area to bind PtdSer than a virion envelope allows. This biological conundrum requires

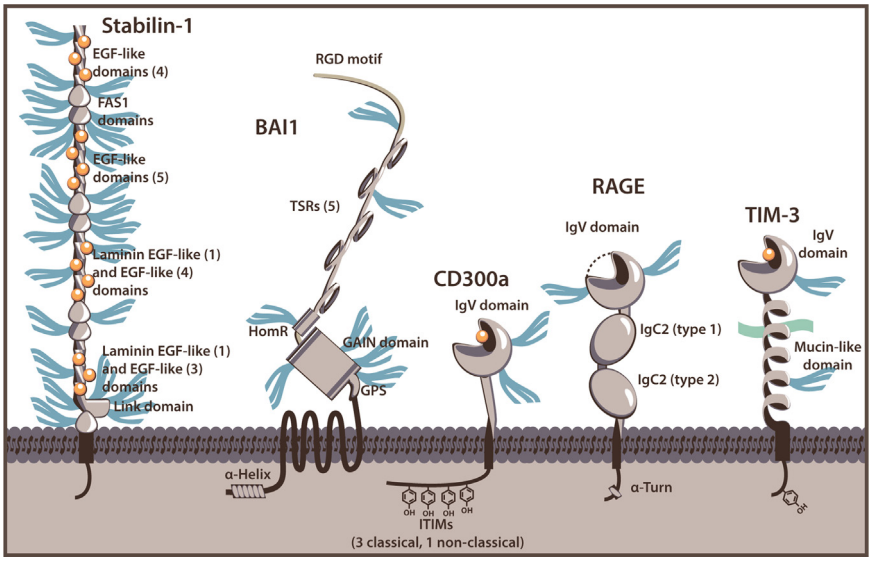

Fig. 3. PtdSer-binding receptors that do not function as PVEERs. Cartoon representations of Stabilin-1, BAI1, CD300a, RAGE, and TIM-3 are shown. Estimations of N-linked glycan sites are indicated with blue tridents and O-link glycosylation sites (TIM-3 only) are indicated with a green line. The binding pocket of the RAGE IgV domain is only hypothesized, as indicated by the presence of a dotted line. Domains for which calcium-binding is necessary for interaction with PtdSer are shown with calcium ions (orange spheres).

further examination and may provide insight for identification of other PVEERs.

RAGE is the only PtdSer receptor listed above for which the PtdSer-binding-domain is unidentified. The extracellular portion of RAGE consists of an N terminal IgV domain followed by two IgC2 domains (Fig. 3) (Park et al., 2010). The IgV domain of RAGE has been suggested to be responsible for PtdSer binding although this has not yet been experimentally shown (Fig. 2) (Friggeri et al., 2011). The lack of a similar PtdSer-binding pocket to that of the CD300a and TIM IgVs and inability to functionally replace the IgV domain of TIM-1 (SMT, unpublished data) would suggest at least the IgV domain of RAGE cannot bind to PtdSer on viral envelopes. Additionally, the condensed structure of the RAGE stalk provided by the IgC2 domains likely also further reduces PVEER efficacy by reducing overall length (Moller-Tank et al., 2014). Thus, both the absence of a clear PtdSer-binding pocket in the IgV domain and the short stalk likely explain the absent PVEER activity of RAGE.

Mechanism of virus entry enhancement

The key factors required for proteins to function as PVEERs are PtdSer-binding activity and attachment to the plasma membrane (Morizono et al., 2011; Meertens et al., 2012; Jemielity et al., 2013; Moller-Tank et al., 2013). While TIM-1 and TIM-4 individually perform both functions, the TAM receptors and αvβ3 or αvβ5 integrins provide membrane attachment and their ligands bind to PtdSer. In the case of the TIM family PVEERs, the spacer domain between the PtdSer-binding pocket and plasma membrane attachment is a MLD. MLDs from other molecules can substitute for the TIM MLDs, provided the MLD is of sufficient length, while the more compact structure of RAGE IgC2 domains is unable to substitute (Moller-Tank et al., 2014). These studies led us to propose that an extended structure was needed in the spacer region, perhaps to extend the PtdSer binding-pocket above the extracellular matrix that surrounds the cell (Moller-Tank et al., 2014). Thus, sufficient distance is necessary between the two essential functions of PVEERs for virus binding.

While we understand how PVEERs bind virus, much less is currently known about the pathways and/or mechanisms for PVEER mediated internalization of virus. There is no evidence for direct internalization. Ebola, baculo-, and vaccinia virus enter predominantly or at least partially through macropinocytosis (Mercer and Helenius, 2008; Aleksandrowicz et al., 2011; Nanbo et al., 2010; Kataoka et al., 2012; Saeed et al., 2010; Mulherkar et al., 2011) and these viruses are amongst those whose entry is most significantly enhanced by PVEER expression. However, entry of flaviviruses and alphaviruses is enhanced by PVEER expression, but primarily occurs through clathrin-mediated endocytosis (Chu and Ng, 2004; Peng et al., 2009; Acosta et al., 2009; Sourisseau et al., 2007; DeTulleo and Kirchhausen, 1998; Marsh et al., 1984). Thus, if PVEERs directly mediate virus internalization, there are currently no data to support entry via a single pathway. It is certainly possible that different PVEERs mediate uptake through different pathways. Alternatively, in some cases, PVEERs may function only as attachment factors to facilitate interaction of viral proteins with other cell surface receptors that trigger internalization. This may be true for New World arenaviruses that are known to enter cells using transferrin receptor 1 (Radoshitzky et al., 2007) and whose entry is only moderately enhanced by PVEER expression (Jemielity et al., 2013). However, this mechanism does not account for the ability of PVEERs to stimulate rapid uptake of viruses lacking a glycoprotein (Moller-Tank et al., 2013; Jemielity et al., 2013).

Incorporation of PtdSer into viral envelopes

Several viruses have been shown to expose PtdSer on the outer leaflet of their membrane (Soares et al., 2008; Morizono et al., 2011; Meertens et al., 2012; Moller-Tank et al., 2013). However, it remains to be determined how PtdSer, which is normally present within the inner leaflet of the cell membrane, is exposed on the outer leaflet of viral membranes. On cellular membranes the asymmetrical distribution of PtdSer is maintained by the activity of flippases and floppases that transfer phospholipids unidirectionally from either the extracellular side to the cytosolic side or the reverse, respectively (Leventis and Grinstein, 2010). Meanwhile, scramblases disrupt asymmetry by mediating random bidirectional transfer of phospholipids. In healthy cells, exposure of PtdSer can be induced by several mechanisms, including apoptosis and elevated levels of intracellular calcium (Leventis and Grinstein, 2010; Boon and Smith, 2002). Some viruses encode

proteins that increase cytosolic calcium levels such as Nef of HIV-1 (Manninen and Saksela, 2002) and p7 of hepatitis C virus (Griffin et al., 2003), reviewed in (Zhou et al., 2009), which may contribute to PtdSer exposure. Entry of flaviviruses into cells also increases intracellular calcium levels (Nour et al., 2013). It is also possible that cellular stresses associated with virus infection trigger apoptosis as is seen with influenza A (Shiratsuchi et al., 2000) and flaviviruses (Su et al., 2002; Liu et al., 2014; Desprès et al., 1996). There is evidence that West Nile, Sindbis, and Chikungunya virus actively activate apoptosis to their advantage (Yang et al., 2008; Krejbich-Trotot et al., 2011; Levine et al., 1993). In contrast, however, apoptosis is not induced in cells that are infected by Ebola viruses (Geisbert et al., 2000; Olejnik et al., 2013), although internalization of Ebola VLPs and infection of Ebola virus is still enhanced by TIM-1 expression (Jemielity et al., 2013; Moller-Tank et al., 2013; Kondratowicz et al., 2011). Further, some viruses for which entry is enhanced by PVEERs also encode anti-apoptotic genes, such as NS1 of vaccinia virus (Maluquer de Motes et al., 2011; Cooray et al., 2007) and P35 of baculovirus (Bertin et al., 1996). Thus, there is not a clear correlation between induction of apoptosis and incorporation of PtdSer on viral envelopes.

Viruses may not utilize cellular functions to induce PtdSer flipping, but rather, concentrate the limited PtdSer present on the outer leaflet. PtdSer may be incorporated into the outer leaflet of viral envelopes during budding for promotion of favorable membrane curvature (Graham and Kozlov, 2010). Alternatively, viruses may associate with PtdSer in the inner leaflet due to its anionic charge as has been suggested for the matrix proteins of Ebola virus (Adu-Gyamfi et al., 2013) and human immunodeficiency virus-1 (Chukkapalli et al., 2013; Vlach and Saad, 2013). The VSV matrix has also been shown to associate with PtdSer enriched domains (Luan et al., 1995). Thus, the inner leaflet would be enriched with PtdSer and, after budding, the absence of flippases that normally regulate PtdSer asymmetry may lead to equilibration of PtdSer between the outer and inner leaflets. Nonetheless, the expression of the matrix protein alone results in sufficient PtdSer accumulation on the outer leaflet of Ebola virus VLPs to allow for TIM-1 enhancement of internalization (Jemielity et al., 2013; Moller-Tank et al., 2013). These data suggest that regardless of the mechanism, activity of the matrix protein is sufficient for PtdSer incorporation into viral envelopes.

Uptake of apoptotic bodies by PVEERs and implications for virus entry

Assuming PVEER enhancement of virus entry occurs through misrecognition of viruses as apoptotic bodies, it stands to reason that the pathways of PVEER-mediated virus internalization overlap with those involved in apoptotic body uptake. Initially it was believed that apoptotic bodies were internalized through macropinocytosis (Hoffmann et al., 2001; Ogden et al., 2001) which involves the ruffling of membrane to form large cups that engulf fluid (Swanson, 1989). Macropinocytosis can be stimulated by receptor signaling induced by a variety of ligands including growth factors (Racoosin and Swanson, 1989) or PMA (Swanson, 1989). While spontaneous ruffling occurs (Sallusto et al., 1995), only signaling-induced macropinocytosis leads to complete closure of the macropinosomes (Li et al., 1997). Contrary to what was previously thought, studies using SEM revealed that while necrotic cells are taken up through macropinocytosis, apoptotic bodies are phagocytosed (Krysko et al., 2006). Unlike macropinocystosis, which does not specifically engulf cargo, phagocytosis involves direct interaction between ligands and receptors. Targets to be engulfed must be entirely covered in ligand and become enclosed as binding between receptor and ligand facilitates the binding of adjacent receptors to ligand (Griffin et al., 1976). This mechanism is appropriately compared to a zipper (Griffin et al., 1975).

In theory, phagocytosis would best explain the mechanism of PVEER-mediated internalization with PVEERs sequentially binding PtdSer on the virion surface. This is particularly fitting for TIM-1- and TIM-4-mediated internalization of apoptotic bodies, as they have been shown to form phagocytic cups around cargo (Ichimura et al., 2008; Wong et al., 2010). However, both PtdSer and VLPs have been shown to induce macropinocytosis (Aleksandrowicz et al., 2011; Hoffmann et al., 2001). Additionally, amiloride and its derivative 5-(N-Ethyl-N-isopropyl) amiloride (EIPA), considered specific inhibitors of macropinocytosis (West et al., 1989) and not phagocytosis (Fukushima et al., 1996), inhibit Ebola virus uptake into and infection of Vero cells or SNB19 cells that express TIM-1 and Axl respectively (Kondratowicz et al., 2013; Saeed et al., 2010; Mulherkar et al., 2011; Hunt et al., 2011). Thus, there exists disparity between mechanisms of apoptotic body and virus uptake. Some of this confusion may be attributed to many components being shared between phagocytosis and macropinocytosis. Both require phosphoinositide 3-kinase (PI3K) signaling (Araki et al., 1996), phospholipase Cγ (Amyere et al., 2000; Cheeseman et al., 2006), Rac1 (Caron and Hall, 1998; Ridley et al., 1992), and dynamin (Liu et al., 2008; Cao et al., 2007; Gold et al., 1999; Tse et al., 2003), making differentiation between the two processes by targeting components difficult. The only macropinocytosis specific inhibitor, EIPA, functions by deregulating intracellular pH and thus may disrupt additional aspects of the viral life cycle that contribute to inhibition of virus infection (Koivusalo et al., 2010).

Neither phagocytosis nor macropinocytosis have been studied in the context of PVEERs. Phagocytosis is associated with phagocytic cells such as macrophages and dendritic cells (Rabinovitch, 1995), while all cells can initiate macropinocytosis. It is possible that both mechanisms are being used and are cell-type dependent. For example Ebola virus initially infects macrophages and dendritic cells, which may occur through phagocytosis, and subsequently spreads and enters a broad variety of tissues and cell types, perhaps by macropinocytosis (Feldmann and Geisbert, 2011). Interestingly, receptors that induce either phagocytosis or macropinocytosis require phosphorylation and recruitment of kinases and adapter proteins (Sobota et al., 2005; Swanson, 2008), but several PVEERs have been shown not to require signaling through cytoplasmic tails for internalization of virus (Meertens et al., 2012; Moller-Tank et al., 2014; Bhattacharyya et al., 2013).

Neither phagocytosis nor macropinocytosis of have been shown to be directly elicited by PVEERs. While Axl has been associated with macropinocytosis in some cells (Hunt et al., 2011), it is unknown whether Axl triggers macropinocytosis. There are, however, several studies that show PtdSer receptors coordinate to induce uptake signaling. In macrophages there is evidence that Mer induces internalization of apoptotic bodies, but requires TIM-4 for initial attachment due to a higher binding affinity for PtdSer (Nishi et al., 2014). Mer has also been shown to work synergistically with integrin αvβ5 (Wu et al., 2005). Similarly, TIM-4 and MFG-E8 have been implicated as partners for uptake of apoptotic bodies in which MFG-E8/integrin signaling triggers uptake (Toda et al., 2012). Several details of these mechanisms remain to be elucidated, such as whether or not TIM-4 actively associates with signaling partners. TIM-4 has also been shown to interact with adenosine monophosphate activating kinase (AMPK) (Baghdadi et al., 2013), a protein important for macropinocytosis of Ebola and vaccinia virus (Kondratowicz et al., 2013; Moser et al., 2010). However, this interaction is believed to occur after phagocytosis and does not explain how initial internalization events are triggered. This is also complicated by evidence that the cytoplasmic tail of TIM-4, the only domain accessible to AMPK, is unnecessary for internalization (Park et al., 2009). Further, these mechanisms do not explain why entry of

viruses that utilize clathrin-coated pits is enhanced by PVEER expression. Thus, additional studies are required to determine if and how PVEERs contribute directly to internalization.

Viruses that do not utilize PVEERs

As mentioned above, PVEER expression does not enhance entry of all enveloped viruses into every cell type. In the case of arenaviruses, there exists an interesting dichotomy between the ability of PVEERs to enhance entry of New World but not Old World arenaviruses. Unlike for filo-, baculo-, alpha-, vaccinia, and flaviviruses, definitive cellular receptors have been identified for both Old World and New World arenaviruses: α-dystroglycan (Cao et al., 1998) and transferrin receptor 1 (Radoshitzky et al., 2007; Abraham et al., 2009), respectively. These viruses also use different entry pathways as New World arenaviruses such as Junín virus enter using clathrin coated pits (Martinez et al., 2007) while Old World arenaviruses such as Lassa and lymphocytic choriomeningitis virus use an unknown pathway that is clathrin, caveolin, and dynamin independent (Rojek et al., 2008a, 2008b). PVEER-mediated enhancement of some New World arenaviruses entry into TIM-1 expressing HEK 293T cells is more modest than that found with filoviruses and flaviviruses, but still significant (Jemielity et al., 2013; Moller-Tank et al., 2013). These New World arenaviruses can bind to host cells and mediate efficient entry through interaction with transferrin receptor 1, and this can clearly be supplemented by PVEER expression. For Old World arenaviruses, expression of and/or affinity to α-dystroglycan may be sufficiently robust that PVEER expression does not notably enhance entry further. Indeed, in cells lacking α-dystroglycan, other attachment factors, including Axl, can enhance Old World arenavirus entry (Shimojima et al., 2012). However, PVEERs are likely not biologically relevant for Old World arenavirus entry as α-dystroglycan expression is ubiquitous (Cao et al., 1998; Sullivan et al., 2013).

When carrying its native glycoprotein, entry of VSV is in most cases, like the Old World arenaviruses, not enhanced by PVEER expression (Table 1). However, in a few cases we (unpublished data) and others (Jemielity et al., 2013) have observed a slight increase in VSV G-mediated entry into cells expressing PVEERs. The modest effect of PVEER expression on VSV entry is not due to an absence of PtdSer on the viral envelope as PtdSer can be readily detected on VSV pseudovirions (Moller-Tank et al., 2013). Instead, as we propose above for LASV, the utilization by VSV of PVEERs would be anticipated to be dependent upon the relative availability of its native receptor. If the native glycoprotein of VSV is sufficient for optimal virus binding to and entry into cells, PVEER expression would make little to no contribution to VSV entry.

Entry of SARS corona-, influenza A, and herpes simplex 1 viruses is not enhanced by PVEER expression (Meertens et al., 2012; Jemielity et al., 2013). Influenza A and SARS-CoV have viral envelope proteins that bind effectively to sialic acid (Weis et al., 1988) and ACE2 (Li et al., 2003) respectively. Expression of TIM-1 on HEK 293T cells enhances internalization of pseudovirions bearing either envelope protein, but does not result in enhancement of transduction (Jemielity et al., 2013). These results indicate that PVEER-mediated or -enhanced internalization results in unproductive infection by these viruses. This could occur due to virions being delivered to compartments with incompatible conditions for fusion (i.e. lacking correct pH or fusion triggers). An alternative possibility is that PVEERs enhance internalization of defective SARS or influenza virions with low or negligible levels of glycoprotein on the viral envelope. These particles would not effectively bind cellular receptors or be able to fuse, and thus their enhanced internalization would not contribute to infection. Internalization into endosomes may similarly inhibit entry of herpes simplex virus 1, which fuses at the cell surface (Akhtar and Shukla, 2009). However, as the effects of PVEER expression on herpes simplex virus 1 internalization have not been tested, it is possible that, in a manner similar to that proposed for Old World arenaviruses and VSV, strong association with cellular receptors masks any enhancement. Interestingly in all cases, PVEER overexpression on permissive cells does not appear to inhibit overall virus entry, suggesting that either a majority of these viruses either escapes these compartments or enters through natural productive routes.

In vivo relevance of PVEERs

A major question remaining regarding PVEER-mediated enhancement of virus entry is its relevancy in vivo. The efficacy of PVEERs on wild-type infectious virus has been demonstrated in vitro with virus harvested from both cell culture and mice (Jemielity et al., 2013; Moller-Tank et al., 2013). Additionally, entry of Ebola virus VLPs into mouse peritoneal macrophages is inhibited by PtdSer liposomes, providing evidence of PVEER importance for filovirus entry into relevant primary cell populations (Jemielity et al., 2013). However, to date only limited studies have been done in mice to determine the effect of PtdSer-binding inhibitors and none using PVEER knock down or knock out. Difficulty of testing in vivo relevancy of PVEERs using knockout mice arises from the potential for compensation by other PVEERs. Additionally, many PVEERs play critical roles in regulating adaptive immunity and single or combination knockout of genes could make interpretation of results difficult and/or lead to development of autoimmunity (Rodriguez-Manzanet et al., 2010; Hanayama et al., 2004; Miyanishi et al., 2012; Xiao et al., 2012; Li et al., 2013). Nonetheless, in a single study, a chimeric antibody that recognizes PtdSer was shown to inhibit infection by the New World arenavirus, Pichinde (Soares et al., 2008). Future studies will benefit from the development of a broad PtdSer-binding inhibitor that can target multiple PVEERs.

Conclusions

Utilization of PtdSer-binding proteins by viruses to enhance internalization provides a broad mechanism of viral entry with little investment by the virus itself. This mechanism may allow some viruses to attach to cells, thereby making viral glycoprotein/cellular receptor interactions more probable. Alternatively, other viruses may rely entirely on PVEERs for internalization into endosomes. This latter mechanism would eliminate the need of viruses to expose sensitive viral epitopes extracellularly, thereby protecting critical receptor binding or membrane fusion motifs from neutralizing antibodies. Once virions are internalized into endosomes, glycoprotein structural alterations that lead to membrane fusion can occur unhindered by antibodies. Additionally, the broad expression of PVEERs might contribute to the extensive tropism of viruses such as flaviviruses and alphaviruses that infect a broad array of insect and mammalian hosts.

Many questions still remain regarding PVEER-mediated entry. Although there is preliminary evidence as discussed above, the most important question is what is the in vivo significance of PVEERs and their relative contribution to infection? If PVEER utilization by viruses in vivo proves to be important, a model for testing inhibitors of PtdSer binding by PVEERs would be valuable and could lead to development of a single antiviral or cocktail capable of inhibiting multiple human viruses. However, as PVEER expression does not enhance entry of all enveloped virus families, targeting of PVEERs as an antiviral therapeutic may be limited to those such as the filoviruses and flaviviruses. Nonetheless, these viral families include highly pathogenic viruses for which limited antivirals are available. Second, how is PtdSer being incorporated into viral envelopes and does it matter which membrane the envelope is derived from? Third, what is the mechanism

mediating PVEER-dependent entry? Is there a mechanism of direct internalization that results in productive infection? Is any cell signaling involved in these events? Finally, are there additional unidentified PVEERs that contribute to this newly appreciated means of viral infection? This may include potential PtdSer receptors that have not been tested as PVEERs. CD36, for example, has been shown to bind oxidized PtdSer for uptake of apoptotic cells into macrophages (Driscoll et al., 2013; Greenberg et al., 2006). HEK 293 T cells do not express a detectable amount of the identified PVEERs on their surface by surface staining, yet support low but detectable levels of transduction of filoviruses, flaviviruses, and alphaviruses. Certainly one possibility is that there are additional undiscovered PVEERs mediating entry. Alternatively, while studies detecting expression of Tyro3 and Mer on HEK 293T cells have been contradictory, low levels of expression may allow for entry (Morizono et al., 2011; Bhattacharyya et al., 2013; Shimojima et al., 2006). Further research on these receptors will elucidate these gaps in knowledge and determine feasibility of broad-spectrum antivirals to target them.

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