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Receptors in Host Pathogen Interactions between Human Cytomegalovirus and the Placenta during Congenital Infection

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KS, STH, AWS, NJH and WDR designed the review, reviewed the results of the search strategy, wrote, and edited the manuscript. All authors reviewed the manuscript before submission.

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Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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We declare no competing interests.

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Summary

Cellular receptors in human cytomegalovirus (HCMV) mother to child transmission play an important role in congenital infection. Placental trophoblast cells are a significant cell type in placental development, placental functional processes, and in HCMV transmission. Different cells within the placental floating and chorionic villi present alternate receptors for HCMV cell entry. Syncytiotrophoblasts present neonatal Fc receptors that bind and transport circulating maternal IgG across the placental interface which can also be bound to HCMV virions, facilitating viral entry into the placenta and fetal circulation. Cytotrophoblasts express HCMV receptors including integrin- $\alpha 1\beta 1$, integrin- $\alpha V\beta 3$, epidermal growth factor receptor (EGFR) and platelet-derived growth factor receptor alpha (PDGFR α). The latter interacts with HCMV glycoprotein-H, glycoprotein-L and glycoprotein-O (gH/gL/gO) trimers (predominantly in placental fibroblasts) and the gH/gL/pUL128, UL130-UL131A pentameric complex in other placental cell types. The pentameric complex allows viral tropism of placental trophoblasts, endothelial cells, epithelial cells, leukocytes and monocytes. This review outlines HCMV ligands and target receptor proteins in congenital HCMV infection.

Abbreviations

cCMV	Congenital cytomegalovirus
EGFR	Epidermal growth factor receptors
FcRn	Neonatal Fc receptors (FcRn)
GCV	Ganciclovir
gB	Glycoprotein B
gH	glycoprotein-H
gL	glycoprotein-L
gM	glycoprotein-M
gN	glycoprotein-N
gO	glycoprotein-O
HCMV	Human Cytomegalovirus
HSPG	Heparan sulfate proteoglycans
IgG	Immunoglobulin G
MTCT	Mother to child transmission
Nrp2	Neuropilin 2
PDGFR α	Platelet-derived growth factor receptor alpha
THY-1	Cell receptor CD90
VACV	Valaciclovir
VGCV	Valganciclovir

1. Introduction

Human cytomegalovirus (HCMV) infection of the fetus is the leading viral cause of congenital birth defects worldwide, with a birth prevalence of ~0.64% in developed countries^[1]. Long term sequelae include neurodevelopmental disability, cerebral palsy, and sensorineural hearing loss^[2-4]. In severe cases, fetal infection can result in fetal and neonatal death^[5, 6].

Receptor mediated signalling between the virus and host cells play an important role in HCMV pathogenesis, viral dissemination^[7] and immune evasion^[8]. Identifying the communication between viral ligands and their host receptor proteins informs the development of vaccine and antiviral therapies. For example, the recent vaccine candidate gB/MF59 elicits an immune response against HCMV ligand gB^[9] with varying efficacy in HCMV seronegative women^[9-12]. At present, studies have evaluated the safety and efficacy of HCMV hyperimmunoglobulin therapy as a potential means of preventing mother to child transmission (MTCT) and treatment of fetal congenital cytomegalovirus (cCMV) disease and infection^[13-16]. However there are inconsistencies in effectiveness of treatment noted during studies of hyperimmunoglobulin therapy^[17, 18] and a recently completed phase III clinical trial, showed no evidence of efficacy^[19].

Antiviral therapies to prevent MTCT during pregnancy in mothers with primary HCMV infection have also been investigated with recent clinical trials and case studies involving valaciclovir (VACV), yielding promising outcomes^[20, 21]. Further clinical investigations of other antivirals, ganciclovir (GCV) and its oral prodrug valganciclovir (VGV), have demonstrated some efficacy in the treatment of hearing loss progression in congenitally infected newborns^[22]. However, due to significant toxicity and teratogenicity issues with GCV and VGV, their use is not recommended during pregnancy^[18, 23].

As transmission efficiency within the placenta is a key determinant of MTCT, better understanding of the receptors for HCMV, and ligand signalling occurring during this process, is essential for development of novel therapeutic approaches. The current paradigm considers fetal transmission of HCMV to occur at the maternal basal decidua. The decidua is thought to function as a reservoir for HCMV replication during the first trimester, and acts as the source of transmission to the connected fetal tissue and invading placenta^[24, 25]. The intrauterine-placental interface contains a vast number of proliferating immune cells, epithelial cells and endothelial cells, which are also likely HCMV targets for viral tropism^[26, 27]. However, the haematogenous spread of HCMV appears to be the most common route of placental and fetal infection and studies suggest trophoblast layers surrounding placental villi play a major role in the materno-fetal transmission of HCMV^[28-31].

Understanding the specific HCMV ligands that bind to host proteins at the uterine-placental interface and facilitate infection is fundamental to interventions to reduce congenital infection. This review explores current knowledge of receptors involved in congenital HCMV infection, and the potential role of these in maternal-fetal transmission.

2. Current model of placental tropism

The placental villous surface is comprised of two major cell populations, the inner cytotrophoblasts and outer syncytiotrophoblasts^[32]. During the first trimester, cytotrophoblasts fuse to form the syncytiotrophoblast, a specialised multinucleated epithelial like layer on the surface of the chorionic 'floating' villi. This syncytiotrophoblast layer allows nutrient, gas, waste and immunoglobulin transfer between maternal to fetal blood. Underneath the specialised syncytiotrophoblast layer, proliferative cytotrophoblasts propagate, and the cytotrophoblasts of the anchoring villi, invade the maternal basal decidua (Figure 1).

Transmission of HCMV to the fetus can result from either a primary maternal infection, reinfection with a different HCMV strain or reactivation of latent maternal virus during pregnancy. Decidual leukocytes and monocytes infected with latent HCMV can reactivate during cytotrophoblast endometrial decidua invasion during early placental development^[33] [34] and are capable of producing lytic cycle transcripts essential for virus replication^[35]. This allows latently infected immune cells to replicate in the maternal decidua during HCMV reinfection or reactivation^[36, 37]. Irrespective of the type of maternal infection (primary or non-primary), HCMV is capable of infecting both cytotrophoblasts and syncytiotrophoblasts of the chorionic and anchoring villi^[38-41].

Syncytiotrophoblasts express epidermal growth factor receptors (EGFR) needed for HCMV entry^[42]. However, key integrin receptors $\alpha 1\beta 1$ and $\alpha V\beta 3$ are absent from these cells^[43-45] and it is believed HCMV virion particles cannot enter the syncytiotrophoblast layer without the presence of neonatal Fc receptors (FcRn) expressed on the cell surface^[46, 47]. The underlying cytotrophoblast layer of the chorionic villi, and the cytotrophoblasts that aggregate into cell columns to form the anchoring villi, both express receptor integrins $\alpha 1\beta 1$ and $\alpha V\beta 3$, as well as platelet derived growth factor receptor alpha (PDGFR α), which enable virion attachment and entry^[31, 48-50].

Expression of FcRn on first trimester syncytiotrophoblasts is believed to allow binding of maternal IgG-virion complexes, which are then endocytosed and sequestered within caveosomes^[51-53]. This process of IgG transport across the floating villi to the fetal tissues is thought to be a key component of the stimulation of maternal innate immunity^[54-56]. The avidity and titre of maternal neutralising antibodies prior to the transport of IgG-virion complexes across the surface of the syncytiotrophoblast is crucial in determining the efficiency of vertical transmission^[57]. Low avidity maternal neutralising antibodies have been shown to promote HCMV infection of the underlying cytotrophoblasts within anchoring villi^[46, 58]. The

internalisation of maternal IgG-virion complexes via FcRn expressed on syncytiotrophoblasts mediates HCMV infection of the underlying cytotrophoblasts^[59].

The broad tropism of HCMV for host cells is associated with two essential viral ligands, i) glycoprotein-H, glycoprotein-L and glycoprotein-O (gH/gL/gO) trimeric complex and/or ii) gH/gL/gpUL128, gpUL130 and gpUL131 pentameric complex. The specificity of HCMV trimeric complexes and pentameric complexes allows HCMV tropism for placental cell types where the former favours tropism for fibroblast cells while the latter mediates viral entry into cytotrophoblasts, endothelial cells, epithelial cells and local monocytes.

3. HCMV Ligands

The HCMV virion envelope contains at least 25 membrane glycoproteins^[60]. Of these, two major glycoproteins, glycoprotein-B (gB) and the heterodimer glycoprotein-H and glycoprotein-L (gH/gL) are conserved *Herpesviridae* ligands that mediate viral entry through membrane fusion to most target cells [61-67] (Table 1). Glycoprotein-O^[62, 68], glycoprotein gpUL132^[69] and gpUL33^[70, 71] are unique to the *Betaherpesvirinae* subfamily and are mediators of viral envelope fusion and entry yet some do not play a role in viral replication^[72-74].

3.1 Glycoprotein-B (gB)

Glycoprotein-B is a core component of the herpesvirus class III membrane fusion proteins with studies identifying gB as an important ligand for viral cell attachment and entry^[44, 75-77]. A number of cell surface proteins such as EGFR^[42, 78], PDGFR α ^[60, 79, 80] and receptor integrins^[44, 81, 82] act as receptors for HCMV gB. Furthermore, vaccines targeted at HCMV gB induce the

production of neutralising antibodies that are a composite of antibody against gB, and the trimeric complex or the pentameric complex in HCMV seropositive test subjects^[83, 84] indicating gB undergoes complex formation. The activation of gB to mediate viral envelope fusion to host cell membranes induces a conformational change in the structure of gB which allows formation of complexes with other HCMV glycoproteins^[83].

3.2 Glycoprotein-H/Glycoprotein-L (gH/gL) are important to HCMV infection

One of the herpesvirus mechanisms for viral envelope fusion involves the heterodimer gH/gL that is co-expressed with gB^[85] on the surface of the virion. The heterodimer gH/gL also forms complexes with gO^[86] for the trimeric complex or gpUL128-131A for the pentameric complex^[87]. The gH/gL heterodimer is essential for HCMV membrane fusion as extracellular virions do not express gH/gL independently for viral entry and the ratio of gH/gL/gO trimeric complex to pentameric expression varies between different HCMV strains^[88]. However, glycoprotein-O from the trimeric complex and the protein products of gpUL129-131A from the pentameric complex compete for adhesion sites on the heterodimer gH/gL, suggesting that gH/gL dimer complex formation and modification with other HCMV glycoproteins is essential for viral entry and tropism of host cells^[88].

3.3 Glycoprotein-M (gM)/Glycoprotein-N (gN)

The gM/gN heterodimer forms one of the most abundant glycoprotein complexes on the HCMV viral envelope^[89]. The gM/gN complex is an important determinant of tropism during host cell infection as one of the few viral envelope glycoproteins conserved among beta-herpesviruses^[90]. One of the earliest reported receptors for HCMV gM/gN was shown to be heparan sulfate proteoglycans (HSPGs) expressed on the cell surface of host fibroblasts. These mediate

attachment^[91], virion assembly and replication^[92, 93]. In addition, the gM/gN heterodimer was shown to induce humoral responses during infection^[93] and polymorphisms within the gene encoding for gN mediated immune evasion^[94].

3.4 Trimeric complex gH/gL/gO

The gH/gL heterodimer is disulphide linked to gO to form the trimeric complex gH/gL/gO^[95, 96]. HCMV utilises the trimeric complex for entry into fibroblast cells via pH independent membrane fusion^[88]. Other reports have implicated two host receptor targets for the HCMV trimeric complex, PDGFR α for infection of fibroblast cells^[50, 97] and EFGR for the tropism of monocytes^[78]. The trimeric complex favours viral entry of fibroblasts however the gH/gL dimer still plays a role in the infectivity of epithelial and endothelial cells when targeted for viral tropism via the pentameric complex^[98].

3.5 Pentameric complex gH/gL/gpUL128, gpUL130, gpUL131

The pentameric complex consists of the gH/gL heterodimer linked to the protein products of the UL128 locus (UL128, UL130 and UL131). The UL128 locus was shown in two observational studies to not play a role in tropism for fibroblasts^[99, 100]. However, the protein products of the UL128 locus are required for infection of macrophage, dendritic cells, epithelial cells, and endothelial cells^[95, 101, 102]. The pentameric complex mediated entry process for HCMV into epithelial cells and endothelial cells requires a stable complex between the gH/gL dimer and the fusogen gB to initiate host cell membrane fusion^[76]. Further, it is believed that this mode of pentameric complex mediated entry for HCMV involves endocytosis of virions at low pH once viral envelope attachment has been established^[103].

Studies exploring the role of maternal immune responses against the HCMV pentameric complex during placental tropism quantified the IgG antibody expression profile in transmitting and non-transmitting mothers during maternal primary HCMV infection^[104]. One study showed antibodies against the pentameric complex are highly abundant in non-transmitting mothers compared to transmitting mothers during the first 30 days of infection^[104]. Recently, two receptors have been implicated as targets for pentameric complex-mediated tropism of host cells. These targets are olfactory receptor OR14I1 for epithelial cells^[105] and neuropilin 2 (Nrp2) for endothelial and epithelial cells^[106].

4. Host Cell Receptors for Human CMV tropism in trophoblasts

Growth factor receptors (GFRs) and integrins play key roles in CMV cell entry. They also synergistically regulate similar signalling pathways that are important for endocytosis and numerous cellular functions (as reviewed in^[107]). GFRs and integrins often colocalise at the cell surface and can cooperate at many different levels including linking for ligand recognition and intracellular signalling. The GFRs Platelet Derived Growth Factor Receptor alpha (PDGFR α) and Epidermal Growth Factor Receptor (EGFR) along with integrins α 2 β 1, α 6 β 1, α V β 3, β 4, β 5 and β 6 have been demonstrated to facilitate CMV entry.

4.1 Platelet Derived Growth Factor Receptor alpha (PDGFR α)

Virus entry into fibroblast cells, which transiently express PDGFR α , is likely mediated through binding of the HCMV gO subunit and not gB as suggested by Stegmann and colleagues^[108, 109]. Inhibition studies have characterised the interaction between PDGFR α and the HCMV trimer complex using solubilised PDGFR α ^[50]. The authors demonstrated that viral inhibition of both endothelial and fibroblast cells can be achieved using solubilised PDGFR α -Fc chimeras.

However, knockdown of PDGFR α expression only prevents infection of fibroblasts but not endothelial cells suggesting an indirect mechanism for tropism of endothelial cells^[79]. The inhibition of HCMV viral entry into endothelial cells was shown using soluble receptor PDGFR α -Fc chimera incubated with the virus allowing saturation of the trimer complex before infection of endothelial cells. As demonstrated by Zhou and colleagues, the trimer complex does play a role in viral entry of endothelial and epithelial cells suggesting saturation of the trimer complex by solubilised PDGFR α Fc chimera molecules may be the reason for inhibition of endothelial infection^[88, 108].

4.2 Integrins: $\alpha 2\beta 1$ integrin, $\alpha 6\beta 1$ integrin, $\alpha V\beta 3$ integrin

Herpesviridae are known to target receptor integrins on the cell surface for viral attachment and entry^[110]. Within the placental villi, syncytiotrophoblasts express the virion receptor EGFR but lack integrin co-receptors to mediate HCMV attachment^[31]. However, cytotrophoblasts in the placental cell column express EGFR and integrin $\alpha V\beta 3$, allowing HCMV attachment^[111]. Within the maternal basal decidua, invasive cytotrophoblasts expressing both EGFR and integrin co-receptors $\alpha 1\beta 1$ and $\alpha v\beta 3$ have shown to be highly susceptible to HCMV infection thereby allowing viral tropism in villous trophoblasts^[31]. Notably, integrins $\alpha 2$, $\alpha 6$ and $\beta 1$ are also reported to play a role during HCMV entry post viral envelope attachment to host cells^[44, 82, 112]. Additionally, integrin $\alpha v\beta 3$ has been shown to interact with the cell receptor CD90 (THY-1) to mediate macropinocytosis, a mechanism of viral entry into macrophages and monocytes for HCMV and other viruses^[113-115]. THY-1 has been reported to initiate HCMV entry into target cells by interacting with both gH and the fusogen gB^[116].

4.3 Epidermal Growth Factor Receptor (EGFR)

The cellular growth factor receptor, EGFR, acts as a HCMV receptor for viral entry of epithelial cells through its interaction with HCMV ligand gB by allowing attachment and downstream induction of phosphoinositide 3-kinases activity^[42]. The rapid phosphorylation of EGFR was demonstrated in trophoblasts^[49] following infection with HCMV. Further, Maidji and colleagues demonstrated that EGFR expression was required for viral entry into cytotrophoblasts^[31]. However, subsequent studies have reported that EGFR does not mediate entry into fibroblasts^[85] and others have shown that PDGFR α instead of EGFR is required for efficient viral entry of fibroblasts^[60] and trophoblasts^[80]. Interestingly studies demonstrate that EGFR plays a key role in HCMV persistence and dissemination, with evidence indicating that viral tropism of monocytes relies on the activation of EGFR^[78, 117]. Similarly, HCMV haematogenous dissemination and latency in haematopoietic cells was shown to rely on the activation of EGFR^[117].

5 Do other Non-Placental Host Cell Receptors play a role in Congenital Infection?

The early maternal-fetal microenvironment is composed of differentiating embryonic cells, forming the trophoblast and subsequently differentiating into trophoblasts. This is supported by maternal endothelial, epithelial, myometrial, decidual and lymphoproliferative immune cells.

There are a number of receptors found on epithelial and endothelial cells that have been implicated during HCMV dissemination and infection^[26, 96, 118, 119]. However their role in host pathogen interactions within the placenta during congenital infection continues to be identified in clinical and *in vivo* studies (Table 2).

Recently, Nrp2 was identified as a receptor for the pentameric complex to facilitate entry into endothelial and epithelial cells^[106]. Similarly, olfactory receptor OR14I1 was found to be a pentameric specific receptor for viral tropism of endothelial and epithelial cells^[105]. The olfactory receptor OR14I1 mediates pH dependent endocytic entry of virions into epithelial cells, which constitutes a large number of basal decidual cells within the maternal placenta (Table 1). However, the transient expression of OR14I1 within the placenta remains to be established.

One likely explanation for HCMV infection of the maternal decidua is viral tropism of monocytes circulating at the materno-fetal interface of the placenta^[25, 36, 45, 52]. Viral entry into monocytes is dependent on the cell surface receptor THY-1 which engages $\alpha\text{v}\beta\text{3}$ integrins to allow adhesion of HCMV via glycoproteins gH and gB^[113, 116]. Macrophages found in the placenta are also known targets for HCMV replication^[120, 121]. The viral tropism of macrophages is enhanced by the surface receptor tetherin, which is an interferon inducible glycosylated transmembrane protein that promotes entry of HCMV virions into macrophages^[122]. Other host glycoproteins, such as HSPGs can also act as receptors for HCMV in macrophages and fibroblasts^[123, 124]. Fibroblasts and macrophages which express HSPGs have been reported by Kari and colleagues to bind gB and the heterodimer complex gM/gN to mediate virus adsorption on the host cell surface^[91, 109, 124, 125].

Non-placental host cell receptors are absent at the materno-fetal interface. However they do provide a possible mechanism for HCMV dissemination at the maternal basal decidua. During maternal infection, virion binding and replication within endothelial cells and leukocytes can mediate infection of circulating macrophages^[126, 127]. This allows the maternal basal decidua to act as a viral reservoir for vertical transmission during fetal development^[111, 128].

6 Concluding Remarks

This review provides new information about host cell receptors and their interaction with viral ligands during congenital HCMV infection. However, the mode of HCMV entry via host receptors continues to be further defined. Recent advances in the field have shed light into how vaccine strategies involving immune responses against viral ligands may be effective in the prevention of HCMV congenital infection. Further, they demonstrate the importance of host cellular receptors on non-placental cells as key components of HCMV dissemination during maternal infection. This suggests that non-placental host receptors should be considered during development of vaccine and treatment strategies targeting congenital HCMV which is pivotal in the prevention of HCMV infection.

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Table 1: HCMV protein complexes and their respective host receptor targets for viral entry.

Host Cell Type	Viral Complex	Host Cell Surface Receptors	References
Epithelial cells	gH/gL/gpUL128,130,131	Nrp2, OR14I1	[105, 106]
Endothelial cells	gH/gL/gpUL128,130,131	Nrp2, OR14I1	[105, 106]
Fibroblasts	gH/gL/gO gM/gN	PDGFR α , α 1 β 1, α V β 3 HSPGs	[31, 75, 79, 82] [91, 124]
Monocytes	gM/gN gB/gH	BST2/Tetherin THY-1, α 1 β 1, α V β 3	[122] [113, 116, 129]

Table 2: HCMV viral complexes and their respective trophoblast receptor targets for placental tropism at first trimester.

Host Cell Type	Viral Complex	Host Cell Surface Receptors	References
Invasive Cytotrophoblasts (Distal)	gB/gH gH/gL/gpUL128,130,131	EGFR, α 1 β 1, α V β 3, β 4, β 5, β 6	[31, 130, 131]
Villous Cytotrophoblasts	gH/gL/gO gH/gL/gpUL128,130,131	EGFR, β 4, β 5, α V β 6 PDGFR α	[130, 132] [80]
Syncytiotrophoblasts	gH/gL/gO	FcRn	[46]

Figures

Figure 1: The receptors involved during HCMV infection at the uterine-placental interface on placental cells. The surface layer is composed of the multinucleated syncytiotrophoblast layer and an underlying cytotrophoblasts layer, which covers the chorionic floating villi (villous cytotrophoblasts) and anchoring villous (invasive cytotrophoblasts). The invasive cytotrophoblasts (distal) express key integrin receptors and EGFR or PDGFR α during their migration towards the maternal basal decidua blood vessels. The syncytiotrophoblast layer is bathed in maternal blood and circulating IgG-virion complexes, allowing viral attachment and entry via FcRn.

