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ORIGINAL PAPER

Heterogeneous Pathways of Maternal-fetal Transmission of Human Viruses (Review)

A. Saleh Younes · Márta Csire · Beatrix Kapusinszky · Katalin Szomor · Mária Takács · György Berencsi

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Abstract Several viruses can pass the maternal-fetal barrier, and cause diseases of the fetus or the newborn. Recently, however, it became obvious, that viruses may invade fetal cells and organs through different routes without acute consequences. Spermatozoa, seminal fluid and lymphocytes in the sperm may transfer viruses into the human zygotes. Viruses were shown to be integrated into human chromosomes and transferred into fetal tissues. The regular maternal-fetal transport of maternal cells has also been discovered. This transport might implicate that lymphotropic viruses can be released into the fetal organs following cellular invasion. It has been shown that many viruses may replicate in human trophoblasts and syncytiotrophoblast cells thus passing the barrier of the maternal-fetal interface. The transport of viral immunocomplexes had also been suggested, and the possibility has been put forward that even anti-idiotypes mimicking viral epitopes might be transferred by natural mechanisms into the fetal plasma, in spite of the selective mechanisms of apical to basolateral transcytosis in syncytiotrophoblast and basolateral to apical transcytosis in fetal capillary endothelium. The mechanisms of maternal-fetal transcytosis seem to be different of those observed in differentiated cells and tissue cultures. Membrane fusion and lipid rafts of high cholesterol content are probably the main requirements of fetal transcytosis. The long term presence of viruses in fetal tissues and their interactions with the fetal immune system might result in *post partum* consequences as far as increased risk of the development of malignancies and chronic pathologic conditions are discussed.

Keywords Syncytiotrophoblast · Fetal endothelium · Virus transcytosis · Maternal-fetal transport

Abbreviations

AAV	adeno-associated parvovirus
CXCR-4	co-receptor of HIV (chemokine receptor)
CXCL-12	chemokine receptor
EBV	Epstein-Barr virus
Env	viral envelope
FcR	Fc-receptor
HBV	hepatitis B virus
HCMV	human cytomegalovirus
HCV	hepatitis C virus
HERV	human endogenous retrovirus
HHV-1–8	human herpesvirus types 1 to 8
HIV	human immunodeficiency virus
HLA-G	unusual transplantation antigen
HTLV-1–3	human T-cell leukemia virus types 1 to 3
HPaV	human papillomavirus
HPV-B19	human parvovirus B-19
HPyV	human polyomavirus
HSV	herpes simplex virus
KSHV	Kaposi's sarcoma herpesvirus
miRNA	micro (regulatory) RNA
NEF	regulatory factor of HIV
PCR	polymerase chain reaction
SCD-1	stromal cell derived factor-1
SV-40	simian (polyoma) virus "40"
TTV	"transfusion transmitted" Anellovirus

Commemorating Judit Czeglédy, who passed away leaving family and friends in November 2007

A. S. Younes · M. Csire · B. Kapusinszky · K. Szomor · M. Takács · G. Berencsi (✉)
Division of Virology, National Center for Epidemiology,
Gyáli Street 2–6,
1097 Budapest, Hungary
e-mail: berencsi.gyorgy@oek.antsz.hu

Introduction

Viruses, which may cause illnesses of the fetus have been reviewed by several authors in the past [55, 63, 70, 80, 81, 91, 166]. Rubella [71], measles [55, 81], Togaviruses [63], Flaviviruses [80], hepacivirus (HCV) [112], Hepadnaviruses (HBV) [19, 212, 223], human immunodeficiency virus (HIV) [21, 101, 169, 204, 205], human cytomegalovirus (HCMV) [45, 56, 66, 197, 226, 230], human herpesvirus types 1 (HSV) [6], 6 (HHV6) [5, 12, 173, 197], 7 (HHV7) [70, 152] and 8 (HHV8) [222], human parvovirus B19 (HPV-B19) [40, 74, 139], dependovirus (AAV) [25], human adenovirus [95, 96], Epstein-Barr virus (EBV) [5, 44, 222], human papillomaviruses (HPaV) [3, 4, 60, 183, 222], human polyomaviruses (HPyV) [10], lentiviruses [193] and the Anellovirus TTV (Dencs, A., Csire, M. and Takács, M. unpublished results) were shown to be able to infect the placenta or cells of fetal origin. The consequence may be accidentally the impairment of fetal development and/or the illness of neonates or children.

The aim of this work was to review recently discovered molecular mechanisms enabling viral infection of the placenta and the transplacental transfer of viruses to the fetus in contrast to the perinatal infection of neonates during delivery [20–22, 147, 212].

There are two barriers separating the maternal tissues from the fetal circulation. Syncytiotrophoblast is the 1st one and the endothelial cells of the fetal blood vessels in the microvilli is the second one through which viruses have to be transported [110, 111, 178, 192] in order to cause fetal infection.

Vertical Transmission of Viruses (Perinatal or Transplacental?)

Thirty years elapsed until the original idea could be proven, that the germ cells may transfer viral genes or viral genomes into the zygote [10, 207]. The first example of the presence of HHV6 in the nuclei of human cells and their transmission to the descendants according to the Mendelian rules (Peter Medveczky, unpublished) has been proven recently [14, 39, 206–209]. About 2 % of the HHV6 subtype "A" carrier persons harbour the viral genome in the germline, too [207–209]. In some individuals, however, chromosomal integration can be detected in many, but not in all cells of the body [113]. It has to be mentioned, that conventional perinatal or transplacental HHV6 transmission is also present in the population [228]. Some findings might suggest that human parvoviruses can be transmitted vertically via zygotes [139], too.

For the examination of semen new developments of molecular techniques were required and the validation of the laboratory procedures had to be done because of the mucopolysaccharide content of semen and because of the presence of other substances inhibiting the polymerase chain reaction [154]. These substances were shown not to interfere with the *in situ* hybridisation techniques, which also allowed the examination of viruses present in the ejaculate. Viruses were found to be associated with spermatozoa [10, 11, 33, 97, 129, 130, 154, 194, 215] identified in the semen or seminal plasma and in genital secretions of women [7, 18, 19, 29, 38, 48, 50, 69, 76, 78, 86, 104, 143, 179, 219]. Lymphocytes of semen might also contain latent viruses [214–216] similar to the KSHV detected in prostatic tissues [129, 195]. The listed data are summarised in Table 1.

Seminal plasma was found to induce proliferation and differentiation of B cells [105] thus potentially reactivating lymphocyte-associated latent herpesviruses. The expression of envelope proteins of endogenous C type retroviruses was also induced on the membranes of oocytes following fertilisation [138]. On the basis of the results listed one may conclude that viruses can be present in all or in several cells of the early developmental stages of the human embryos. It has been discovered recently, that the induction of syncytiotrophoblasts is regulated by the product of the *syncytine* gene coded by an endogenous human retrovirus [126].

The Perinatal Transmission and Transplacental Transfer of Viruses could be Differentiated only Recently

Reactivation of different viruses has been observed in connection with the modulation of the maternal immune system during pregnancy. The perinatal infection of the newborn babies has been recognised first in the case of papillomaviruses [27, 38, 164, 165, 174], herpesviruses [12, 50, 70, 112, 143, 152, 196, 197], TT virus [29], hepatitis B virus (HBV), HIV and hepatitis C virus (HCV) [112, 117, 147, 169] during delivery. Molecular characterisation of viruses in sexual partners [196] and that in the parents and neonates [102, 165, 183, 196, 197] supported perinatal transmission, too.

The probability of transplacental transmission of HBV [212] cannot be more than 0.9 % in Hungary, since the perinatal infection of the neonates can be prevented in 99% by active and passive immunisation of them immediately upon birth [185].

Evidence has been presented that in a proportion of HIV-infected pregnants, the *quasispecies* of the fetal virus was significantly different from that harboured by the mother [101, 169]. This phenomenon can only be explained by the transplacental transmission of HIV followed by an inde-

Table 1 References on viruses detected in semen, prostate and in genital secretions of women

Virus species in semen or prostatic tissues	Virus isolation or immuno-fluorescence	PCR	*In situ* hybridisation
HSV	[33]	[7, 19, 52, 86, 179, 219]	[48, 97]
HCMV		[7, 18, 19, 33, 86, 216, 219]	
HPaV		[7, 19]	
HPyV	[10]		
EBV	[18]	[18, 19, 86]	
HHV6		[19, 39]	[39, 113, 208]
HHV8		[69, 75, 78, 130, 154, 195]	[11, 78, 129]
Adenovirus	[33]	[10]	
Virus in female genital tract			
HSV			[48]
HCMV		[219]	
EBV	[18]	[50]	
HHV6		[12, 143, 208]	
HpaV		[38, 164]	[38]
HHV8		[104, 194]	
TTV		[29]	

pendent evolution of fetal and maternal variants of the *quasispecies*. The transplacental transmission was found to be facilitated by homozygosity of certain genes for example that of HLA-G [1, 100, 156]. Transplacental transmission was increasing when interleukin and TNF alpha [147, 151] production were found to be enhanced in the placental tissues due to inflammation [21]. The production of facilitator molecules can probably be stimulated by the increase of toll-like receptor-4 during gestational aging [59, 194], which was shown to react with endotoxins.

A series of publications reported the presence of viral nucleic acids in fetal hydrops (HHV6) [5] or in the amniotic fluid, cord blood and neonatal blood samples (Papillomaviruses [3, 4, 166, 222], herpesviruses [6, 63, 66, 113, 114, 152, 206, 222], HBV [20], AAV [25, 40], rubellavirus [71], and TTV Anellovirus [Csire M., Dencs A., Takács M. unpublished]) taken immediately following parturition.

In contrast to the previous findings an exceptional multiple PCR screening [121] of amniotic fluid samples taken in the first trimester of symptomless pregnancies was unable to detect the presence of any viral DNA. Several possible reasons might explain the findings of the authors. 1.) Ontogenetic differentiation of the fetal tissues may probably facilitate penetration of viruses without clinical consequences only in the second half of the pregnancy [45, 56, 65]. 2.) Because of the different metabolism, the presence of viruses resulted in abortion and therefore in healthy pregnancies no viral DNA could be detected in samples taken within the first trimester. 3.) The viral DNA, if present, was probably within or adsorbed to the cells of the amniotic fluid, since it contains soluble lactoferrin, which would inactivate papillomaviruses or polyomaviruses [46, 51, 145].

Later, however, the majority of viral DNA was detected in the meconium and cell debris of the amniotic fluid samples [222] taken at birth at the end of normal pregnancies.

Indirect Observations Supporting the Transplacental Transmission of Viruses in Healthy Pregnancies

Two additional indirect observations supported the existence of transplacental transmission of papillomaviruses and that of Kaposi's sarcoma herpesvirus into the fetal tissues without any clinical consequences. In elderly patients, suffering from cancers of the head and neck, early protein E6 coded for by papillomavirus 16, but no late proteins were expressed in non-tumorous cells (neural structures and endothelial cells) [60] of the patients. This finding might indicate, that the infection had to occur early in fetal ectodermal or mesodermal stem cells and only the expression of early proteins was possible in the absence of DNA replication upon birth when neural structures do not replicate any more.

Another finding which supported exposition of the fetal immune system to viral proteins was the peculiar difference in the serological response of patients directed to antigens of KSHV in contrast to those of HCMV, EBV and HHV6 in myeloma multiplex and B-cell lymphoma patients [34]. Humoral immune response was present in the case of patients positive for the DNA of HCMV, EBV and HHV6. In contrast to these only 5 of 40 patients, who had viral DNA in the white blood cells detected by nested PCR, were able to produce detectable serological response to KSHV-

specific antigens [34]. The absence of humoral immune response might indicate fetal exposure to KSHV antigens similar to "self" antigens during the ontogenesis of the fetal immune system [54, 123].

One cannot exclude the possibility that viruses can be vertically transmitted by the germ lines, through the placenta and perinatally during delivery. How can the transplacental transmission occur?

Replication of Viruses in Fetal Tissues In Vitro and In Vivo

Fetal syncytiotrophoblast cells form the maternal-fetal barrier. Both cytotrophoblast cells and syncytiotrophoblast cultures were shown to support the growth of HCMV [8, 56, 81, 114, 115, 190, 198], HIV1 [9, 13, 35], HHV6 [14, 35], HSV1 [176], HTLV1 [198, 199], EBV [199] and HPV-B19 [74, 211]. In spite of the fact, that trophoblast cells do not express CD4 [225] receptors only the CXCR4 co-receptor of HIV1, the cells could be infected with the virus [204, 205, 217]. In addition to these trophoblast cells were shown to be resistant to the effect of alpha interferon, which could reduce virus replication [32]. Human trophoblast cells could also be infected with adenovirus recombinants [95, 96].

Receptors for herpesviruses are present on fetal cells. These receptors are the complement receptor CD21 for EBV [76], the cystine transporter CD98 for KSHV [47, 85, 98], integrins for HCMV [49, 53, 86, 88–90] which are also co-receptors for AAV [16, 188], ganglioside GD1a for polyomavirus [64], CD46 for HHV6 [70], globoside receptor (erythrocyte P antigen) and Ku80 co-receptor for HPV-B19 [87, 91, 133, 134, 167, 211, 213] heparan sulfate proteoglycan for AAV and Papillomaviruses [187, 221], laminins for Papillomaviruses and Alphaviruses [84, 183, 186].

Herpesviruses penetrate the target cells by membrane fusion. The genetic basis for the fusion of the cell membrane and the viral envelopes is carried on the gene of glycoprotein gB. This part of the viral gB glycoprotein was shown to be related to the disintegrin metalloproteases [53, 93, 200].

Herpesviruses, however, were shown to possess the property to cause "fusion from without" of the cellular membranes. This property of the virus means that the membrane fusion can occur without expression of viral genes and multiplication of the viruses [89, 93, 122, 131, 153, 171, 182, 202, 226] is not required. The penetration of parvoviruses is facilitated by the phospholipase A activity of the virus and conformational changes of the capsid proteins [87, 167]. Thus the penetration of the syncytiotrophoblast by herpesviruses is a plausible phenomenon as shown by many *ex vivo* experiments [8, 198].

The infected cytotrophoblasts, however, downregulate adhesion and immune molecules required for invasiveness and maternal immune tolerance. Expression of metalloproteinase-9 was shown to be reduced and degradation of the extracellular matrix was impaired [190]. Cell surface proteins (i.e. E-cadherin, VE-cadherin, HLA-G, and HCMV receptors, epidermal growth factor receptor, integrins beta1, 6, alphaV-beta3 and alpha9) were expressed following infection of purified cells. HCMV replication in late gestation placentas with considerable reserves could deplete cytotrophoblast progenitors, thereby impairing syncytiotrophoblast development and increasing the risk of virus transmission to fetal blood vessels [190]. The infection of human microvascular endothelial cells requires the sustained expression of NF-kappa-B in order to support gene expression of Kaposi's sarcoma herpesvirus [172]. In contrast to the consequences of HCMV infection, stromal cell-derived factor-1 (SDF-1) may prolong trophoblast cell survival [82].

The Maternal-fetal Barrier and Immunomodulation of the Mother

Transplacental transmission of fetal cells into the maternal circulation is a well known phenomenon, which has been reviewed recently [17, 92]. The molecular barrier between the fetal and maternal tissues was shown to be the HLA-G antigen, which possesses 7 exons and it is preventing the activation of the maternal cellular immune response by fetal antigens. The expression of HLA-G on fetal cells transferred into the maternal circulation is one of the factors enabling survival of them for years without the activation of maternal immunity [79, 178].

The non-classical HLA-G, however, may be expressed on different other cell types, too [142]. Cytomegalovirus could induce the degradation of cellular HLA-G1, but the soluble form of the antigen was unimpaired by HCMV infection [15]. The US3 and US6 gene products were responsible for the downregulation of MHC class I genes of the trophoblasts [83]. HCMV was coding for a viral HLA class I homologue (UL18), which inactivated the Ig-like inhibitory receptor of the cells (CD85j), thus protecting infected cells against NK cell attack [28], in contrast to the induction of HLA-G expression caused by HCMV in Guillain-Barré syndrome [148].

HIV-1 was also able to downregulate the non-classical MHC class I molecule HLA-G1 [42, 156]. HLA-G antigens were also induced under certain conditions in B lymphocytes immortalised by Epstein-Barr virus [61]. Neurotropic viral infections modulate HLA-G expression preventing the effective immune defense mechanisms of the patient [100, 124]. Soluble HLA-G was found to support renal graft acceptance in transplant recipients [160]. In contrast to these HLA-G expression on the surface of cells of chronic

lymphatic leukemia was shown to be associated with unfavourable outcome [141]. Thus, HLA-G is responsible for immunomodulaton of a series of compromising maternal immune functions including those directed to virus-infected or virus-carrier cells.

Cellular infection with herpes simplex virus (HSV) and human cytomegalovirus (HCMV) were each associated with the downregulation of surface expression of HLA-A and HLA-B. The effects of HSV and HCMV infection on HLA-G and HLA-C in the trophoblast have revealed similarities and surprising differences between trophoblasts and classical MHC class I products [176–178].

HLA-G was selectively presenting different epitopes. Epstein-Barr virus-induced gene 3 (EBI3) encodes a soluble hematopoietin receptor related to the p40 subunit of interleukin-12. EBI3 was shown to be expressed at high levels in full-term placenta. EBI3 levels were strongly up-regulated in sera from pregnant women and gradually increased with gestational age. It is an important immunomodulator in the fetal-maternal relationship, possibly involved in NK cell regulation [44, 168].

Transfer of Whole Maternal Cells into Fetal Tissues

It has been discovered recently that the maternal-fetal barrier can be passed by maternal cells including lymphocytes in spite of the hermetic separation by syncytiotrophoblast layer and HLA-G protection [65, 91, 155]. Pathologic conditions may facilitate or induce the transfer of maternal cells [75, 125]. This phenomenon may represent an alternative way for lymphotropic viruses to pass the maternal-fetal barrier, since one of each million maternal lymphocytes harbours latent herpesviruses. The transfer of such cells might result in the reactivation of herpesviruses in the fetal tissues. Under certain immunosuppressive conditions the heterogeneity of maternal B lymphocyte population has been shown to be impaired [37]. It is hypothesised that under such conditions the frequency of transferred maternal B-lymphocytes harbouring latent beta or gamma herpesviruses might be elevated, as suggested by a series of publications in connection with the transplacental transfer of hepatitis B virus [20, 212]. The transport of human parvoviruses seems to be also very probable by maternal cells [139].

Apical to Basolateral Transcytosis in Syncytiotrophoblast and Basolateral to Apical Transcytosis of IgG in Fetal Capillary Endothelium

It is usually not discussed in general reviews, that maternal-fetal transcytosis requires two different polarities of transcytosis. The transport across the syncytiotrophoblast is similar to the apical to basolateral transport of the molecules observed in the tubuli of the kidney [224], when the recycling of albumin or recycling of transferrin and other substances occur in the gut [109, 158]. Albumin recycling in the placenta was found to be also a clathrin-mediated process [103]. Dynamin was shown to participate in the endocytosis of riboflavin in placental trophoblasts [58]. It is, however, not required for the endocytosis and transcytosis of HIV-1 [205] in spite of the fact, that it is required for the uptake of papillomaviruses by keratinocytes [174] and it was found to participate in the NEF-mediated enhancement of HIV-1 infectivity [157].

The transcytosis in the fetal capillary endothelial cells, however, is a basolateral to apical transcytosis resembling those of IgA in enteric cells or enzymes in the thyroid cells or liver cells [73, 116, 201].

Active transcytosis of maternal IgG subclasses 1 and 3 occurs through the fetal barrier into the fetal circulation throughout pregnancy [23, 57, 181]. Both Fc gamma receptor I and a distinct Fc gamma RIIIb receptor are expressed on the surface of syncytiotrophoblasts [114]. In term villi the receptor is concentrated in the apex of the syncytiotrophoblast, suggesting a possible role in the maternal-fetal transmission of passive immunity [23]. All 3 subtypes of Fc-receptors are expressed by the fetal Hofbauer cells [23].

Fc gamma RIII, however is also expressed (CD16) on the surface of invasive trophoblasts carrying CXCL12 chemokine receptors attracting natural killer cells to the maternal-fetal barrier [72, 217, 220]. These chemokine receptors take part also in the maternal-fetal immune tolerance and vascular remodelling [220]. In addition to these functions they can support the replication of multiple types of human papillomaviruses [221].

The second layer, the villus endothelium, was until recently thought to allow IgG movement nonspecifically by constitutive transcytosis in caveolae. Recently it has been shown, however, that the villus endothelium expressed a separate FcR for IgG, the inhibitory motif-bearing Fc gammaRIIb2 seen most notably on macrophages and on a minor fraction of B cells.

Fc gammaRIIb2 is expressed in an unidentifiable novel organelle of the villus endothelium, unassociated with caveolae. About half of these Fc gammaRIIb2 organelles contain IgG; the remainder lack IgG. These findings are compatible with Fc gammaRIIb-mediated transfer of IgG across the villus endothelium, independent of caveolae [128, 192].

This difference of ligand-induced receptor-mediated transcytosis is probably due to the different polarities of transcytoses. The simplified model of the maternal-fetal transports are summarised in Fig. 1.

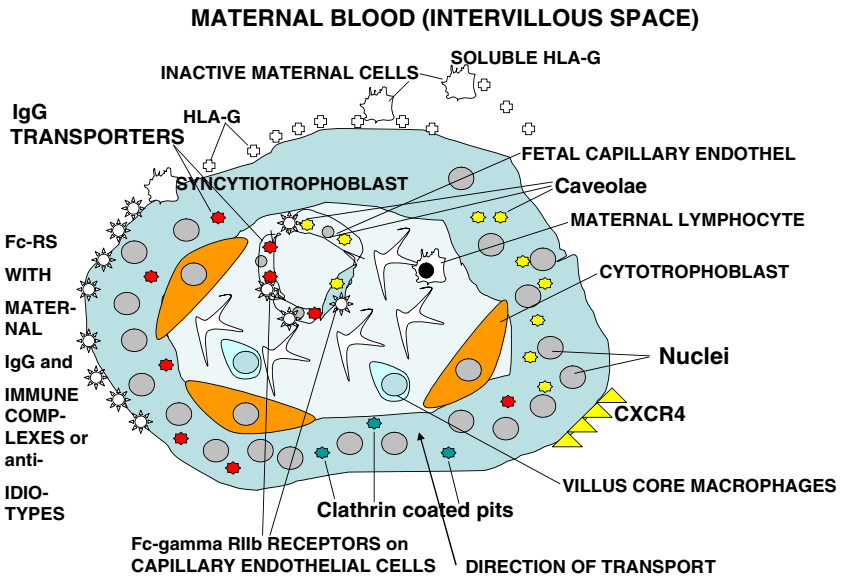

Fig. 1 Receptors and transporters on the microvilli of the fetal placenta. The maternal blood is separated from the fetal tissues by the syncytiotrophoblast. The transport through the syncytiotrophoblast occurs in the apical-basal direction. The outer surface of the syncytiotrophoblast is covered by HLA-G, which is responsible for the silencing of maternal cytotoxic cells [43]. Fc-receptors are also present on the outer surface of the syncytiotrophoblast collecting maternal IgG for transcytosis into the fetal part of the barrier. Virus-antibody complexes and anti-idiotypes might be transported by the transporter vesicles, too. Villus core macrophages take the transporter vesicles to the fetal capillary endothel cells, where the Fc-gamma-RIIb receptors take over the IgG and transporter vesicles independent of caveolae forward the maternal IgG and its complexes into the fetal blood. The transport through the fetal capillary cells is a basal-apical transport. Caveolae were shown not to be involved in the IgG transportation. CXCR4 coreceptors are also present on the maternal surface of the syncytiotrophoblast preventing its apoptosis regulated by the ligand CXCL12 (Stromal cell derived factor-1=SCD1) contributing to the maternal immunotolerance to fetal tissues. Clathrin coated pits of syncytiotrophoblasts are responsible for the albumin recycling into the fetal circulation. Maternal lymphocytes are passing syncytiotrophoblasts by a yet unknown mechanism

Antibody Facilitated or Inhibited Uptake and Transcytosis of Viruses

Antibody dependent enhancement of virus infection was shown in the case of HCMV [114] and HPV-B19 [40, 134]. Under certain conditions an IgG-HCMV complex will be transcytosed by the neonatal Fc receptors across syncytiotrophoblasts, infecting underlying cytotrophoblasts in chorionic villi. The infection may occur when the maternal IgG has a low neutralizing titer. In placental villi, syncytiotrophoblasts express the virus receptors, but lack integrin co-receptors and the virion uptake occurs without replication. Transcytosed virions will reach cytotrophoblasts that selectively initiate expression of alphaV integrin [114, 115].

In case the concentration of maternal neutralising antibodies is high, these will prevent antibody facilitated virus uptake [114]. In spite of the previous observations, HCMV could be detected in the placenta, amniotic fluid and fetuses of seropositive mothers [222, 230].

Free HBV was shown to be transcytosed across trophoblastic cells at a rate of 5% within 30 min. Viral transport occurred in microtubule-dependent endosomal vesicles. Additionally, confocal microscopy showed that the internalized virus traverses a monensin-sensitive endosomal compartment. Differentiation of the cytotrophoblasts to syncytiotrophoblasts resulted in a 25% reduction in viral transcytosis, suggesting that placental maturity may protect the fetus. Virus translocation was also reduced in the presence of HBV-specific immunoglobulin [20]. HHV6 and HHV7 were found also in the amniotic fluid of seropositive mothers [222], but the role of antibodies has not been examined yet.

Biopsy specimens often contain HCMV virion-specific glycoprotein B and DNA in syncytiotrophoblasts and in core macrophages of the villi without productive infection. Focal replication was shown to occur in placentas of women with low to moderate neutralizing antibody titres [115].

Possible Transcytosis of Virus-specific anti-idiotype Antibodies

The possibility, that rheumatoid factors may contain anti-idiotype antibodies carrying an “internal image” of different herpesviruses, has been suggested many years ago [119]. The possible role of anti-idiotypic antibodies transported into the fetal circulation and carrying images of viral

surface antigens had been proposed, too [144]. Recently the influenza vaccination of pregnant women has been recommended in the United States in the second trimester of pregnancy. The vaccines used were split- or subunit-vaccines. One group has tested the influenza specific immune response detectable in the umbilical blood upon birth. Surprisingly, IgM-type antibodies specific to the influenza viral subunits could be detected in a large proportion of the newborns [162]. These findings might be considered to be indirect evidence that anti-idiotype antibodies were transported into the fetal circulation and induced the formation of influenza subunit-specific fetal IgM [162]. It is very unlikely, but it cannot be excluded that viral glycoproteins might be transcytosed in the form of immunocomplexes into the fetal circulation by the above mentioned mechanism, too.

The presence of anti-idiotypes causing immunomodulation has been suggested previously in human intravenous gamma globulin preparations [163]. Therefore, the question will remain open against which epitopes the fetal immune system produced the virus-specific IgM molecules.

Antibody Independent Transcytosis of Viruses into Normal or Tissue Culture Cells

In normal tissue culture cells polyomavirus JCV enters cells by clathrin-dependent endocytosis and it is transported immediately to early endosomes. It is then sorted to a caveolin-1-positive endosomal compartment. This latter step is dependent on Rab5-GTPase, cholesterol, caveolin-1, and pH. JCV enters cells by clathrin-dependent endocytosis and is then sorted from early endosomes to caveosomes [31, 159, 179]. The clathrin polymerisation was shown not to be required always for endocytosis in rat cells [36]. Adeno–associated viruses are taken up by clathrin coated pits, but these viruses are released from the endosomes and accumulated in the perinuclear region as free particles [16] in tissue culture cells. Mouse polyomaviruses enter Rab 11 endosomes using the transferrin cargo [108]. The integrity of the lipid rafts, however, is required for the efficient multiplication and even *in vitro* transformation of certain viruses (EBV) [107]. SV40 polyomavirus bypasses the Golgi complex using a caveolae–mediated pathway [140].

Intracellular trafficking of HIV-1 was shown to depend on the interaction of dynamin-2 and NEF. Thus, the transcytosis is dependent on clathrin-coated pits completed by the dynamin-2 NEF complex [157]. Caveolin-1 and dynamin-2 are required for the entry pathway of human papillomavirus type 31 into keratinocytes [184] probably requiring phosphorylation as described recently [189].

Transcytosis of Viruses within Fetal Tissue Cultures

Trophoblasts also contain caveolin-1, but its level is reduced greatly during their differentiation into syncytiotrophoblast [110]. This is probably the reason why a group was unable to detect caveolae in syncytiotrophoblasts [111]. Caveolin-1 was shown to be also a regulator of apoptosis. Trophoblast syncytialisation involves the apoptotic cascade. Cytotrophoblast caveolin-1 may also play a role in regulating fusion events involved in syncytium formation.

The differentiation of cytotrophoblast cells may increase the efficiency of the artificial transduction of infection by an AAV vector construct, but the uptake of herpes simplex virus construct was shown to be inhibited [150]. Lipid raft fractions contain the raft-associated proteins caveolin 1 and 2, flotillin 1 and 2, stomatin and the heterotrimeric G protein, “Galphaq”. Caveolin-1 was shown to be internalized to the mitochondria, but not to the Golgi or endoplasmic reticulum. It was relocated to the plasma membrane upon confluence. Apical microvillous membranes of the syncytiotrophoblast cells revealed a high degree of similarity to lipid rafts [149]. The authors identified 57 proteins from microvillous membranes isolated from human syncytiotrophoblast cells and a considerable part of them was shown to take part in viral transcytosis in other systems.

Lipid rafts are detergent-insoluble. These are composed of low-density membrane domains that are rich in cholesterol and sphingolipids. Caveolae were found to be the subdomain of the biochemically defined glycolipid raft and its expression was associated with the protein caveolin-1. This protein associates with numerous signaling molecules, regulating their activity by holding them inactive. Rock-1 is a protein, which promotes cytoskeletal re-organisation important for syncytialisation and apoptosis, too. It was shown to be associated with caveolin-1. A proportion of the total cellular Rock-1 content was found in lipid raft fractions, confirming its presence in the membrane of confluent BeWu (trophoblast culture) cells. This close association of plasmalemmal caveolin-1 with Rock-1 protein raises the possibility that caveolin-1 may regulate Rock-1 within the trophoblasts [161].

The initial presence of HIV-1 within the endosomes is mandatory for infection to take place. This process is independent of the viral envelope proteins gp120 and gp41. The Rab family of small GTPases coordinates the vesicular transport between the different endocytic organelles [203, 227]. Distinct Rab proteins have been identified and each is specifically associated with a particular organelle or pathway. For instance, Rab5 is needed for early endosomes, Rab7 for transport from early to late endosomes, and from late endosomes to lysosomes, whereas recycling endosomes are enriched in Rab11 [108, 227]. Caveolae are stable vesicles,

which are activated by SV40 [191] transporting the virus to the nuclear membrane. The internalization pathway leading to HIV-1 infection of trophoblasts is independent of clathrin-coated pits and caveolae but it was found to be sensitive to raft-perturbing drugs [203, 205].

Early events associated with HIV-1 infection in polarized human trophoblasts involved an active participation of the endocytic machinery during the internalization of HIV-1 by endocytosis, which resulted in the presence of viral material within the endosomes. This was shown to be an obligatory step for the HIV-1 uptake by human trophoblasts [203–205].

HIV-1 does not initially co-localise with transferrin, some virions migrate at later time points to transferrin-enriched endosomes, suggesting an unusual transit from the non-classical pathway to early endosomes. Finally, virus internalization in these cells does not involve the participation of microtubules but relies partly on actin filaments [203–205].

One may conclude on the basis of the above findings, that the uptake and transcytosis of viruses examined up to now is very different from the mechanisms detected in differentiated human cells [117]. Lipid rafts seem to possess a crucial role in the transcytosis of viruses in fetal cells.

Possible Consequences of the Prolonged Interaction of Viral Antigens with the Developing Fetal Cells and Immune System

The differentiation of the human fetal immune system is a process lasting up to the first days after birth. The fetal cord-blood of women vaccinated with live rubella vaccine during pregnancy contained specific IgM upon delivery [70] without any clinical consequences of the virus infection. Antibody production begins usually in the 22nd week of the fetal life. The pregnant women who were administered with influenza vaccine during the second half of the pregnancy also possessed influenza-specific IgM in their cord-blood [68, 162]. What might be the mechanism of the fetal immunisation? The vaccines did not contain whole virus particles. The products used for immunisation were split- or subunit-vaccines.

The production of DNA-specific cord blood antibodies could be detected as early as in 1995 [210]. The normal human cord blood also contained (anti-idiotype) IgM recognising the F(ab')2 portion of IgG inhibiting its binding to dsDNA. It was concluded that the human cord blood may contain cells that form an idiotype/anti-idiotype network [123, 144]. The idiotype is expressed on IgG and the anti-idiotype is an IgM antibody that interferes with its interaction with dsDNA [210]. Autoantibodies were shown to be produced by normal fetal B lymphocytes [123] and some of them might be associated with later autoimmune diseases.

The reviewed findings indicate that certain viral antigens introduced into the fetal organism are not accepted as self. There are mechanisms, which allow specific but delayed immune response directed against different proteins of viruses. It has been suggested that interaction between CXCR4 and CXCL12 are involved in maternal-fetal immunological tolerance in all three trimesters of gestation and contribute to the invasion of extra villous trophoblasts during pregnancy [54, 217]. These extravillous trophoblasts, however, may carry maternal viruses accidentally [19, 44, 56, 95, 96, 101, 211, 221]. The interferon alpha insensitivity of these cells may facilitate viral transport [32].

It has been suggested that the infection of cells with human herpesviruses might induce the expression of human endogenous retroviruses (HERVs) [24, 30, 76, 99, 106, 135, 170]. The vast majority of human endogenous retroviruses are not expressed during pregnancy. The transfer or reactivation of different herpesviruses in later stages of the pregnancy might initiate expression of gene products of human endogenous retroviruses, probably interacting with the fetal immune system. It has been discovered recently, that syncytin inducing the formation of syncytiotrophoblasts is a gene product of the HERV-W *Env* gene [126].

In the case of the perinatal infection of the newborns by symptomless hepatitis B-carrier mothers, neither the mothers nor 45 % of the babies were shown to be able to produce antibodies against the hepatitis B surface antigens. 90 % of the mothers, however, had antibodies against the hepatitis B core antigen. In addition to this a prospective study of four generations of families with vertically transmitted hepatitis B virus indicated, that the virus is spontaneously eliminated from the majority of the 3rd and 4th generations of the families [147]. The virus elimination was dependent on the "non-immune non-cytocydal" virus elimination mechanisms even in the case of the first generation of symptomless persistant HBV carriers after decades from the onset of carrier state [147].

The African Burkitt's lymphoma has been studied by de-Thé and colleagues in another major prospective study in the seventies in Uganda [41, 42, 62]. Blood samples were collected from 42,000 children who were tested for EBV between 6 months and 2 years of age. After 7 years follow up Burkitt's lymphoma developed in 16 children. Surprisingly all 16 children with the tumour already had EBV-specific antibodies against Epstein-Barr virus at 6 months of age. The authors concluded that an early and severe primary EBV infection during the first months of life represented the key event for later development of the malignant disease. According to their hypothesis the source of infection was probably the saliva, and breast milk of the mothers since 65 % of all African women of reproductive age shed infectious EBV in their saliva, compared with 12% of the women in the Western world [41, 42, 62].

Four decades earlier the authors could not obtain convincing information about the possibility of perinatal and transplacental transmission of EBV. They have documented minor serological differences in EBV specific antibodies of tumour bearing children in comparison to those without lymphomas. In the light of the above discussed data one cannot exclude the possibility that early transplacental infection could have impaired the immunoreactivity of the children resulting in the development of Burkitt's lymphoma. The serological techniques used at that time had not been sensitive enough to detect faint serological differences between tumour bearing and healthy children at the end of the study.

Conclusions and Perspectives

In spite of the tremendous experimental work on tumorigenesis new and new hypotheses are published in the literature [94, 127, 136]. Alternative pathogenetic pathways had been suggested by them for the role of Epstein-Barr virus in the pathogenesis of autoimmune diseases, too [137].

Vertical transmission of human viruses occurs probably more frequently than supposed previously. The acute consequences of the transmission are probably very little as reviewed and shown by several authors recently [34, 55, 71, 152, 222].

As far as the formation of malignancies is concerned, two new pathogenetic hypotheses can be put forward. The interaction of the fetal immune system with a growing series of viruses and viral antigens might reduce the *post partum* immune response of the individuals against many different virus-coded proteins in the different stages of tumour development from preneoplastic into neoplastic tissues. The impairment of the B-cell populations due to fetal depletion had been already documented [37].

The other possible, but yet unexamined effect of the presence of viruses in fetal cells or tissues might be the impairment of differentiation of virus carrier cells by the micro-RNAs (miRNAs) produced or regulated by the viral genomes [218, 229]. Viruses are also coding for microRNAs. It has been shown, that polyomaviruses [26], human cytomegalovirus [67], Kaposi's sarcoma herpesvirus [120], adenoviruses [2] and HIV-1 [146] are producing miRNA molecules, which are able to modify the expression of different host cell proteins. LMP-1 of Epstein-Barr virus induces the expression of miRNA-146a [132] by the host cell. The adenovirus coded virus-associated RNA molecules were shown to be processed to functional interfering miRNAs involved in virus production [2]. Papillomavirus, however, was not shown to produce miRNAs, but its presence can reduce the expression of miRNA-218 of the malignant host cells [118].

The final conclusions of this synopsis are the following. The transcytosis of the viruses is either enabled by the antiviral IgG and the maternal fetal transport of maternal antibodies [114], or the lipid rafts in the fetal tissues [149]. The transfer of virus carrier maternal lymphocytes may also be the source of maternal-fetal virus transmission [17, 65, 92, 155, 175, 212]. The virus transmission by the oocyte and spermatozoa had been proposed many years ago [10], direct evidences, however, could only be presented regarding the chromosomal integration of the human herpesvirus type 6 in the last decade [12, 207, 209, 228].

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