During human gestation, viruses can cause intrauterine infections associated with pregnancy complications and fetal abnormalities. The ability of viruses to spread from the infected mother to the fetus arises from the architecture of the placenta, which anchors the fetus to the uterus. Placental cytotrophoblasts differentiate, assume an endothelial phenotype, breach uterine blood vessels and form a hybrid vasculature that amplifies the maternal blood supply for fetal development. Human cytomegalovirus – the major cause of congenital disease – infects the uterine wall and the adjacent placenta, suggesting adaptation for pathogen survival in this microenvironment. Infection of villus explants and differentiating and/or invading cytotrophoblasts offers an in vitro model for studying viruses associated with prenatal infections.

Intrauterine infections associated with pregnancy complications
Fewer than 50% of all pregnancies in healthy women survive beyond early gestation [1]. Many failures are due to chromosomal abnormalities; the etiology of others is unknown. Certain viruses and pathogenic bacteria are associated with mid to late pregnancy complications, but little is known about infection early in gestation when the placenta undergoes transformations that are crucial for fetal survival. Recent studies on biopsy specimens from the maternal–fetal interface infected with human cytomegalovirus (CMV) in utero suggest molecular defects that underlie intrauterine growth retardation, one consequence of infection during gestation [2]. Transmission routes and patterns of infection are probably linked to the unusual nature of placental cell development and interactions in the uterine wall (Figure 1). To understand the potential effect of virus-induced changes on the development of the placenta, we first discuss trophoblast (see Glossary) differentiation and essential functions.

Development of the human placenta
The human placenta is composed of villi that float in maternal blood and also villi within the uterine wall that anchor the placenta and attach the fetus to the mother.
The individual chorionic villus contains a connective core that contains fetal blood vessels and numerous macrophages (Hofbauer cells) that often lie under a thick basement membrane (see Figure I in Box 1; Zone I). Placentation is a stepwise process whereby cytotrophoblast progenitor cells, attached to the basement membrane as a polarized epithelium, leave the membrane to differentiate along one of two independent pathways depending on their location. In floating villi, they fuse to form a multinucleate syncytiotrophoblast covering attached at one end to the tree-like fetal portion of the placenta. The rest of the villus floats in a stream of maternal blood, which optimizes exchange of substances between the mother and fetus across the placenta. In the pathway that gives rise to anchoring villi, which attach the placenta to the uterine wall (see Figure I in Box 1; Zone II), cytotrophoblasts aggregate into cell columns of non-polarized mononuclear cells that attach to and penetrate the uterine wall. The ends of the columns terminate within the superficial endometrium, where they give rise to invasive cytotrophoblasts. During interstitial invasion, a subset of these cells, either individually or in small clusters, invades the decidua and commingles with resident decidual cells, myometrial cells and emigrant immune cells. During endovascular invasion, masses of cytotrophoblasts open the termini of uterine spiral arterioles and veins they encounter, then migrate into the vessels, thereby diverting maternal blood flow to the placenta (see Figure I in Box 1; Zone III). In arterioles, cytotrophoblasts replace the endothelial lining and partially disrupt the muscular wall, whereas in veins they are confined to the portions of the vessels near the inner surface of the uterus. These hybrid vessels anchor the placenta, increase the blood supply to the surface, provide nutrients to the fetal compartment and transport maternal IgG to the fetal circulation for passive immunity. Together, the two components of cytotrophoblast invasion anchor the placenta to the uterus and permit a steady increase in the supply of maternal blood that is delivered to the developing fetus. In early gestation, an unusual leukocyte population is attracted to the pregnant uterus [3]; decidual granular leukocytes intermingle with resident maternal cells and invasive fetal cells. These immune cells are involved in innate pattern recognition, mostly an unusual population of natural killer (NK) cells (CD56 bright) and some macrophages (CD68+), dendritic cells and a few T lymphocytes [4]. Dendritic cells expressing ICAM-3-grabbing nonintegrin (DC-SIGN+) are abundant and associate with NK cells in the uterine wall [5]. Novel expression of chemokine–receptor pairs in the decidua, as well as specialized adhesion molecules on uterine vessels, attracts immune cells that probably function in protection and cytotrophoblast differentiation [6,7].

**Invasive cytotrophoblasts express novel differentiation molecules**
During placentation, cytotrophoblasts switch from an epithelial type to a mesenchymal type: a precisely regulated process [8]. Cytotrophoblasts express novel adhesion molecules and proteinases that enable the cells’ attachment and invasion, as well as immune-modulating factors that play a role in maternal tolerance of the hemialogene fetus (Box 1) [9]. Interstitial invasion requires downregulation of integrins characteristic of epithelial cells and expression of novel integrins that promote migration [10]. Endovascular cytotrophoblasts that remodel maternal blood vessels transform their adhesion receptor phenotype to resemble the endothelial cells they replace [11]. The cells upregulate matrix metalloproteinase 9 (MMP-9), which degrades the basement membrane and extracellular matrix of the uterine stroma [12], and the tissue inhibitor of metalloproteinases 3 (TIMP-3), which regulates invasion depth [13]. Molecules that function in maternal immune tolerance, including major histocompatibility complex (MHC) class I molecule human leukocyte antigen (HLA)-G and interleukin (IL)-10, are also produced [14,15]. This remarkable transformation (novel expression of differentiation molecules that correlates with invasiveness) illustrates the extraordinary plasticity of these cells. As described below, CMV-infected cytotrophoblasts dysregulate selected differentiation molecules in vitro.

**Intrauterine viral infection**
Intrauterine viral infections can ascend from the genital tract or spread via the hematogenous route (Table 1). Circumstantial evidence for ascending CMV infection...
including high rates of bacterial vaginosis (i.e. pathogenic bacteria) and infection of the cervical epithelium [16]. Patterns of placental infection in utero suggest hematogenous spread from the infected uterus [17]. CMV, a ubiquitous virus secreted in bodily fluids, causes asymptomatic infections in healthy individuals and is seroprevalent (50 to 100%) in various populations. Nonetheless, CMV is the most common intrauterine infection associated with congenital defects (Figure 2). Seroconversion (20% per year) can occur in sexually active women

Box 1. Histologic organization of the uterine–placental interface at midgestation and expression of stage-specific differentiation molecules

Cytotrophoblasts (Figure 1a), which are specialized (fetal) epithelial cells of the placenta, differentiate and invade the uterine wall, where they also breach maternal blood vessels. The basic structural unit of the placenta is the chorionic villus, composed of a stromal core with blood vessels, surrounded by a basement membrane and overlain by cytotrophoblast progenitor cells. As part of their differentiation program, these cells detach from the basement membrane and adopt one of two lineage fates. They either fuse to form the syncytiotrophoblast that covers floating villi or join a column of extravillous cytotrophoblasts at the tips of anchoring villi. The syncytial covering of floating villi mediates nutrient, gas, and waste exchange and passive transfer of IgG from maternal blood to the fetus (Figure 1b; Zone I). The anchoring villi, through the attachment of cytotrophoblast columns, establish physical connections between the fetus and the mother (Figure 1b; Zone II). Invasive cytotrophoblasts penetrate the uterine wall up to the first third of the myometrium (Figure 1b; Zone III). A portion of the extravillous cytotrophoblasts breach uterine spiral arterioles and remodel these vessels by destroying their muscular walls and replacing their endothelial linings.
and in those who care for toddlers. Mothers with primary infection during gestation have a high transmission rate, and their babies are born with severe infections [18]. Hematogenous spread correlates with low-avidity maternal antibodies with poor neutralizing activity predominant in primary infection [19]. Another possibility is that latently infected cells could reactivate CMV during inflammatory responses to pathogenic bacteria in the pregnant uterus [17] (Box 2).

Certain viruses are associated with intrauterine infections (Table 1). With regard to herpes simplex virus type 2 (HSV-2) infections, asymptomatic shedding from the cervix during pregnancy could cause perinatal infections [20]. Prenatal infections are rare and, if untreated, cause severe morbidity and mortality [21]. Focal patterns of HSV-2 infection suggest limited spread in the decidua of seropositive women and sparing of the placenta [17,22]. Villitis and deciduitis, evidence of inflammatory responses to infection, low-avidity maternal antibodies to human immunodeficiency virus (HIV) escape mutants, and viral RNA levels in blood are all associated with increased risk of HIV transmission [23]. Clinical HIV strains can penetrate cytotrophoblasts from term placentas, but limited replication occurs in vitro. Variable levels of CD4 receptor and chemokine co-receptor expression suggest that viral entry might be independent of these molecules [24]. By PCR analysis, human papilloma virus was detected more frequently in spontaneous early-gestation abortions compared with elective terminations [25]. Analysis of placental biopsy specimens by in situ hybridization showed that the syncytiotrophoblast often contained viral DNA.

![Figure 2. CMV transmission, prenatal infections and birth defects in symptomatic and asymptomatic children.](TRENDS in Microbiology)
Box 2. Properties of human cytomegalovirus (CMV)

Clinical and immunological features
The medical impact of CMV results from its role as the leading cause of congenital infection [18,46]. Discovery is linked to pathology of fetuses and newborns that died from multisystem disease characterized by prominent central nervous system, liver, kidney, lung, salivary gland and hematologic abnormalities (see Figure 2 in the main text). In children and adults, virions enter the host following contact with mucosal surfaces, particularly epithelium of the upper alimentary or respiratory tract, urogenital tract, blood transfusion and transplanted organs. Leukocytes and vascular endothelial cells spread infection in the body. After seeding, virus commonly replicates in ductal epithelia, and virions are shed in secretions (saliva, urine, semen, cervical fluid and breast milk). Although virus is efficiently transmitted, hand-washing can prevent acquisition. In primary infection, viremia continues for a long period of time after an adaptive immune response can first be detected. Pathogenesis is directly linked to the immune status of the host, and virus can be transmitted by solid organ and bone marrow transplantation. Innate and specific immune responses control infection and are central in protection from disease. Antibodies to immunogenic viral proteins can be detected in seropositive individuals; the virion envelope glycoprotein B is a major neutralizing target.

Cell infection, persistence and latency
A member of the betaherpesviruses with a 235-kb linear, double-stranded DNA genome, CMV replicates in the nucleus and encodes over 200 open-reading frames [33]. CMV exhibits a highly restricted host range owing to a postpenetration block in gene expression. Clinical isolates, more pathogenic than laboratory strains, encode more than 60 glycoproteins and have specific tropism for endothelial cells, macrophages and neutrophils. CMV encodes genes that are associated with immune modulation functions (see Table 2 in the main text) [34]. Virions attach to cell membranes using heparan sulfate [47], bind to EGFR [48] and integrins [49], and penetrate by interactions with coiled-coil domains in gB and gH [50–52] and disintegrin domains of integrins α1 and αv. Replication is temporally regulated in a cascade fashion: immediate-early γ, early β and late γ genes encode regulatory proteins, enzymes for DNA synthesis and structural proteins, respectively. Myeloid-lineage hematopoietic cells are important targets for lifelong latency, and committed progenitors give rise to granulocytes, macrophages, dendritic cells and possibly endothelial cells. Viral gene expression is restricted to latency-associated transcripts; however, gene expression changes toward productive infection under proinflammatory conditions. Cytokine stimulation and viral amplification in latently infected cells caused by reduced immune surveillance leads to cell differentiation and reactivated infection.

Patterns of CMV infection at the uterine–placental interface
CMV infection is the major viral cause of well-documented birth defects [18] (Figure 2). Symptoms range in severity depending on primary or reactivated maternal infection during, or shortly before, gestation [26,27]. Examination of biopsy specimens from early-gestation placentas revealed that intrauterine CMV infections could spread to the placenta [17]. As illustrated by immunohistological staining, when the decidua and placenta were actively infected in utero, viral replication proteins were present in epithelia of endometrial glands in decidua and cytotrophoblasts in floating villi and cell columns (Figure 3a,b). When few cells with viral replication proteins were detected, macrophages and dendritic cells in the uterine and placental compartments contained phagocytosed virions, suggesting suppressed infection (Figure 3c,d). Infection of villus explants in vitro as a model for CMV transmission showed that cytotrophoblast progenitor cells underlying the syncytiotrophoblast expressed viral replication proteins (Figure 4a–d). This striking pattern resembled early infection in utero and suggested virion transcytosis across the surface layer [2].

Diagrams that depict staining patterns of CMV proteins observed in biopsy specimens from the decidua and adjacent placenta are shown in Figure 5 [17]. In the first pattern, cell islands in both compartments stained strongly for CMV-infected-cell proteins, and neutralizing antibody titers were low (Figure 5a). In the decidua, glandular epithelial cells, cytotrophoblasts and resident decidual cells stained for viral replication proteins. In the adjacent portions of the placenta, floating villi syncytiotrophoblast and cytotrophoblast progenitor cells were infected. Vesicles close to the plasma membrane of the villus surface contained glycoprotein B (gB), a virion envelope component. Placental fibroblasts and fetal capillaries in the villus core were infected. Invasive cytotrophoblasts in developing cell columns also stained. By contrast, macrophages and dendritic cells within the villus stroma contained cytoplasmic vesicles with viral structural proteins, suggesting phagocytosis without replication. In the second staining pattern, the number of cells with infected-cell proteins was reduced in the decidua, and occasional focal infection was found in the placenta (Figure 5b). This pattern predominated in samples with low-to-intermediate neutralizing titers and some bacterial pathogens. In the third staining pattern, few infected cells were found in the decidua and none in the placenta (Figure 5c). This pattern predominated in donors with high neutralizing titers, sometimes with bacterial pathogens. In the adjacent portions of the placenta, the syncytiotrophoblast contained numerous gB-positive vesicles but were not infected. Similarly, cytoplasmic vesicles in villus core macrophages and dendritic cells accumulated gB. Syncytiotrophoblasts contained numerous vesicles with maternal IgG, some co-localizing with CMV gB, whether uterine infection was active or suppressed. This picture suggested that the neonatal Fc receptor for maternal IgG expressed in early-gestation placentas [28] might bind IgG–virion complexes from maternal blood in the intervillous space, protecting them from degradation, and transcytose some virions across [2,17]. Whether focal infection of underlying cytotrophoblasts progenitor cells follows (Figure 4) would depend on CMV neutralizing titers of maternal IgG.

Notably, DNA from other viral and bacterial pathogens was detected in paired biopsy specimens from the decidua and placentas of women with uncomplicated early-gestation pregnancies [22]. CMV DNA was present in 69% of specimens, and varying bacteria were present in 38%. DNA from HSV-1 and HSV-2 was found less often (6 and 14%, respectively). The detection rate for viruses was higher in the decidua than in the placenta. Selected bacteria (Ureaplasma urealyticum, Mycoplasma hominis and Gardnerella/Bifidobacterium) were mostly found in the placenta. These findings show that pathogenic bacteria infect the placenta and suggest that inflammatory responses could reactivate CMV from latently infected cells in women with strong immunity.
These studies show that CMV often infects cells in the pregnant uterus, specifically the basal plate, and is selectively transmitted to the adjacent placenta, illustrating how a persistent virus exploits the hyporesponsive uterine environment. Infection that leads to fetal transmission probably involves viral replication in the uterine and placental compartments in women with the lowest neutralizing titers and some with intermediate titers and bacterial pathogens. Infection was suppressed in women with high neutralizing titers, suggesting that humoral immunity enhances local protection conferred by innate immune cell functions, thereby suppressing infection.

**CMV infection downregulates cytotrophoblast differentiation molecules and impairs invasion**

Congenital CMV infection is associated with intrauterine growth restriction (Figure 2), a placental defect related to impaired remodeling of uterine arteries by invasive cytotrophoblasts, compromising blood flow to the placenta [11]. CMV productively infects isolated placental cytotrophoblasts in vitro [2,29–31]. Infected cytotrophoblasts alter differentiation, as evidenced by dysregulated expression of stage-specific immune and adhesion molecules and MMP-9 [2,32]. At late stages of infection, staining for HLA-G was either greatly reduced or lost in contrast to uninfected cells. Integrin α1β1 is an adhesion molecule that mediates invasion in vitro (Box 1). In CMV-infected cells, α1 integrin staining was absent, whereas α5, a fibronectin receptor that counterbalances invasion, was not affected, thereby amplifying the effect of the reduced integrin α1β1.

CMV biology includes latent infection in a small population of myeloid and dendritic cell progenitors and expression of immunomodulatory genes thought to enhance survival and transmission in the infected host (Table 2) [33,34]. CMV produces a viral IL-10 homolog, cmvIL-10 [35], which has similar affinity for the hIL-10 receptor 1 as the natural ligand and comparable immunosuppressive activity [36]. Human IL-10 expression in differentiating cytotrophoblasts is an autocrine inhibitor of MMP-9 production and invasiveness [37]. Examination of protein and gelatinase activity of cytotrophoblasts infected with a clinical CMV strain showed reduced MMP-9 activity [32]. When MMP-9 was evaluated in differentiating cytotrophoblasts treated with purified cmvIL-10, human IL-10 was upregulated and the cells contained less MMP-9 protein and activity. The results indicated that cmvIL-10 alters proteinase activity and impairs extracellular matrix degradation and cytotrophoblast functions via paracrine activities that probably occur in focal sites of infection.

Next, the invasiveness of the cells was examined using an in vitro assay that tests the ability of differentiating cells plated on the upper surfaces of Matrigel-coated filters.
to penetrate the surface, pass through pores in the underlying filter, and emerge on the lower surface of the membrane [10]. The invasiveness of CMV-infected cells was dramatically impaired compared with uninfected cells [2]. Interestingly, the effect on invasion was greater than the number of infected cells, suggesting that the presence of infected cells, possibly by a secreted viral factor in the aggregates, influences the behaviour of the population as a whole. When cmvIL-10-treated cytotrophoblasts were analyzed, invasion was impaired, although not to the level of cells infected with a clinical CMV strain [32]. Progress in understanding CMV pathogenesis (Table 2), including immune modulation functions, tropism for specialized cells and reactivation from latency, could answer the outstanding questions about intrauterine infections and virus transmission at the uterine–placental interface (Box 3).

**Animal models for congenital CMV infection**

Because CMV is species-specific, the main obstacle to developing animal models is the difference in placental architecture, which precludes virus transmission across the placenta and congenital infection. The exceptions are endogenous CMV infections in humans, rhesus macaques and guinea pigs [3]. Some placental types do not directly contact maternal blood, and those that do have multiple cell layers separating the maternal and fetal circulations (e.g. murine placenta). Maternal–fetal transfer depends

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**Table 2. CMV properties that could modulate immune responses to infection**

<table>
<thead>
<tr>
<th>Immune modulation</th>
<th>Viral function</th>
<th>Gene(s)</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocyte function, trafficking, infection</td>
<td>Latent infection in myeloid-dendritic cell progenitors and reactivation</td>
<td>Unknown</td>
<td>[59–61]</td>
</tr>
<tr>
<td></td>
<td>Virion transfer to leukocytes (monocytes) and neutrophils</td>
<td>UL131–UL128 UL146–UL147</td>
<td>[62]</td>
</tr>
<tr>
<td></td>
<td>DC-SIGN binding and virion transport</td>
<td>UL55 (gB)</td>
<td>[63]</td>
</tr>
<tr>
<td></td>
<td>Impair antigen presentation</td>
<td>US2, US3, US6, US11</td>
<td>[34]</td>
</tr>
<tr>
<td></td>
<td>Engage NK inhibitory and activating receptors</td>
<td>UL18, UL16, UL40</td>
<td>[64–66]</td>
</tr>
<tr>
<td></td>
<td>Cytokine and chemokine homologs</td>
<td>UL111a (cmvIL-10), UL146 (vCXCL1)</td>
<td>[35,36,68]</td>
</tr>
<tr>
<td></td>
<td>Tumor necrosis factor receptor homolog</td>
<td>UL144</td>
<td>[69]</td>
</tr>
<tr>
<td></td>
<td>IgG Fc receptor homologs</td>
<td>UL118–119, TRL11/RL11</td>
<td>[70]</td>
</tr>
<tr>
<td>Leukocyte behavior</td>
<td>Block apoptosis</td>
<td>UL36, UL37, UL122, UL123 (IE1/2)</td>
<td>[71–73]</td>
</tr>
<tr>
<td>Cell cycle</td>
<td></td>
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</table>
Box 3. Outstanding questions about intrauterine CMV infection

- Do latently infected immune cells transmit CMV to the pregnant uterus?
- Do bacterial pathogens cause inflammation and viral reactivation or persistent uterine infection?
- Are IgG–virus complexes from maternal blood carried across the syncytiotrophoblast to underlying cytotrophoblasts by FcRn-dependent transcytosis?
- Does reinfecion occur at the uterine–placental interface in immune women?
- Does intrauterine infection resolve after delivery and, if so, what is the timeframe?

on the thickness of the separating layers and is affected by the number and type of layers. In the hemochorial placenta, the maternal blood vessels are completely destroyed by the fetal trophoblasts that directly contact maternal blood. Maximal exchange surface is provided by a tree-like branching pattern of the chorion, resulting in floating villi. Rats and mice have a hemochorial placenta, whereas humans, rhesus monkeys and guinea pigs have a hemochorial and, at term, hemomonochorial placenta. In species with invasive implantation, the trophoblast forms a syncytium that can be passed only transcellularly by transport mechanisms, such as diffusion, facilitated transfer, active transport and vesicular transfer. In humans, the syncytiotrophoblast is the decisive barrier that limits or supports transplacental transfer processes. The architecture of the guinea pig and rhesus placentas, similar to the human, could allow studies of prenatal infection in these animal models.

Analysis of guinea pig CMV transmission showed placental infection and fetal transmission in dams inoculated at midgestation [38]. Hematogenous spread of infection from the mother to the placenta occurred early in the course of infection. Virus was present in the placenta for weeks after clearance from blood and replicated in placental tissues in the presence of specific maternal antibodies. Viral nucleocapsids were present in trophoblasts and virions in surrounding infected cells. Pathological lesions with CMV proteins were frequently localized at the transitional zone between the capillarized labyrinth and the non-capillarized region. Whenever CMV infected the fetus, virus was isolated from the associated placenta. Among placental–fetal units with infected placentas, there was a delay in fetal infection, suggesting that the placenta serves as a virus reservoir but also limits transmission to the fetus. Later studies established that neutralizing antibodies to CMV glycoproteins suppressed fetal infection. Dams passively immunized with hyper-immune anti-glycoprotein B serum had a shortened duration of primary maternal viremia, and fewer pregnancy losses occurred [39]. Placentas from recipients of negative-control serum had more focal necrosis and infection and more intrauterine growth restriction in the pups than those of passively immunized dams, suggesting that passive immunity decreases fetal infection. Dams immunized with the guinea pig CMV glycoprotein vaccine seroconverted, and when challenged late in pregnancy, immunization significantly improved pregnancy outcome [40]. Virus was isolated from half of the live-born pups from immunized mothers, in contrast to most pups born to controls, indicating that immunization significantly reduced in utero transmission in surviving animals.

The rhesus macaque model has strong potential as an experimental system to resolve questions about the initial steps in intrauterine infection and whether persistent and latent infection can transmit virus to the placenta and fetus. Drawbacks include the cost of housing and handling large animals and breeding colonies infected with rhesus CMV. All juveniles and adults are seropositive and most infants were exposed to virus in the first year of life and seroconverted [41]. Fetal rhesus monkeys inoculated intraperitoneally showed severe disease, including intrauterine growth restriction and microcephaly, calcification, inclusion-bearing cells and degeneration of the cerebral parenchyma [42]. Immune responses to primary rhesus CMV infection increase over time and reduce pathogenesis, but do not eliminate reservoirs of persistent viral gene expression [43]. Given the similarity to human infection and pathogenesis in the developing fetus, generation of CMV-free colonies of rhesus macaques, difficult in conventional settings, would provide an invaluable resource for understanding conditions that affect maternal immunity and the associated risk of congenital infection.

Concluding remarks

Villus explants and differentiating cytotrophoblasts infected in vitro offer models to study human CMV and viruses that infect the placenta and the fetus. However, many questions remain unanswered (Box 3). Understanding basic molecular pathogenic mechanisms is the crucial first step in the rational design of treatments that address the causes, rather than the consequences, of intrauterine infection. Conceivably, there are several points at which intervention is possible. Women could be routinely monitored for primary viral infection or reactivation in early gestation and ascending bacterial infections could be eradicated. Species-specific animal model systems could be used to assess virus transmission routes, impaired placental and fetal development under experimental conditions, vaccines for protective immunity, strategies to bolster the barrier function of the placenta and novel...
antiviral drugs that reduce infection at the uterine–placental interface.

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