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Dendritic cell biology in human cytomegalovirus infection and the clinical consequences for host immunity and pathology

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Human cytomegalovirus (HCMV), a member of the herpesvirus family, establishes life-long persistence and latency after primary infection and can be reactivated later in life. In immunosuppressed patients, it is an important pathogen that can cause severe disease. HCMV is also thought to play a causative role in inflammatory diseases and cancer. The virus can infect different immune cells, including dendritic cells (DCs) and can take advantage of host immune functions to avoid immune recognition. These characteristics have sparked major interest in understanding HCMV and its interaction with immune cells and their relevance to disease pathogenesis. In this review, we focus on the complex host-pathogen relationship between HCMV and DCs, including the persistence of the virus in these cells, their function in the immune response to HCMV infection and the potential clinical consequences of HCMV infection in DCs.

Introduction

Human cytomegalovirus (HCMV) belongs to the herpesvirus family, and 60–100% of individuals in populations worldwide are persistently infected with and carry the virus. Usually acquired early in life, the infection can be transferred through all bodily fluids. Interest in HCMV as an important human pathogen has risen over the past decades, owing to increases in the numbers of AIDS patients and patients undergoing immunosuppressive therapy after organ or bone marrow transplantation.[1] HCMV infection is usually subclinical in immunocompetent individuals, but the virus can cause fatal disease in immunocompromised patients. HCMV infections occur in about 50–90% of patients after bone marrow and organ transplantation. In HIV-infected patients, however, the prevalence of HCMV approaches 100%.[1] Furthermore, HCMV infection is the most common congenital viral infection (~1% of live births); it may cause viral hepatitis with jaundice as well as permanent disabilities, including hearing loss, visual impairment, mental retardation and other neurological impairments.

In immunocompetent hosts, the infection rarely causes symptoms. However, mononucleosis caused by HCMV infection is sometimes observed (reviewed in ref. 2). For many years, HCMV was not considered to be a major human pathogen, but active HCMV has been found in tissue specimens from immunocompetent patients with inflammatory diseases, including inflammatory bowel disease (IBD), systemic lupus erythematosus (SLE), psoriasis and atherosclerosis; it has also been implicated in the development of these diseases and in restenosis after coronary angioplasty, chronic rejection in organ transplant patients, chronic graft-vs.-host disease in bone marrow transplant patients and tumors (reviewed in ref. 3).

After primary HCMV infection, the virus persists in a latent state and can be reactivated later in life. Latency is characterized by persistence of the viral genome without production of infectious virus—a strategy that enables the virus to co-exist with its host by reducing its visibility, leading to an avoidance of immune recognition. HCMV infects many different immune cells, including monocytes, macrophages, dendritic cells (DCs) and granulocytes, and takes advantage of host immune functions to escape immune recognition to avoid viral clearance.

In this review, we focus on the complex host-pathogen relationship between HCMV and DCs, including the persistence of the virus in these cells, their function in both the innate and adaptive immune response to HCMV infection and the potential clinical consequences of HCMV infection in DCs.

HCMV Immune Evasion Strategies

A functional immune system is of utmost importance to efficiently combat viral infections. HCMV has developed multiple immune evasion strategies to establish latency and co-exist with its host. Increasing evidence suggests that HCMV infection adversely affects both innate and adaptive immune responses. For example, HCMV escapes immune recognition by $CD8^+$ and $CD4^+$ T cells by downregulating expression of major histocompatibility complex (MHC) class I and II on infected cells. HCMV

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interferes with MHC class II expression in several ways, including US2- and pp65-dependent degradation of MHC class II proteins;[4,5] binding of US3 to class II α/β complexes and preventing their association with the invariant chain;[6] inhibiting CD10 and CD13 metalloproteinases, which participate in peptide trimming in both the MHC class I and II antigen presentation pathways and interfering with the CIITA (class II activator)/JAK-STAT signaling pathway, which tightly controls the promoter of the MHC class II region (reviewed in ref. 7).

Cytotoxic T cells (CD8 T cells) are crucial for clearing viral infections, and decreased expression of MHC class I molecules on virus-infected cells potentially facilitates the establishment of a persistent or latent infection. The antigen-presentation route of MHC class I peptide complexes can be blocked by several HCMV genes, including US2, US3, US6, US10 and US11 (reviewed in ref. 8) as well as by the tegument proteins UL82 (pp71) and UL83 (pp65),[8] and by specific downregulation of ERAP1, an aminopeptidases that reside in the endoplasmic reticulum, by the HCMV microRNA miR-US4-1.[9] Downregulation of MHC class I molecules and avoidance of $CD8^+$ T-cell responses appear to be critical in allowing superinfection of persistently infected hosts,[10] which generally occurs in immunocompetent hosts who may carry multiple strains of HCMV.

The downregulation of MHC-class I antigens on the cell surface would render the cells susceptible to lysis by natural killer (NK) cells, which respond to the absence of MHC class I molecules. However, HCMV-infected cells are resistant to NK lysis. Potential mechanisms for this resistance have been extensively reviewed.[11] In short, two HCMV proteins act on the NK cell inhibitory receptors to prevent lysis mediated by NK cells. The first is UL18,[12] an MHC class I homolog that mediates resistance to NK cells. However, cells infected with a UL18 knockout strain of HCMV are less sensitive to NK lysis, implying additional pathways for the lytic effect.[13] The second is a UL40-derived peptide that promotes the cell-surface expression of HLA-E, which suppresses lysis by NK cells by interacting with the NK cell inhibitory receptor complex CD94/NKG2A.[11] HCMV also encodes several genes that act on NK cell activating receptors: UL16, UL83, UL141, UL142 and microRNA-UL112.[11]

DCs and macrophages are specialized antigen-presenting cells (APCs) that are important mediators of immunity. Professional APCs capture, digest and present antigens to lymphocytes, produce cytokines and respond to stimuli from responding lymphocytes. APCs constitutively express MHC class II proteins and normally present antigens as MHC class II-bound peptides to resting $CD4^+$ T cells. Since DCs play a major role in both the innate and adaptive immune responses and affect most immune cells, interference with their functions by HCMV is a powerful potential mechanism for the virus to inhibit the immune response and thereby avoid immune recognition.

Development and Function of Different Human DC Subsets

DCs play a central role in activating T and B cells and thereby direct the immune response against invading microorganisms. DCs vary in their function, location and cell-surface markers, and all but Langerhans cells (LCs) are believed to be derived from hematopoietic stem cells (CD34) residing in the bone marrow.[14,15] Different subsets of DCs are found in distinct tissue locations throughout the body, where they mediate key functions of the innate and adaptive immune responses. Immature DCs reside in peripheral tissues, such as the lungs, skin and gastrointestinal tract. Upon exposure to pathogens, immature DCs becomes activated, mature, migrate to lymph nodes and present their captured antigens to naïve T cells. Their activation is influenced by pathogen-associated molecular patterns and their vertebrate receptors, including toll-like receptors (TLRs). MHC class I and II molecules present the captured antigen to immature DCs, which mature and are transported to draining lymph nodes to prime naïve T cells. Two major subtypes of DCs have identified in human blood: $CD11c^+$ myeloid DCs (mDCs) and $CD11c^-CD123^+$ plasmacytoid DCs (pDCs).

Myeloid DCs. The complex heterogeneity of DCs makes it difficult to define their origin or their divergence from monocytes and macrophages; this concept has been extensively reviewed elsewhere.[14,15] In brief, monocytes are considered to be progenitors of both DCs and macrophages and can differentiate into either cell type in vitro, depending on the cytokine stimuli they are exposed to. Upon stimulation with granulocyte-monocyte colony-stimulating factor (GM-CSF) and interleukin (IL) 4,[16] monocytes differentiate into immature DCs; these monocyte-derived DCs (moDCs) express high levels of CD11c and MHC class II.[15] Upon stimulation with cytokines, such as mononuclear phagocyte colony-stimulating factor (M-CSF) and IFN-γ/tumor necrosis factor (TNF)-α or allogeneic cytokines, monocytes differentiate into macrophages of the mononuclear phagocyte system.[17,18] Stimulation with GM-CSF results in type 1 macrophages, which are proinflammatory, while stimulation with M-CSF results in type 2 macrophages, which have anti-inflammatory functions.[19]

LCs reside in the skin and migrate to the lymph nodes to present antigens, and have many features of DCs. LCs are believed to be self-renewing in situ from a local population of myelomonocytic precursor cells in the skin. These cells appear to resemble the bone marrow precursors of myeloid cells that are present in the early fetal development and colonize the skin and proliferate around birth.[14,15]

Plasmacytoid DCs. Plasmacytoid DCs (pDCs) originate in the bone marrow from myeloid and lymphoid precursors[20] and are important mediators of antiviral immunity. They are primarily involved in the innate immune response as they secrete large amounts of type I IFNs upon viral infection, which is largely mediated through the TLR pathway[20] and results in the activation of T cells, NK cells and B cells. pDCs develop fully in the bone marrow, are released into the bloodstream and are found in small numbers mainly in secondary lymphoid organs and the thymus.[21] Upon viral infection, pDCs sense viral nucleic acids within the early endosomes through TLR7 and TLR9.[22] TLR9 senses double-stranded DNA of bacteria and viruses rich in unmethylated CpG sequences. TLR7 detects single-stranded viral RNA. TLR9 is required for pDCs to respond to DNA viruses, such as

herpesviruses (HSV-1, HSV-2, murine CMV and HCMV).[23-26] Type I IFNs produced by pDCs inhibit viral infection by augmenting the antiviral state through induction and activation of numerous antiviral molecules and functions in other types of lymphoid and myeloid cells (NK cells, mDCs and B and T cells) involved in innate and adaptive immunity.

HCMV Resides In and Can Reactivate from Latency in Cells of the Myeloid Lineage

An important biological property of HCMV is its ability to persist in a latent form and be reactivated under certain conditions. One of the key cell types in HCMV infection and latency are cells of the myeloid lineage, which develop from hematopoietic stem cells. HCMV can infect monocytes, macrophages, DCs, granulocytes, fibroblasts and endothelial, epithelial, neuronal and smooth muscle cells. Neutrophils are considered to be the major cell type carrying the virus during acute infection,[27] but they cannot support viral replication. Monocytes/macrophages are thought to be responsible for dissemination of the virus and are the primary reservoir of latent HCMV in the peripheral blood in seropositive individuals.[28]

Current evidence suggests that HCMV cannot efficiently replicate in monocytes. In these cells, HCMV infection is nonpermissive, as viral gene expression and transcription are either absent or restricted to immediate-early gene products.[29-32] The absence of late gene expression and viral production is consistent with the hypothesis that monocytes or premonocytic cells are reservoirs for latent virus. In contrast, tissue macrophages in HCMV-infected patients can express late viral genes[33] and produce infectious virus. Differentiation of monocytes into macrophages is a prerequisite for productive HCMV infection.[18,29,34]

HCMV infection behaves differently in macrophages generated by different stimuli. For example, HCMV infects relatively few macrophages generated by cocultivation of monocytes with concanavalin A stimulated autologous nonadherent cells, but infects the majority of macrophages generated by allogeneic stimulation of peripheral blood mononuclear cells.[35] The state of cellular differentiation is therefore a major factor in the ability of the virus to replicate, which is also the case for reactivation of latent HCMV. Since peripheral blood monocytes have a short half-life, reactivation of HCMV in macrophages suggests that HCMV is maintained in a precursor population of the myeloid cell lineage. Such cells would provide an ideal latency site for a virus whose activation is closely linked to the immune system. HCMV can infect $CD34^+$ pluripotent stem cells both in vitro and in vivo.[36-38] HCMV DNA follows the myeloid differentiation pathway.[39] Latent HCMV can be reactivated in myeloid DCs from HCMV-seropositive donors after ex vivo differentiation to mature DCs[40] or in macrophages produced by allogeneic stimulation of peripheral blood mononuclear cells (PBMCs).[41] The inflammatory cytokines IFN-γ and TNF-α produced by allo-stimulated T cells are important for the reactivation of latent virus and the growth of HCMV in differentiated macrophages.[42] IL-6 and subsequent signaling are important for reactivation from both experimental and natural latency in differentiating DCs.[43,44] Clinically, immune activation and concomitant production of pro-inflammatory cytokines appear to be essential for reactivation and replication of HCMV in infected patients.[45-47] Thus, immune activation, production of inflammatory cytokines and myeloid cell differentiation are likely to be important for viral reactivation and replication in HCMV-infected patients.

HCMV Inhibits Differentiation of Myeloid Cells

The maintenance of latency and reactivation is closely linked to the stage of cellular differentiation, and differentiation of all infected cells after viral entry would efficiently eliminate the virus during the infectious cycle. We showed that, after stimulation with IL-4 and GM-CSF, HCMV-infected monocytes fail to differentiate into moDCs and have a decreased ability to further mature in response to stimulation with lipopolysaccharide (**Fig. 1**).[48] The infected cells also had severe impairments in immunological functions, including endocytosis, phagocytosis, migration in response to inflammatory chemokines and induction of T-cell responses in vitro. In a recent study, monocytes were infected with an endothelial cell-adapted HCMV strain, and differentiated into moDCs; the resulting CMV-moDCs did not acquire the standard $CD1a^+$ immature phenotype of moDCs, but instead acquired the maturation marker CD83.[49] CMV-moDCs had decreased STAT5 phosphorylation, indicating defective GM-CSF signaling that was mediated by soluble factors and involved the secretion of IL-6 by infected cells. Consistent with our findings, CMV-moDCs had a decreased ability for phagocytosis and stimulating T-cell proliferation and failed to induce a T_H1 response.[49]

Besides affecting DC differentiation, HCMV reversibly blocks cytokine-induced macrophage differentiation, leading to impairments in phagocytosis and migration of these cells and possibly to a depressed immune response during an acute HCMV infection.[50] The cell-surface molecule CD13 (a putative HCMV receptor)[51] and HCMV glycoprotein B seem to be involved in the inhibition of macrophage differentiation.[52]

The inhibitory effect of HCMV on monocyte differentiation, either directly or by viral proteins such as glycoprotein B or monocyte-produced cytokines, and the central role of monocytes, DCs and macrophages in innate and adaptive immunity are consistent with the increased sensitivity of HCMV-infected patients to other infections.[53-55]

Monocyte-Derived DCs and HCMV Infection

Interest in HCMV-infected DCs, especially moDCs, has grown with improvements in experimental conditions for infecting myeloid cells with HCMV in vitro. MoDCs are produced by stimulating peripheral blood ($CD14^+$) monocytes with IL-4 and GM-CSF,[16] resulting in the generation of immature moDCs that mature in response to treatment with TNF-α or lipopolysaccharide. Although HCMV can productively infect moDCs in vitro,[56] laboratory-adapted HCMV strains do not exhibit a full replication cycle in DCs, which is dependent on mutations in the UL128-

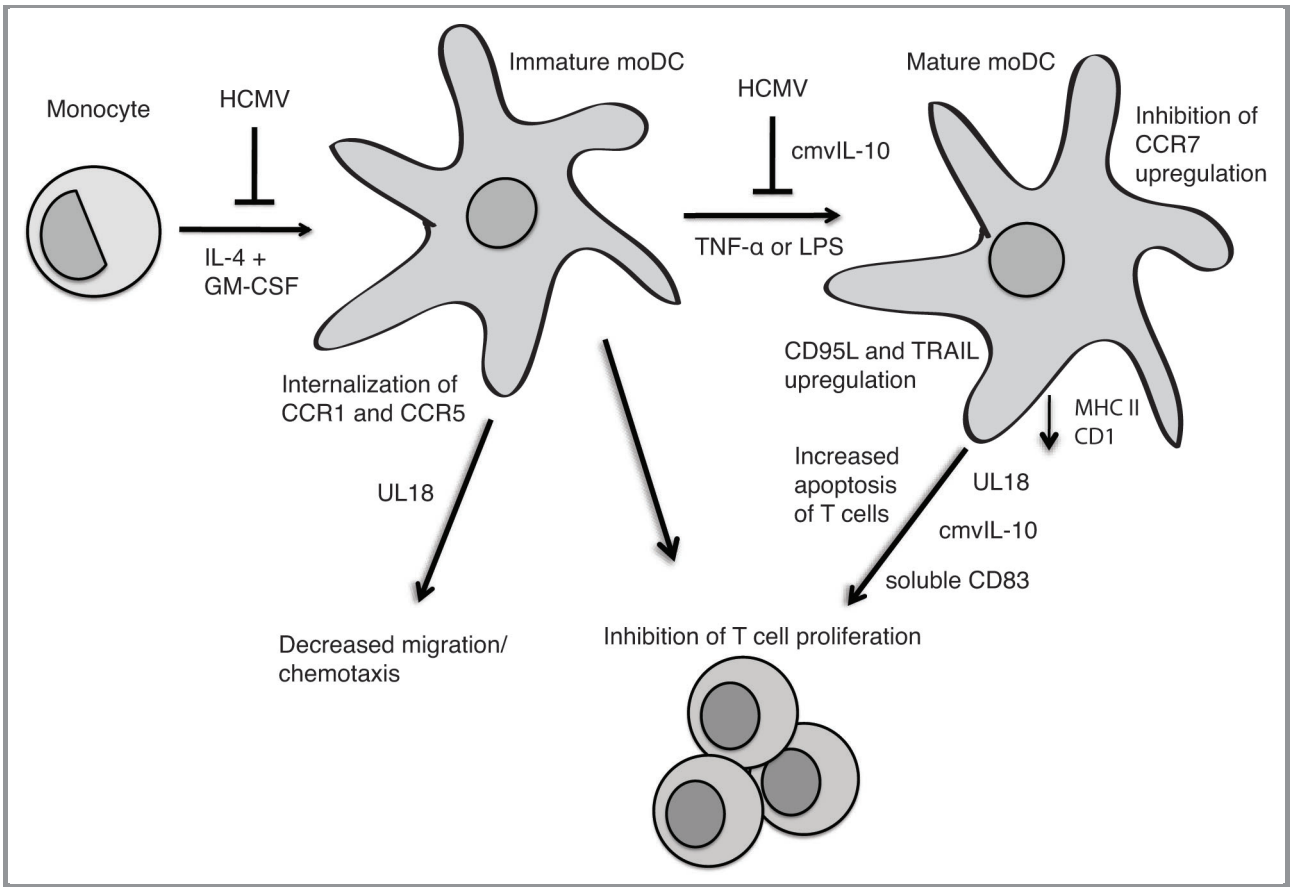

Figure 1. HCMV-infected monocytes fail to differentiate into MoDCs upon cytokine stimulation. HCMV infection of moDCs further impairs the function of these cells, whose maturation is impaired both by HCMV infection and the virally encoded protein cmvIL-10. HCMV infection of moDCs impairs the ability of the DCs to present antigens to T cells and subsequent T-cell proliferation, through mechanisms such as downregulating class II and CD1 expression, inducing apoptosis of T cells via CD95L and TRAIL, and altering cytokine production as well as mechanisms involving release of soluble CD83 and virally encoded UL18 and cmvIL-10. HCMV infection of moDCs also impairs the ability of the DCs to migrate in response to chemokines by causing the cell to internalize CCR1 and CCR5, by inhibiting the switch from CCR5 to CCR7, and by mechanisms involving virally encoded UL18.

UL131A gene region, leading to loss of dendritic and endothelial cell tropism.[57-59] Instead, clinical isolates grown in endothelial cells that maintain the UL128–131A locus can be used to infect DCs.[60] HCMV strains that productively infect cells of myeloid origin (monocytes/macrophages and DCs) in vitro include TB40/E, VHLE, VR1814 and FIX.[44,56,59] HCMV infection of moDCs is facilitated by the binding of HCMV glycoprotein B to the DC membrane protein DC-SIGN, which increases the susceptibility of moDCs to HCMV.[61] Soluble DC-SIGN (sDC-SIGN), which is increased in body fluids in inflammatory settings and upon HCMV infection in human tissue explants, enhances HCMV infection in moDCs, potentially by serving as an opsonin for HCMV virions.[62]

HCMV enters DCs via a macropinocytosis-like pathway.[63] An early study showed that HCMV infection in moDCs results in maturation of the surviving cells, upregulation of the costimulatory molecules CD40, CD80 and CD86, and downregulation of MHC class I and class II molecules.[64] HCMV-infected mature moDCs suppressed T-cell proliferation and induced apoptosis in T cells through CD95L and TRAIL (**Fig. 1**).[64] However, subsequent studies yielded somewhat different findings, including an HCMV-induced block of DC maturation, decreased expression of co-stimulatory molecules, and unaffected or slightly reduced levels of CD86 and MHC class II expression.[65,66] HCMV infection of DCs also decreased production of the cytokines TNF-α and IL-12 and impaired the proliferation and cytotoxity of T cells.[66]

DCs are essential for generating an antiviral response, in part by inducing cytokine and chemokine responses. For example, type I IFNs produced by immune cells limit viral spread and activate cytotoxic T-cell and B-cell responses against infected cells. HCMV infection in moDCs upregulates the expression of genes encoding proinflammatory cytokines and chemokines, TLR3 expression and expression of genes whose products function downstream of the TLR3 signaling pathway (e.g., IFN-α and IFN-β).[67] However, the early HCMV-triggered immune response in human moDCs appears to be independent of TLR3, as silencing of TLR3 expression before HCMV infection of the cells does not influence IFN-β expression.[67]

One of the major effects of HCMV infection in moDCs in vitro is inhibition of T-cell proliferation, possibly because the virus inhibits the maturation of moDCs.[65,66] HCMV infection of

mature moDCs results in release of the soluble form of CD83 that specifically inhibits T-cell proliferation (**Fig. 1**).[68] Furthermore, the HCMV-encoded MHC class I homolog UL18 impairs induction of T-cell proliferation after CD40L-induced DC maturation (**Fig. 1**).[69] Although the binding of UL18 to immature moDCs increased secretion of IL-10 and IL-6, the decreased T-cell proliferation was not explained by IL-10. UL18 also induced the expression of the maturation marker CD83 on moDCs.

To fulfill their function and activate the immune response, DCs must migrate from the site of infection to the lymph nodes, the site of T-cell priming, in response to CCL19 and CCL21, chemokines produced by secondary lymphoid organs. A switch from CCR5 to CCR7 during DC maturation enables the cells respond to these chemokines. However, HCMV can prevent this chemokine receptor switch in infected moDCs—and thereby inhibit migration of mature moDCs in response to CCL19 and CCL21.[70] In immature moDCs, HCMV infection impairs chemotaxis in response to CCL3 and CCL5, and internalizes CCR1 and CCR5, but does not affect CCR7.[71] The HCMV protein UL18 also reduces the chemotaxis of moDCs in response to RANTES.[69] Evidently, HCMV uses multiple strategies to alter DC trafficking, which is important for an adequate immune response upon infection (**Fig. 1**).

During latency, HCMV appears to produce a latency-associated form of the HCMV-encoded IL-10 homolog cmvIL-10[72] through altered splicing.[73] Treatment of myeloid cell populations with recombinant latency-associated cmvIL-10 (LAcmvIL-10) downregulates MHC class II expression in granulocyte-macrophage progenitor cells and monocytes but does not affect the maturation of moDCs or their production of proinflammatory cytokines.[74] cmvIL-10 inhibits differentiation of DCs from latently infected $CD34^+$ progenitor cells, possibly by suppressing the transcription of proinflammatory cytokines.[75] cmvIL-10 can also inhibit the maturation of moDCs and production of the proinflammatory cytokines IL-6, IL-12 and TNF-α;[76] however, cmvIL-10-treated moDCs that did mature migrated to a greater extent than mock-treated moDCs.[76] Furthermore, cmvIL-10 impairs the functional maturation of immature moDCs, suppressing their production of IL-10 and IL-12, increasing apoptosis of the cells.[77] By upregulating DC-SIGN, cmvIL-10 increases the susceptibility of DCs to HCMV infection.[77] In moDCs, cmvIL-10 interferes with CD1 antigen presentation by decreasing transcription of CD1 through an unknown mechanism.[78]

HCMV Infection in Langerhans DCs

HCMV infection of Langerhans DCs (LCs) has been studied in an in vitro system in which LCs are derived from $CD34^+$ progenitor cells.[79] The susceptibility of LCs to HCMV was dependent on the stage of maturation. Specifically, immature LCs supported productive infection with endotheliotropic strains of HCMV to a very low degree (3–4%), whereas LC-derived mature DCs were highly susceptible to infection.[79] In LC-derived mature DCs, HCMV infection downregulates MHC class I and II, CD1a, CD80, CD86, CD83 and CD54, reduces the ability to stimulate a T-cell response,[79] lowers cell-surface expression of MHC class II, mostly by binding or penetration by HCMV particles, since conditioned medium from infected cells did not mediate this effect,[80] leads to a dramatic loss of dendrites and inhibits migration in response to lymphoid chemokines.[80] In addition, HCMV infection of LC-derived mature DCs inhibits constitutive expression of class II transcriptional regulators, most likely at the transcriptional level, resulting in reduced biosynthesis of MHC II.[81]

HCMV Infection in Plasmacytoid DCs

Plasmacytoid DCs (pDCs), the main producers of type I IFN in response to viral infection, are essential for antiviral immunity. Circulating blood plasmacytoid DCs (bpDCs) have low susceptibility to HCMV infection, and one group suggested that bpDCs are resistant to HCMV infection in vitro.[82] In that study, few $CD11c^+$ DCs isolated from peripheral blood were sensitive to in vitro HCMV infection, while immature and mature moDCs were more readily infected. Upon HCMV exposure, both bpDCs and $CD11c^+$ DCs produced high amounts of IFN-α and exhibited increased survival. In $CD11c^+$ DCs, production of IFN-α decreased sensitivity to HCMV; upon HCMV exposure, the cells matured and increased their levels of MHC class I, MHC class II and CD83; and even though class I and CD83 expression decreased on HCMV antigen-positive cells, the DCs retained full T-cell stimulatory capacity.[82]

In contrast, we showed that HCMV infection of bpDCs is nonpermissive,[26] induces partial maturation of the cells and upregulates their expression of MHC class II and CD83. By engaging the TLR7 and/or TLR9 pathways, HCMV increased production of IFN-α and secretion of IL-6 and IL-10 (**Fig. 2**).[26] HCMV infection inhibited T-cell proliferation but triggered activation and proliferation of B cells by soluble factors produced by HCMV-infected bpDCs and induced plasma cell differentiation and antibody production in the presence of T cells or IL-2 (**Fig. 2**).[26] Even though bpDCs are relatively resistant to HCMV infection, the virus causes them to release large amounts of IFN-α, which renders other cell types more resistant to HCMV infection.[83] Since cmvIL-10 suppresses the production of type I IFNs by bpDCs, this may be a potential immune evasion mechanism to increase viral susceptibly of surrounding cell types.

HCMV-infected pDCs can also induce NK cells to increase their expression of activation markers, produce high levels of the inflammatory cytokines IFN-γ and TNF-α and increase migration via soluble factors; however, the infected pDCs impair the cytotoxicity of NK cells (**Fig. 2**).[84] pDCs isolated from peripheral blood or lymphoid organs (tonsils) consist of two subpopulations that behave differently upon HCMV infection: blood-pDCs (bpDCs), which are resistant to HCMV infection, and tonsillary pDCs (tpDCs), which are fully permissive.[85] In tpDCs, HCMV infection reduces expression of adhesion and costimulatory molecules and the ability to allogeneically stimulate T cells and impairs IFN-α production.[85] In bpDCs, infection leads to activation, increases expression of MHC class I, adhesion

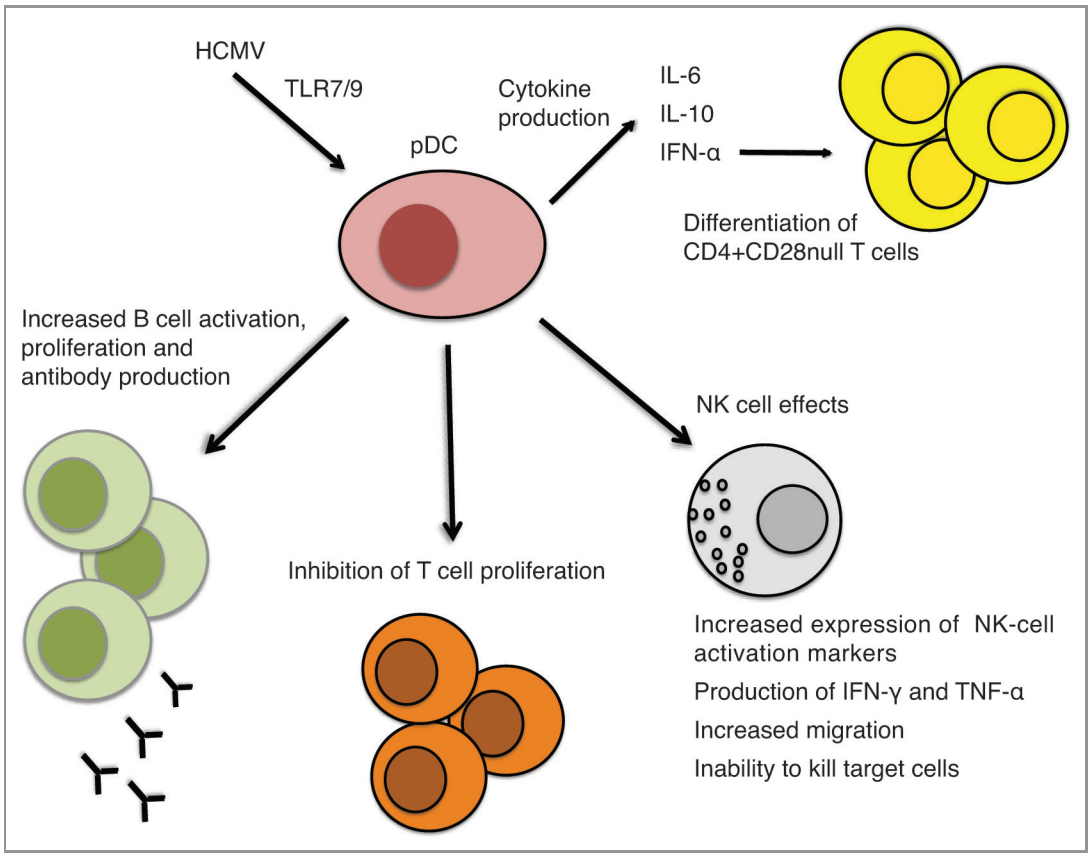

Figure 2. HCMV infects pDCs nonpermissively. Through engagement of the TLR7 and/or TLR9 pathways, HCMV induces production of IFN-α and secretion of IL-6 and IL-10. HCMV infection in pDCs has an inhibitory effect on T-cell proliferation, but triggers B-cell activation and proliferation and antibody production. HCMV infection of pDCs has a pronounced effect on NK cells: it increases expression of NK-cell activation markers, induces production of high levels of inflammatory cytokines, and increases migration, but impairs the ability to kill target cells. IFN-α production by HCMV-infected pDCs together with chronic HCMV antigen stimulation may lead to differentiation of $CD4^{+}CD28$-null T cells.

molecules and costimulatory molecules and production of IFN-α,[85] but markedly reduces allogeneic T-cell stimulation. The decrease in allogeneic T-cell stimulation in infected tpDCs and bpDCs was mediated by an HCMV-induced soluble factor.

The effects of HCMV-infected pDCs on T cells, NK cells and B cells emphasize the role of pDCs in controlling innate and adaptive immune system responses and HCMV's ability to subvert important mediators of the immune response.

HCMV-Induced Cross-Presentation by DCs

A cytotoxic T-cell response is dependent on the activation of native cytotoxic T lymphocytes (CTLs) by professional APCs, usually DCs. Since HCMV can compromise the endogenous MHC class I pathway and infect DCs to a variable degree, the immune system could take advantage of cross-presentation to evoke a CTL response. Cross-presentation occurs when the APCs present extracellular antigen on their MHC class I molecules.[86] Indeed, HCMV infection of fibroblasts induces cross-presentation to CD8 T cells.[87,88] Since immature moDCs are not permissive to fibroblast-adapted laboratory strains of HCMV, cross-priming has been studied in an in vitro system that uses strain AD169. Uninfected immature moDCs internalized pp65-positive apoptotic HCMV-infected fibroblasts, which led to an anti-pp65 CD8 T-cell response, suggesting that the moDCs acquired and processed pp65 from the apoptotic fibroblasts.[87,89] In addition, HCMV-infected fibroblasts induced maturation of moDCs and upregulated expression of CD83 and HLA class II.[88]

Cross-Talk between NK Cells and DCs during HCMV Infection

DCs play a key role in innate immunity through bidirectional cross-talk with NK cells. The NK cell-mediated response to HCMV infection has mostly been studied in fibroblasts, so data on NK-DC crosstalk in HCMV infection are limited. In an autologous system, NK cells upregulated the surface expression of activation markers, secreted high concentrations of IFN-γ and degranulated in the presence of HCMV-infected moDCs, an effect that was mainly attributed to NKp46 and DNAM-1.[90] In a similar system, HCMV infection of M1 and M2 macrophages triggered NK cell cytotoxicity involving NKp46, DNAM-1 and 2B4 receptors.[91] Even though HCMV-infected M1 and M2 macrophages caused similar levels of NK cell degranulation, only

M1 macrophages produced IL-12 and effectively activated NK cell-mediated IFN-γ secretion. Thus, distinct subsets of APCs (e.g., DCs or macrophages) trigger NK cell response through different mechanisms, highlighting the importance of studying mechanisms in a suitable cellular system.

Impact of HCMV in DCs on Clinical Pathology

HCMV infection and reactivation in the immunocompetent host. The numerous mechanisms by which HCMV avoids recognition and elimination by the host immune system may have implications for the host during acute infection or after reactivation of latent virus. In immunocompetent hosts, primary HCMV infection can be asymptomatic, although viral shedding can persist for months or, after congenital infection, for many years.[1,92] In patients who have a normal immune response, most diagnosed primary HCMV infections cause an acute infection accompanied by a transient immunosuppression lasting weeks or months,[93] along with clinical symptoms of mononucleosis. The immunosuppression most likely reflects direct effects of the virus on cell types involved in the normal immune response as discussed above. Peripheral blood lymphocytes from patients with an acute HCMV infection exhibit a diminished proliferative response to mitogens and an increase in $CD8^+$ cells that reverses the CD4/CD8 ratio.[94] HCMV-infected monocytes also suppress the autologous lymphocyte response to concanavalian A.[95]

Acute HCMV infection is associated with a loss of DCs in peripheral blood. As described above, in vitro studies provide evidence that HCMV affects DCs at multiple levels to impair or enhance their functions. For example, HCMV can induce DCs to secrete proinflammatory factors, inhibit the immunostimulatory and migratory abilities of DCs, and in cooperation with virally encoded IL-10, cause long-term inhibition of DC function. However, there are only limited data on the potential relevance of HCMV infection of DCs in vivo and the resultant DC homeostasis in HCMV-infected patients. We showed that patients with HCMV-induced mononucleosis have fewer mDCs and pDCs in peripheral blood than healthy controls.[96] The decrease correlated with elevated levels of inflammatory mediators, in particular with high TNF-α levels, which activate DCs and endothelial cells. Further, the decreased level of DCs in blood correlated with the high levels of TNF-α and IL-8 by a hyperbolic function, suggesting a direct relationship.

At high levels, inflammatory factors facilitate alterations in DC homeostasis during primary HCMV infection, and DCs are the most potent APCs that stimulate naive T cells and modulate the effector response to infections. Therefore, the reduced numbers of circulating DCs may result from enhanced compartmentalization of these cells in peripheral tissue during HCMV infection, as in other infections.[97,98] This scenario could lead to HCMV-induced modulation of host immunity and thereby contribute to HCMV-related diseases. If this scenario is dependent on TNF-α, the same situation may arise in acute infection, chronic inflammation or autoimmune diseases that increase TNF-α levels (e.g., sepsis, cardiovascular disease, IBD, rheumatoid arthritis and SLE). TNF-α induces DC maturation and migration, upregulates the production of vasodilatatory mediators, adhesion molecules and chemokines and alters the junctional organization of endothelial cells, thereby facilitating transendothelial migration of DCs.[99,100]

In addition, monocyte-derived DCs from symptomatic HCMV-infected immunocompetent subjects had an altered immunophenotype characterized by decreased expression of MHC class II molecules.[101] These DCs had an impaired ability to stimulate T-cell proliferation and a proinflammatory pattern of cyto-chemokine secretion characterized by significantly increased production of IL-1β, TNF-α, CCL2 and CCL3 and reduced secretion of the anti-inflammatory cytokine IL-10.[101]

Reactivation of HCMV in immunocompetent hosts is associated with different types of stress (e.g., work stress or oral herpesvirus lesions), suggesting that the virus can be reactivated in the absence of a clinical diagnosed immunodeficiency.[102] Indeed, in multiple studies, HCMV was reactivated in more than 30% of immunocompetent patients admitted to the intensive care unit and increased both the length of hospitalization and the risk of death.[103,104] Typically, the virus is reactivated 1–3 weeks after hospitalization.[104] Patients with bacterial sepsis have a greater risk of HCMV reactivation.[45,103] Critically ill immunocompetent patients with reactivated HCMV seem to die not from HCMV viremia but from other mechanisms, such as cytopathology in the affected organ, immunopathology from the immune response to the virus and bacterial and fungal superinfections (reviewed in ref. 105). More studies on the specific cell types involved in the reactivation of HCMV infection under these conditions are necessary. However, continuous HCMV monitoring and prophylaxis or early treatment may reduce HCMV reactivation and secondary infection in immunocompetent patients with critical illnesses.

Effects on HCMV infection and reactivation in transplant patients. HCMV is one of the most important pathogens in recipients of stem cell and organ grafts. A key risk factor for HCMV-related disease is the serostatus of the donor and recipient; the risk is highest for HCMV-negative recipients of tissue from HCMV-positive donors.[106,107] In transplant recipients, HCMV infection produces symptoms such as fever, bone marrow suppression and organ-invasive disease, usually of the transplanted organ itself, which also appears to be more susceptible to the direct effects of HCMV infection than native organs.[108]

Low pretransplant levels of mDCs are associated with higher incidence of post-transplant HCMV infection and death in kidney transplant patients, but no association has been found between pDC levels and HCMV infection.[109] Purified DCs from kidney transplant patients with HCMV viremia contain HCMV DNA, showing that DCs indeed are infected in vivo.[65] In subsets of blood DCs and monocyte-derived DCs from heart-transplant patients undergoing an acute HCMV infection, both HCMV RNA and antigens could be detected,[110] indicating active replication. Infection was associated with an impaired immunophenotype characterized by increased secretion of IL-10 by immature DCs and reduced ability of mature DCs to stimulate allogeneic T-cell proliferation.[110]

The ability of HCMV to infect mDCs may contribute to HCMV reactivation and pathogenesis. In allogeneic stem-cell

transplant patients, certain DC-SIGN alleles are associated with HCMV reactivation (G allele of rs735240) and HCMV disease (C allele of rs2287886).[111] In healthy subjects, these alleles influence the expression levels of DC-SIGN on immature DCs;[111] HCMV infection in DCs was more efficient in subjects carrying alleles that correlate with higher DC-SIGN expression levels.

The effects of HCMV infection in transplant patients extend beyond the acute phase; such patients are more susceptible to bacterial, fungal and other opportunistic infections (for a review, see refs. 106–108). HCMV has also been implicated in acute and chronic rejection of transplanted organs, and the relation between rejection and HCMV appears to be bidirectional, with HCMV causing rejection, and the inflammation caused by rejection increasing viral replication.[108,112] HCMV may also mediate post-transplant diabetes mellitus, cardiovascular diseases and malignancies.[112] Strong evidence from epidemiological and clinical treatment studies suggests a causal relationship between HCMV and these diseases; however, the virus has been difficult to detect in the patients. Therefore, the term "indirect effects" has been used to describe the contribution of the virus to these complications. However, it is difficult to imagine how latent HCMV can affect so many different diseases. Indeed, using optimized staining protocols to examine kidney grafts after chronic rejection, we detected high levels of viral protein expression in a majority of the samples.[113] This finding challenges the notion that HCMV has indirect effects in this disease. Thus, HCMV may be more active in the affected tissue than previously recognized and confer direct molecular effects relevant in disease pathogenesis of chronic rejection in the graft, rather than mediating its pathogenic effects indirectly.

Evidence for a role of HCMV in common diseases: associations between HCMV, chronic inflammation and autoimmunity. Although primary HCMV infection is generally mild in immunocompetent subjects, symptomatic disease may develop, and some case reports have implied a connection with immune dysfunction and autoimmune phenomena; primary HCMV infection may trigger or exacerbate inflammation and autoimmunity in seemingly immunocompetent hosts. For example, active HCMV infection is often detected in patients with SLE, where it is associated with higher disease activity scores and has been implicated in both the development and progression of the disease (reviewed in ref. 114). HCMV is also associated with rheumatoid arthritis, myositis, Guillain-Barre syndrome, Wegner granulomatosis, psoriasis, vasculitis, atherosclerosis and IBD (reviewed in ref. 114).

HCMV infection is associated with various manifestations of autoimmunity. Primary HCMV infection often results in production of autoantibodies against endothelial cells and smooth muscle cells (i.e., antinuclear, antiphospholipid and anti-CD13 autoantibodies) (reviewed in ref. 114). The immunogen may be CD13, a structural component of HCMV particles; CD13-specific auto-antibodies were detected in stem cell recipients and in IBD patients who had had an HCMV infection but not in those who were HCMV negative.[115,116] Thus, during HCMV infections, the HCMV-associated auto-antigen CD13 may become immunogenic through its presence in the viral particle. This novel mechanism of autoimmunity may be further enhanced by DCs. pDCs induce plasma cell differentiation by producing type I IFN and IL-6;[117] HCMV induces IFN-α secretion from bpDCs through the TLR7/TLR9 signaling pathways and induces IL-6 production,[26] which would increase antibody production.

Although HCMV infection sometimes seems to precede the onset of autoimmune disease, the presence of auto-antibodies during primary HCMV infection is usually not associated with clinical autoimmunity. Clinical autoimmunity likely occurs more frequently in people who are genetically predisposed to the condition, but no clear risk profile has been identified. Most likely, autoimmunity depends on the functionality of the immune system and is influenced by inherited defects in immunity, such as polymorphisms in the genes encoding TLR and mannose-binding lectin, cytokine and chemokine defects, HCMV-specific T-cell compartments and expression of programmed cell death 1 and immune-evasion genes (reviewed in ref. 106).

Allogeneic hematopoietic stem cell transplant patients diagnosed with HCMV infection have a significantly higher frequency of the T-1237C (TLR9) polymorphism than patients without infection,[118] implying a potential role for TLR9 in the recognition and response to HCMV in vivo. Patients with chronic mucocutaneous candidiasis have a higher frequency of a TLR3 variant (L412F), and an increased frequency of autoimmune disorders and severe viral infections, including HCMV infections.[119] These patients also have a weak proliferative response to HCMV antigens in vitro. In human moDCs, TLR3 is localized in intracellular endosomal compartments and detects pathogens after cellular uptake. This finding implies that antiviral mechanisms related to TLR3 functions may not be working properly in these patients.

HCMV may be linked to autoimmunity through several different mechanisms, such as molecular mimicry, epitope spreading, cross reactivity or virally induced expression of cryptic antigens normally hidden to the immune system.[114] Patients with HCMV-induced autoimmunity may be coinfected by other pathogens,[120] which may increase TLR activation and complement activation, resulting in an enhanced immune response. Recently, it was reported that a majority of SLE patients have antibodies to the C terminus of the HCMV protein pp65, in particular to a subfragment of pp65.[121] Immune reactivity against this peptide was also found in 14–20% of patients with rheumatoid arthritis, Sjögren syndrome and systemic sclerosis but only in 4% of healthy controls.[121] Antibodies against HCMV pp65 cross-reacted with nuclear proteins and double-stranded DNA and were therefore proposed to be pathogenic.[121] This hypothesis is further supported by animal experiments; in lupus-prone mice, immunization with pp65 resulted in autoantibody production and glomerulonephritis.[122] Immunization of BALB/c mice with the subfragment of pp65 resulted in production of multiple antibodies that recognize nuclear structures, including chromatin, centriole mitotic spindle type I/II and double-stranded DNA.[121] Interestingly, TLR3, TLR7 and TLR9, which induce IFN-α production upon ligand binding, are associated with SLE and linked to production of auto-antibodies and IgM rheumatoid factor.[123,124]

We recently described a previously healthy woman who had a primary HCMV infection and bacterial infection of the urinary tract. Subsequently, she developed systemic vasculitis and had extraordinarily higher plasma levels of proinflammatory cytokines, auto-antibodies and viral DNA than other patients with primary HCMV infection.[120] We also described a previously healthy patient who acquired a symptomatic primary HCMV infection that resulted in severe autoimmune encephalitis.[125] None of these patients had a family history of autoimmunity, and it is not known why they developed severe infection and subsequent clinical autoimmunity. Mice that are deficient in TLR7/9 pathways are more susceptible to murine CMV infection and have a higher mortality.[126] Thus, viral persistence due to an inability to clear the active infection may be connected to TLR functions. Studies are needed to further define the genetic susceptibility to HCMV-induced pathologies in patients with HCMV infection and autoimmunity.

HCMV infection in chronic inflammatory diseases. HCMV may trigger autoimmune disease in genetically susceptible people. However, the virus is more likely to contribute to autoimmune or chronic inflammatory diseases after reactivation by an inflammatory insult initiated by other antigens; thereafter, HCMV proteins would sustain and exacerbate inflammatory processes. HCMV can most likely be reactivated in monocyte-derived macrophages or moDCs in tissues with active inflammation; HCMV peptides will further drive immune reactions locally, as the immune system will consider them non-self antigens. Furthermore, viral mechanisms that induce inflammation and autoimmune reactions will further sustain and exacerbate inflammation. For example, HCMV infection induces expression of COX-2 and 5-LO and production of PGE2, LTB4 and IL-6—all potent inflammatory mediators. Through interactions with TLRs on pDCs, HCMV induces production of type I cytokines.[26]

A better understanding of the role of HCMV in chronic inflammation would likely improve our understanding of the pathogenesis of inflammatory diseases and the potential impact of antiviral therapy on disease progression. Indeed, in many case reports, antiviral therapy appeared to result in clinical improvement of IBD patients with HCMV infection. HCMV nucleic acids and proteins are frequently found in biopsy specimens of patients with IBD.[127] In particular, HCMV infection should be suspected in patients with steroid-resistant ulcerative colitis.

As a target organ for HCMV, the gut is especially interesting from the perspective of immune regulation. The gut can mount an immune response against pathogenic bacteria and viruses but not against commensal bacteria. It is unclear why this is so. DCs in the gut would be the main primers of naive T cells to the invading pathogen. IBD patients appear to have lower levels of immature DCs in peripheral blood,[128] and these DCs have increased levels of CD86, which further increase upon stimulation ex vivo.[128] We showed that the loss of peripheral blood DCs correlates with high levels of TNF-α,[96] which increase during flare-ups of IBD and during HCMV infection.[45,129] The apparent chronic presence of HCMV antigens in the bowel of a majority of IBD patients would challenge DCs to prime an immune response against HCMV and direct the it toward expansion of T helper 1 cells, T helper 2 cells or regulatory T cells. Regulatory T cells (Tregs), a subpopulation of CD4 T cells expressing the FoxP3 transcription factor and CD25, are involved in the control of a number immunological conditions, including autoimmunity, transplant rejection and host response to pathogens,[130] and also seem to be involved in the control of CMV disease. For example, impaired Treg reconstitution after allogeneic bone marrow transplantation (BMT) was suggested to be associated with HCMV viremia as well as acute graft vs. host disease.[131] Increased levels of Tregs seems to protect against HCMV infection after allogeneic BMT, possibly depending on the lower ability of patients with lower Treg numbers to recover their HCMV-specific CD8 T cells.[132] In agreement with these findings, adoptive transfer of Tregs in a murine GVHD-model led to protection against lethal MCMV infection due to MCMV-specific immunity with increased viral clearance.[133] In contrast, MCMV infection in vitro and in a murine BMT-model suggest that high numbers of Tregs suppress the immune response to MCMV via effects on effector T cells and by the suppression of peripheral T cell generation.[134,135]

Expansion of antigen-specific Tregs can be controlled by antigen-specific DC subsets in the peripheral tissues.[130] MCMV infection of mouse fibroblasts was found to stimulate the differentiation to Tregs in vitro.[135] Presence of HCMV antigens in different peripheral tissues during HCMV infection in autoimmune and inflammatory conditions would challenge DCs to prime an immune response against HCMV and would thereby be able to induce a Treg expansion. However, since HCMV infection in DCs impairs their function with effects on the maturation, T cell proliferation and migration, the ability of DCs to induce an HCMV-specific Treg expansion might be suppressed by the virus, thereby potentially leading to loss of viral control. Further studies would be necessary to define the effect HCMV on Tregs in patients with HCMV infection and different autoimmune and inflammatory conditions. Thus, a greater understanding of the interactions between HCMV, DCs and the resultant T-cell phenotypes expanded in autoimmune and inflammatory conditions should shed further light on the pathogenesis of the diseases.

HCMV in cardiovascular diseases. HCMV is associated with atherosclerosis, restenosis after coronary angioplasty, aortic aneurysms, transplant vascular sclerosis and other vascular diseases.[136] Inflammation is thought to be a key feature of these diseases, and T cells are considered to be the major disease-promoting cells, often triggered by oxidized low-density lipoproteins, which may be an auto-antigen in atherosclerotic plaques.[137] Since DCs direct the adaptive T-cell response, it will be interesting to assess their role in atherosclerosis. Both mDCs and pDCs are present in early lesions in healthy subjects and in atherosclerotic plaques,[138,139] and advanced and vulnerable plaques appear to have higher numbers of DCs.[140] It has been suggested that different vessels have specific TLR profiles, suggesting that a vessel-specific risk may exist in inflammatory and pathogen-mediated vascular diseases.[141,142]

Although HCMV has been detected in atherosclerotic plaques,[143,144] it has not been determined whether HCMV is an

epiphenomenon of vascular diseases or contributes to the pathogenesis.[3,136] Most likely, HCMV acts locally in the plaque and does not produce signs of systemic infection in most patients with atherosclerosis. However, we found that active HCMV replication is more common in monocytes from patients with stable or unstable coronary artery disease; specifically, CMV RNA was detected in blood monocytes in 15% of patients with acute coronary syndrome and 10% of those with stable angina, but in only 2% of age- and sex-matched controls.[145] Furthermore, two large clinical studies of more than 14,000 and 1,400 subjects, respectively, provide compelling evidence that high HCMV antibody titers and enhanced CRP levels are strongly predictive of cardiovascular mortality.[146,147] Thus, HCMV antibody levels may be a hitherto unrecognized prognostic factor for cardiovascular events and a useful biomarker for identifying patients at risk for MI and stroke. The relationship of high HCMV IgG antibody levels to mortality may be mediated mainly by IL-6 and TNF-α,[146] further supporting the importance of a high-inflammatory state in patients with clinical complications of HCMV infection. We showed that high TNF-α levels are linked to lower levels of DCs in the blood of patients with HCMV mononucleosis. HCMV induces production of IL-6 and TNF-α, and TNF-α acts directly on the HCMV immediately early promoter to drive reactivation and replication of the virus.[148] TNF-α levels are also elevated in several chronic inflammatory and autoimmune diseases and used as a target for therapy.

CD28-null T cells: a novel T-cell population associated with chronic inflammation in HCMV-infected patients. Emerging evidence implies that HCMV can be reactivated silently in immunocompetent subjects, leading to expansion of memory T cells that lose expression of the co-stimulatory molecules CD27 and CD28 and express CD57 and the NK cell marker CD244. This population, often referred to as CD28-null T cells, expands with HCMV infection, increasing age and during inflammatory conditions such as myositis, rheumatoid arthritis, IBD, Wegner granulomatosis, SLE, atherosclerosis and chronic transplant rejection.[114,149-152] These T cells are mainly directed against HCMV and provide high inflammatory activity, as they contain high perforin levels and produce high levels of IFN-γ and TNF-α upon stimulation,[153] and thereby contribute to inflammation. However, $CD4^+CD27^-CD28^-$ T cells that are in vitro stimulated with HCMV was shown to exhibit a Treg phenotype and inhibit de novo HCMV-specific proliferation of autologous PBMC.[154] Thus, their role in pathogenesis remains obscure. While $CD8^+$ cells lacking CD28 are described in patients who are infected with HCMV, HIV, hepatitis C and EBV,[155] $CD4^+CD28^-$ cells exist only in HCMV-infected individuals.[149] Since most carriers of HIV, hepatitis C or EBV also are HCMV positive, it is possible that HCMV drives the expansion of these cells by unknown mechanisms.[156] Experimental data suggest that pDCs and IFN-α are necessary to induce differentiation of CD28-null T cells (**Fig. 2**).[156] However, this scenario would exist during many microbial infections, and, thus, it is not known why $CD4^+CD28^-$ T cells are present only in HCMV-infected individuals and what the role is of these cells.

Conclusions

DCs play a crucial role in initiating and maintaining immune responses, and HCMV infection of DCs may inhibit their functions, lead to virus-induced immunopathology, enable the virus to persist in its host and control reactivation of the virus. Viral infection of progenitor cells in the bone marrow and further differentiated cells of myeloid and lymphoid origin, including multiple DC subsets, may contribute to HCMV-induced immunosuppression in patients with primary HCMV infection and in immunosuppressed patients with HCMV disease, and increase the risk for invasive fungal and bacterial infections. Increasing numbers of patients are being treated with immunosuppressants, and there is emerging evidence of an active HCMV infection in many inflammatory diseases and cancer. Thus, further research on the interaction of HCMV and DCs, is needed to understand the role of HCMV in the pathogenesis of these diseases and to develop new therapies that target this interaction.

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