Research Progress on Cytomegalovirus and Chronic Kidney Disease

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Abstract: Chronic kidney disease (CKD) is a major risk factor for end-stage renal disease (ESRD), and its prevalence continues to rise. Increasing evidence suggests that cytomegalovirus (CMV) is not only a common opportunistic pathogen but also a potential pathogenic factor involved in the progression of CKD.CMV infection is characterized by lifelong latency, periodicity, and reactivation, which can cause continuous immune activation and inflammatory states. This article reviews the biological characteristics, latent infection, reactivation mechanisms, microRNAs, and immune cells associated with CMV, aiming to explore the potential mechanisms of kidney disease progression from a new perspective of viral infection and immune regulation, and to provide new insights and potential intervention targets for the prevention and treatment of CKD.

***Keywords*:** chronic kidney disease, cytomegalovirus, immune cells, microRNAs

1. Overview of Cytomegalovirus

1.1 Biological Characteristics of Cytomegalovirus (CMV)

CMV is a pathogen classified within the Herpesviridae family and ranks among the most prevalent infectious agents worldwide. Commonly abbreviated as CMV, the cytomegalovirus that infects humans is designated Human Cytomegalovirus (HCMV). It is a β-herpesvirus characterized by double-stranded linear DNA, with a genome size of approximately 230 kb, making it the largest and most intricate among herpesviruses. HCMV is widespread in nature, and the human population generally remains susceptible to infection. Despite this ubiquity, HCMV exhibits limited viability in external environments, being sensitive to lipid solvents, heat, ultraviolet light, and acidic conditions, and can only survive for a few days at 4°C.There are four primary modes of transmission for HCMV: vertical transmission, horizontal transmission, contact transmission, and iatrogenic transmission. CMV can persist in a latent state within the body for an extended period. In immunocompetent adults, it may cause only mild or subclinical symptoms; however, it can induce opportunistic infections in immunocompromised, immature, or suppressed individuals, potentially resulting in life-threatening outcomes[1-2].

1.2 Latency and reactivation of CMV

Latent cytomegalovirus infection refers to a type of infection where, under the pressure of the host's immune system, the virus evades the immune system by shutting down the expression of most of its genes, maintaining only its presence in the host cells, while retaining the ability to reactivate when specific conditions are met[3]. In the human body, latent HCMV primarily resides in bone marrow CD34+ hematopoietic progenitor cells (HPCs) and peripheral blood monocytes[2]. The key to establishing latency lies in the effective silencing of the viral genome, the core mechanism of which is the suppression of major immediate-early (MIE) gene expression. Previous studies suggested that this is the result of high levels of host transcriptional repressors acting together with viral proteins to establish and maintain a repressive chromatin state in the MIE promoter (MIEP) region, leading to transcriptional silencing of the crucial lytic cycle genes IE1/IE2[4].

CMV reactivation refers to the process where the latent virus in the host is re-induced to enter the lytic replication cycle, leading to viral replication and potential disease occurrence[1]. Its core molecular mechanism is the expression of the viral MIE genes, which is mainly driven by cell differentiation and inflammatory signals. When latently infected myeloid progenitor cells differentiate into macrophages or dendritic cells, this process drives CMV reactivation. Cell differentiation induces the transcription of MIE genes through the activity of host chromatin remodeling enzymes. At the same time, inflammation-related signaling pathways are also key drivers of reactivation. Inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) can induce MIE gene expression. These signals exert their effects through pathways like extracellular signal-regulated kinase (ERK) and Src family kinases (SFK), while the binding sites for multiple transcription factors present in the MIE promoter, such as nuclear factor-κB (NF-κB), cAMP response element-binding protein (CREB), and activator protein 1 (AP1), play an important role in controlling MIE gene expression during reactivation[2]. In terms of immune mechanisms, the occurrence of reactivation usually signifies the failure of immune regulation, especially in hosts with compromised immune function after transplantation[5].

1.3 CMV microRNAs

MicroRNAs (miRNAs) encoded by cytomegalovirus play a complex and critical role in the biological processes of the virus, involving multiple aspects of latent infection, reactivation, immune evasion, and virus-host interactions. HCMV-encoded miRNAs can promote viral infection and suppress the host's immune response by regulating the gene expression of both the virus itself and the host cells[6]. These viral miRNAs are not only present in infected cells but can also be packaged into virions and dense bodies, referred to as circulating miRNAs, and delivered to target cells, potentially influencing cellular processes from the early stages of infection[7].

Regarding latent infection and reactivation, the expression patterns of viral miRNAs show significant differences. Studies have indicated that compared to latent infection, the expression levels of various viral miRNAs are significantly elevated in kidney transplant recipients (KTRs) with active CMV infection[8]. Another study focusing on HCMV miRNAs in serum also found that from the latent phase to the reactivation phase, the profile of HCMV miRNAs in the circulatory system undergoes a distinct shift, wherein 8 miRNAs, including HCMV-miR-US25-1-3p, are significantly upregulated in patients with viremia. The level of HCMV-miR-US25-1-3p is significantly correlated with HCMV DNA load and can serve as a predictive indicator for monitoring antiviral therapy in patients with autoimmune diseases[9]. These findings suggest that specific viral miRNAs can act as potential biomarkers to distinguish between latent and active infections and to monitor the reactivation process.

In terms of immune evasion and regulating host responses, HCMV miRNAs exert precise regulatory roles by simultaneously targeting the gene expression of the virus itself and the host cells through post-transcriptional regulatory mechanisms, thereby favoring viral survival and spread. The main mechanism of action is that viral miRNAs bind to complementary sequences (usually the 3' untranslated region) of target mRNAs through base pairing, thereby promoting RNA cleavage or inhibiting translation[10]. Further research revealed that viral miRNAs can directly interfere with key immune signaling pathways. HCMV-miR-US5-1 and miR-UL112-3p can block the activation of the NF-κB signaling pathway by directly downregulating the mRNAs of IKKα and IKKβ, thereby suppressing the production of pro-inflammatory cytokines such as interleukin-6 (IL-6), CCL5, and tumor necrosis factor-α (TNF-α)[11]. These mechanisms collectively reveal how HCMV utilizes its miRNAs to reshape the host immune environment to favor its own replication and persistent infection.

1.4 CMV and immune cells

There is a complex and dynamic interaction between cytomegalovirus and host immune cells, particularly T cells, B cells, and NK cells, which profoundly affects the infection process and disease outcomes[12]. In immunosuppressed individuals, CD8+ T cells are the key immune cells controlling CMV reactivation and viremia[13]. CMV infection drives a unique "memory inflation" phenomenon in CD8+ T cells, giving them a special phenotype expressing markers associated with effector memory and natural killer cells[14]. While the classical view of CD4+ T cells is as helper cells, studies have shown that HCMV-specific CD4+ T cells are necessary for HCMV-specific CD8+ T cells to exert antiviral effects[15]. At the NK cell level, CMV reactivation triggers long-term expansion and differentiation of the NK cell repertoire, particularly driving the expansion of the NKG2C+ NK cell subset with "adaptive-memory" features, which is crucial for effectively controlling viral replication[16]. For B cells, CMV-specific antibody responses are an important component of humoral immunity, and CMV serostatus (i.e., B cell memory resulting from past infection) is a key factor in risk assessment after transplantation[17]. Therefore, the interaction between CMV and various immune cells is a continuous process from viral evasion, host control, to immune exhaustion, deeply affecting the clinical prognosis of high-risk populations such as transplant recipients[18-19].

2. Chronic Kidney Disease

2.1 Overview of CKD

Chronic Kidney Disease (CKD) is characterized by a reduced glomerular filtration rate or elevated proteinuria, affecting approximately 15-20% of adults worldwide. It is classified into 5 stages based on the degree of renal functional impairment, with end-stage patients relying on renal replacement therapy[19]. As the ninth leading cause of death globally, the etiology of CKD encompasses two major categories: primary and secondary. Primary CKD refers to kidney diseases originating in the kidneys with unclear etiologies, including IgA nephropathy and focal segmental glomerulosclerosis (FSGS). Patients mainly present with symptoms such as edema, hematuria, or proteinuria, and as the disease progresses, it can lead to chronic renal failure (CRF) and cause complications such as anemia, infection, or cardiovascular disease (CVD).Secondary CKD refers to kidney diseases caused by other distinct diseases or factors, including metabolic disease-related nephropathies (such as diabetic nephropathy, hypertensive nephropathy), immune-mediated renal inflammatory diseases (such as lupus nephritis), and nephropathy caused by kidney transplantation, which are common and relatively difficult to treat[20].

2.2 Pathogenesis of CKD

The core pathogenesis of chronic kidney disease lies in the irreversible loss of renal cells or nephrons, accompanied by hemodynamic and metabolic overload of the remaining nephrons, which leads to further loss of nephrons. The abnormal activation of the immune system and chronic inflammation play an important role in the progression of CKD; immune components not only mediate acute kidney injury but are also crucial factors driving the progression of chronic kidney disease towards the end stage[21]. Among many immune-related pathways, the Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway is particularly important. The sustained or excessive activation of STAT3 has been proven to have toxic effects in various models of kidney disease[22]. For CKD patients, cytomegalovirus infection is an important external immune disrupting factor. Studies indicate that in non-dialysis-dependent CKD patients, CMV seropositivity is associated with the prevalence of cardiovascular disease (CVD), and the risk of developing CVD in CMV-seropositive patients is almost twice that of seronegative individuals[23]. Moreover, latent CMV infection impairs immune function, and after kidney transplantation, CMV infection is one of the leading causes of morbidity and mortality[24].

2.3 CKD and immune cells

There is a close correlation between chronic kidney disease and immune cell dysfunction, with mutually promoting mechanisms. CKD patients, especially those progressing to end-stage renal disease (ESRD), exhibit significant alterations in peripheral blood immune cell composition, including a reduction in B cells and T cells, and an increase in antigen-presenting cells (such as myeloid dendritic cells)[25]. CKD can be viewed as a state of accelerated aging, characterized by the accumulation of senescent cells in the kidneys. From the perspective of immunosenescence, CKD patients, particularly ESRD patients, possess a premature immunosenescence phenotype, manifesting as reduced thymic output, shortened telomeres, and an increased proportion of terminally differentiated T cells. These changes are independently associated with elevated risks of death, infection, and cardiovascular events in patients[26]. In addition, local "inflammaging" driven by senescent cells and systemic immunosenescence together form a vicious cycle, which not only accelerates renal fibrosis[27] but also greatly increases the patients' risk of developing complications.

3. CMV and CKD

3.1 Latent CMV infection and CKD

Latent HCMV infection is an important pathogenic factor in chronic kidney disease and kidney transplant recipients, affecting disease progression through persistent immune activation and inflammatory responses. Latent CMV infection itself profoundly shapes the host's immune state, for example, causing the expansion of senescent or terminal effector T cell subsets such as CD57+ KLRG1+ CD8+ TEMRA[24]. Latent CMV infection profoundly reshapes T cell immunity. During latent infection, antigen presentation by lymphatic endothelial cells drives CD8+ T cell memory inflation[28]. This long-term immune alteration is not limited to CMV-specific cells but affects the systemic immune status. Dedeoglu et al. reported that in patients with end-stage renal disease, CMV seropositivity led to a significant expansion of highly differentiated terminal effector CD28null T cells in circulation, and these cells were found almost exclusively in peripheral blood, not in lymph nodes [29]. For kidney transplant recipients, CMV is the main pathognic viral agent post-transplantation, significantly increasing morbidity and mortality[30]. Latent CMV induces IL-23, which may be an inflammatory mediator of latent CMV infection in ESRD patients, making patients more susceptible to CMV reactivation post-transplantation[31]. Research indicates that CMV viremia is significantly associated with chronic rejection of the transplanted kidney and graft loss, and long-term monitoring has identified asymptomatic CMV infection during the chronic phase as a risk factor for graft failure[32]. The underlying mechanisms involve acute and long-term systemic gene expression changes caused by CMV viremia, implicating pathways related to macrophages, interferon signaling, and cytotoxic T cell function. These persistent immune dysregulations may promote chronic graft injury.

3.2 CMV reactivation and CKD

The reactivation of latent HCMV is a significant complication of chronic kidney disease; meanwhile, the inflammatory environment of chronic kidney disease may also lead to cytomegalovirus reactivation, forming a vicious cycle. In IgA nephropathy, the expression rate of CMV antigens in IgAN renal tissues is significantly higher than in other types of primary glomerulonephritis, and the expression intensity is positively correlated with the severity of glomerular damage, suggesting that CMV infection may directly participate in the process of kidney damage[33]. In focal segmental glomerulosclerosis (FSGS), CMV reactivation can serve as a strong immune stimulus and environmental trigger, and active CMV infection may act as one of the "second hits" to induce or exacerbate FSGS[34]. For metabolic kidney diseases like diabetic

nephropathy, CMV reactivation may indirectly promote disease progression by exacerbating endothelial dysfunction and chronic inflammation[35]. Multiple studies have confirmed that CMV infection is an unexpectedly high and independent risk factor in organ transplantation for CKD and immunodeficient patients, and its reactivation under immunosuppression can lead to fatal complications[36]. A study by Jochimsen et al. found that a patient's CMV reactivation may indicate an additional disorder in the immune defense system during severe illness, and may even necessitate a temporary reduction in immunosuppressive therapy[37]. Following organ transplantation with latent infection, ischemia/reperfusion, DNA damage, and inflammation stimulate viral gene expression and local viral production. Post-transplant immunosuppression (IS) allows the reactivated virus to spread within the recipient[38].

3.3 CMV-related microRNAs and CKD

MicroRNAs encoded by cytomegalovirus and host miRNA responses to HCMV infection play a central role in regulating viral replication, host immune responses, and disease progression. These processes are closely related to inflammation, autoimmune diseases, and kidney diseases [9]. HCMV infection profoundly alters the miRNA expression profile of host cells. Its own encoded miRNAs (such as HCMV-miR-US25-1) are upregulated during infection and target host genes, which can directly downregulate the Jag1 factor crucial for neurogenesis, thereby interfering with cell fate[38]. In terms of inflammatory regulation, host miRNAs such as hsa-miR-200b-3p and hsa-miR-200c-3p can bind to the 3' untranslated region of the mRNA of the HCMV immediate-early protein IE72 to suppress its expression, thereby inhibiting viral lytic replication[39]. A study by Soffritti et al. demonstrated that HCMV and HHV-6 infections can significantly regulate the miRNome of human dermal fibroblasts, profoundly altering the expression of dozens of miRNAs, including many that play key roles in fibrosis, and co-infection showed a synergistic enhancement effect on the expression of pro-fibrotic miRNAs[40], suggesting that viral infections may drive the tissue fibrosis process through miRNAs. CMV-encoded miRNAs have been considered diagnostic and differential biomarkers for various diseases. Regarding the risk of post-transplant HCMV infection, the expression levels of CMV miR-UL112-3p/5p, -UL22A-3p/5p, -US25-1-5p, -US25-2-3p/5p, -UL36-3p/5p, and -UL70-3p are extremely high in kidney transplant recipients with active CMV infection, possibly playing an important role in the return to latency after viral activation[41]. The expression of hsa-miR-125a-5p is downregulated in the whole blood of patients developing CMV viremia after kidney transplantation, with its targets involving the cell cycle and apoptosis[42].After activation under immune dysregulation, HCMV-encoded miRNAs and the triggered host miRNA responses may participate in the immune injury and fibrotic processes of kidney tissues by regulating local inflammation, affecting apoptosis and fibrotic pathways, and interfering with immune cell functions, thereby exacerbating the development of kidney diseases.

3.4 CMV-related immune cells and CKD

Cytomegalovirus infection regulates immune cells through various mechanisms, displaying specific action patterns in different types of kidney diseases. HCMV infection specifically promotes the adaptive differentiation, expansion, and survival of monoclonal mature NK cell subsets with characteristic phenotypic/functional and epigenetic features, marked by high expression of the activating CD94/NKG2C NK receptor [43]. HCMV infection induces specific M1 and M2 differentiation markers through the PI3K/SHIP1/Akt signaling pathway, promoting the polarization of monocytes into different macrophages[44]. Macrophages play a critical role in the progression of progressive renal fibrosis, and most cases of acute kidney inflammation involve the infiltration of accompanying M1 macrophages [45]. CMV infection is a major factor driving CD8+ T cell senescence. In primary glomerular diseases, chronic transplanted kidney failure, and kidney transplant recipients, CMV may exacerbate the disease process by inducing immunosenescence and chronic inflammatory states. CMV seropositivity is associated with the expansion of terminally differentiated CD28 null T cells in peripheral blood, which possess pro-inflammatory properties[46-48]. In diabetic nephropathy, research by Chen et al. confirmed the involvement of the immune system in its pathogenesis, involving cells of innate and adaptive immune responses targeting the kidneys and activating pro-inflammatory responses, and CMV infection may further amplify this inflammatory process[49]. By driving immunosenescence, expanding terminally differentiated pro-inflammatory T cell, NK cell, and macrophage subsets, and maintaining a chronic inflammatory microenvironment, CMV infection plays an important regulatory role in the occurrence and progression of multiple chronic kidney diseases.

4. Summary and Discussion

This article systematically examines recent research developments concerning the role of cytomegalovirus (CMV) in the pathogenesis of chronic kidney disease (CKD), emphasizing latent infection, reactivation, microRNAs (miRNAs), and immune cell interactions. The progression of CKD is closely associated with immune system dysregulation and persistent inflammation. CMV infection, particularly its reactivation, serves as a significant external factor contributing to immune

perturbation. The key pathogenic mechanisms include: CMV-induced remodeling of the host immune response; reactivation leading to depletion and impairment of CMV-specific immune cells, thereby intensifying inflammation; and the virus's ability to modulate both viral and host gene expression through encoded miRNAs, facilitating immune evasion and the maintenance of latency. Additionally, circulating miRNAs present potential as biomarkers. These mechanisms collectively position CMV not merely as a complicating infectious agent but as an active contributor to CKD progression through amplification of chronic inflammation, immunosenescence, and tissue fibrosis.

Future research should concentrate on several key aspects. First, the exploration of underlying mechanisms must address the limitations inherent in peripheral blood immune analysis by emphasizing the study of local microenvironmental regulation within the kidneys. Advanced techniques such as single-cell sequencing, spatial transcriptomics, and kidney organoid infection models should be employed to investigate the infiltration and functional phenotypes of cytomegalovirus (CMV)-specific cells in renal tissues. Second, targeting immunosenescence presents a promising therapeutic avenue; interventions aimed at senescent cells or specific inflammatory pathways — such as JAK/STAT inhibitors — may concurrently attenuate chronic kidney disease (CKD) progression and mitigate CMV-related immunopathology. Third, a deeper mechanistic understanding can be achieved through artificial intelligence and bioinformatics, which could elucidate the precise modulation of immune cell subsets, including T cells, natural killer (NK) cells, and B lymphocytes, in the context of CKD. Additionally, investigating the interaction between viral microRNAs and host regulatory networks may reveal novel therapeutic targets. Furthermore, exploring the role of CMV in mediating complications such as cardiovascular diseases, infections, and malignancies in CKD patients — by accelerating immunosenescence and inflammatory processes — would provide valuable insights for developing targeted, combinatorial treatment strategies.

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