HCMV-Specific Immune Monitoring in Solid Organ Transplant Recipients

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Abstract
Solid organ transplant recipients (SOTRs) are at high risk of viral opportunistic infections, especially during the first six months post-transplant. Human cytomegalovirus (HCMV) remains one of the most important pathogens in transplant recipients, despite the great efforts in diagnosis and effective antiviral therapies [1]. Immunological monitoring could be useful in order to guarantee a better management of the patients. In this setting, several methods have been employed. The review summarizes the most important approaches in immunological monitoring of HCMV-specific T-cell response in transplant setting.

Keywords: Human cytomegalovirus; Transplant; T-cell response; Quantiferon; Elispot assay

Abbreviations: SOTR: Solid Organ Transplant Recipients; HCMV: Human Cytomegalovirus; IFNγ: Interferon gamma

Introduction
Solid organ transplant recipients (SOTRs) are at high risk of viral opportunistic infections, especially during the first six months post-transplant, due to the immunosuppressive treatments. Human cytomegalovirus (HCMV) remains one of the most important pathogens in transplant recipients, despite the great efforts in diagnosis and effective antiviral therapies [1]. HCMV infections are thought to be responsible of both "direct effect" in the allograft, including inflammation, vasculopathy and fibrosis, and "indirect effect", that are mainly immune-mediated [2]. Great efforts have been devoted in order to implement advanced diagnostic techniques for monitoring HCMV infections in transplant recipients [3-5]. Furthermore, in recent years, the introduction of antiviral prophylaxis and pre-emptive strategies reduced HCMV-related mortality and morbidity [6].

So far, evaluation of HCMV serological status in organ donor (D) and recipient (R) represents the only available marker of risk stratification [7]. However, this traditional stratification presents some limitation. In fact, HCMV seropositive recipients are considered at intermediate risk, but they could present HCMV reactivation with consequent HCMV-related complication. On the other side, a role of HCMV-specific T-cell response has been suggested. In this setting, there has been a growing interest in the development of new approaches for monitoring immune response [8]. However, unique immunological monitoring strategies for evaluation of HCMV-specific T-cell response have not been defined yet.

Several methods have been suggested and developed in order to quantify HCMV-specific T-cell response in transplant setting, based on IFN-γ production after appropriate HCMV-specific stimulation, including intracellular cytokine staining (ICS), Enzyme-linked Immunospot (ELISPot) assay and QuantiFERON-CMV (QF-CMV) assay. The two more used assays are QF-CMV assay and CMV ELISPOT assay. While both QF-CMV and CMV ELISPOT assays measure IFN-γ to detect HCMV-specific T-cell response, their characteristics and principles, as well as their results are different. QF-CMV is an assay for detection of IFN-γ on whole blood by enzyme-linked immunosorbent assay (ELISA) after ex vivo stimulation of CD8+ T cells with human leukocyte antigen (HLA)-restricted HCMV peptides [9].

The ELISPOT assay is a sensitive and specific method for measuring antigen-specific T-cell responses after appropriate stimulation, by detection of functionally relevant cytokines, such as IFN-γ [10]. Whole antigens, proteins or peptides could be used as HCMV-specific stimuli. In different settings, we observed
that the use of antigen-specific 15-mer overlap peptide pools represents a good compromise for stimulating both CD4+ and CD8+ T-cell response [11-13]. However ELISPOT assay does not allow to distinguish between CD4+ and CD8+ T cell responses unless antigens for detecting CD4+ and CD8+ response are used separately or lymphocyte subset depletion is performed [11]. Alternatively, the normalization of net spots/million of PBMC on CD4 and CD8 T cell count could be performed in order to estimate the role of HCMV-specific CD4+ and CD8+ T-cell response [12]. Standardization and cut-off values for positive HCMV-specific ELISPOT response have to be better defined.

ICS allows the characterization of both CD4+ and CD8+ T cells after T-cell stimulation with appropriate antigens in the presence of secretion inhibitors (Brefeldin A or Monensin) by flow cytometry analysis, using markers for lymphocytes differentiation and for measurement of T cell function. However, the assay is complex and labor-intensive [14]. In this setting, the characterization of HCMV-specific T-cell response among transplant recipients should be employed in order to better stratify the risk of HCMV reactivation or infection, allowing a personalized management of the patients. HCMV-specific T cells, especially effector CD4+ and CD8+T cells are considered to be crucial in the control of HCMV replication. Furthermore, interferon-γ (IFN-γ) has been suggested to play a critical role in controlling HCMV infection [15].

The lack of IFN-γ production detected by QF-CMV was predictive of development of HCMV disease in high-risk patients after discontinuation of antiviral prophylaxis [16]. In a study performed on 124 HCMV-seropositive kidney transplant recipients, evaluating HCMV-specific T-cell response using both QF-CMV and CMV-ELISPOT assay, it was observed that post-transplant HCMV-specific T-cell response measured by ELISPOT assay could be useful for identifying patients at risk of HCMV DNAemia. On the contrary, no differences were observed between KTR with CMV DNAemia (+) and KTR with CMV DNAemia (-) from QF-CMV assay results [17]. Furthermore, study evaluating CMV-specific CD4+ and CD8+ T-cell response detected using CMV-infected immature dendritic cells and flow cytometry analysis showed that CMV-specific CD4+ and CD8+ T-cell level > 0.4/µl in the first month post transplant could confer protection from CMV infection [18].

A possible role of CMV-specific T-cell response detected by ELISPOT assay at pre-transplant could be suggested [19]. In another study [20] CMV-specific T CD8+ response at pre-transplant seemed to be predictive of the risk of CMV replication after transplantation in solid organ transplant recipients. In more detail, pre-transplant immediate early 1 (IE1-) specific T-cell response could be involved in protection for CMV infection after kidney transplant, supporting the potential value of CMV-specific T-cell response evaluation as prognostic marker of CMV infection or reactivation [21]. Conclusion and Perspectives Studies have highlighted the role of CMV-specific CD8+ and CD4+ T cells, measured at pre-transplant and in post-transplant in controlling CMV infection after transplant. Although a great effort has been pursued, further analysis are required in order to standardize immunological methods for the evaluation of CMV-specific T-cell response as well as to better characterize its possible prognostic role.

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References


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