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**CD4**⁺ T cells, human cytomegalovirus and end-stage renal disease

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**CD4**⁺ T cells are activated through their T-cell receptors, which recognize foreign antigenic peptides in the context of Major Histocompatibility Complex (MHC) II molecules [1,2]. They have classically been regarded as facilitators of acquired immunity, providing cytokine help that aids the development of either the cellular cytotoxic CD8⁺ T cell (Th1) or humoral B-cell responses (Th2). However, the
rapid expansion of our knowledge of cytokines and their function has resulted in the definition of further unique CD4+ T-cell subsets associated with specific immune conditions and intracellular transcription factors that drive their differentiation. It is now accepted that Th1 and Th2 differentiation are driven by the transcription factors T-bet and GATA-3, respectively [3,4]. Th17 cells are defined by the expression of RORγt (known as RORC in humans) and RORα, express IL-23R and CCR6, secrete the cytokines IL-17 and IL-22 and are considered essential for the development of inflammatory and autoimmune disease [5–8]. Regulatory T cells (Tregs) are identified by the transcription factor FoxP3 and provide a negative buffer to immune responses through the release of suppressive cytokines such as TGFβ and IL-10 [9–11]. More recently, Th9 cells have been identified that release IL-9 and IL-10, adoptive transfer of which results in colitis and neuritis [12,13], while Th22 cells produce IL-22 and IL-13, are defined by the transcription factors RORγt and AHR, express skin-homing receptors and are believed important in skin and mucosal pathology [14]. A summary of the above list is provided in Figure 1, but it is by no means exhaustive and there are CD4+ cell types that do not fit into these categories. However, it serves to demonstrate the complexity and plasticity of CD4+ T-cell immunity and highlights our continuing attempts to understand it.

Cytotoxic CD4+ T cells were identified considerably earlier than some of the CD4+ subsets described above as they have been recognized since the late 1980s [15], but transcription factors that drive their specific development have not yet been determined. This subset of cells remains MHC II-restricted and is often directed towards viruses from acute (dengue virus [15], measles [16] or influenza [17]) to persistent [herpes simplex [18], Epstein Barr [17] and human cytomegalovirus (HCMV) [19] infections. Specificity against self-proteins such as heat-shock proteins [20] have also been recorded. Detailed interpretation of the function of cytotoxic CD4+ T cells has been limited in part by the absence of either functional assays and/or detailed phenotyping in many studies. Unless identified in cytotoxic assays or through the detection of cytotoxic granules such as granzyme B or perforin, such cells would normally be included within the Th1 grouping as they produce high levels of interferon gamma (IFN-γ) [15]. Many reports that describe cytotoxic CD4+ T cells identify them through a CD28null phenotype [20] associated with maturation and previous antigenic exposure, but more extensive analysis is now achievable with the expansion of multiparameter flow cytometry to 17+ colours [21]. Unfortunately, such studies are still restricted by expense and the availability of technology, and to date, few have investigated cytotoxic CD4+ T cells at this level of detail. HCMV-specific cytotoxic CD4+ T cells can release macrophage inflammatory protein-1α and tumour necrosis factor-α (TNF-α) as well as IFN-γ, often express CD57, and exhibit an ‘effector memory’ phenotype [22] that is associated with a lack of lymph node homing receptors, a reduced ability to proliferate but rapid cytokine responses following antigenic stimulation [23]. This may prove to be an exceptional system of study as HCMV is unique in the way it imprints on the immune system, driving the largest, persistent expansions of highly differentiated, oligoclonal CD4+ and CD8+ T cells known to man [24,25]. Even in healthy subjects, up to 10% of the circulating CD4+ T [24] and 40% of the CD8+ T-cell [26] pool is directed at HCMV.

It is in this context that Yadav and Jha [27] have reported an increase in circulating CD4+CD28null T cells expressing cytotoxic granules in end-stage renal disease (ESRD) patients on peritoneal dialysis (PD). This in itself is not novel as there have been previous reports describing this patient grouping. Betjes et al. [28] described 50-fold increases in the proportion of circulating CD4+CD28null T cells in HCMV-seropositive ESRD patients over the age of 50 years compared to age-matched HCMV-seronegative healthy controls. The impact of background HCMV infection was highlighted in this latter study as the effect was reduced to 5-fold when comparing to HCMV-seropositive healthy subjects, while there were no expansions in HCMV-seronegative ESRD patients. Yadav and Jha’s report confirm the finding that chronic kidney disease itself is associated with increased cytotoxic CD4+ T cells as their subjects were all HCMV seropositive. The potential influence of HCMV cannot, however, be excluded from this cohort as it infects all HCMV seropositive. The potential influence of HCMV cannot, however, be excluded from this cohort as it infects all HCMV seropositive. The potential influence of HCMV cannot, however, be excluded from this cohort as it infects all HCMV seropositive. The potential influence of HCMV cannot, however, be excluded from this cohort as it infects all HCMV seropositive. The potential influence of HCMV cannot, however, be excluded from this cohort as it infects all HCMV seropositive. The potential influence of HCMV cannot, however, be excluded from this cohort as it infects all HCMV seropositive. The potential influence of HCMV cannot, however, be excluded from this cohort as it infects all HCMV seropositive. The potential influence of HCMV cannot, however, be excluded from this cohort as it infects all HCMV seropositive. The possibility remains that chronic inflammation provides a permissive environment for HCMV reactivation [29], which then drives the expansion of HCMV-specific T cells, whether they be cytotoxic CD4+ or otherwise. While the mechanisms regulating HCMV latency and reactivation during natural infection remain poorly understood, this is in keeping with what is known in vitro, namely that the differentiation of myeloid dendritic cell (DC) progenitors to mature DCs (such as through the action of proinflammatory cytokines) can trigger HCMV reactivation from a latent state [30,31]. Further study is required to determine the antigen specificity of the cytotoxic CD4+ T cells and the HCMV load in ESRD patients, to evaluate the degree that HCMV contributes to these T-cell expansions.

Prior HCMV infection has been linked as a risk factor with multiple other chronic inflammatory conditions, including inflammatory bowel disease [32] and cardiovascular disease (CVD) [33] to name just a few. CVD is particularly significant in ESRD patients, as the risk of mortality is doubled in individuals suffering both [34,35]. Furthermore, there is an appealing association with increased numbers of circulating CD4+CD28null T cells [20] that have been described within atherosclerotic plaques [36]. The cytotoxic capacity of these cells has also provided a potential mechanism through which damage can be achieved to the vasculature and organs. Perhaps significantly, apoptosis-inducing receptors and their ligands [specifically death receptor 5 (DR5) and TRAIL—members of the TNF receptor (TNFR) and TNF superfamily of genes known to be involved in immune modulation and lymphoid tissue development], and not cytotoxicity induced by granule release, have been implicated in this process [37]. The latter requires MHC-restricted activation, while apoptosis through death receptors can occur in a non-MHC-restricted manner. Thus, a foreign antigen like HCMV would not need to be present in any given tissue for these T cells to be active and instead, increases in the expression of DR5 on target tissues.
could induce susceptibility. Intriguingly, this can be achieved by pro-inflammatory cytokines such as IFN-γ and TNF-α [38].

HCMV-positive serostatus in ESRD patients is strongly associated with atherosclerotic disease [39]. However, the study by Yadav and Jha [27] selected ESRD patients with no clinical signs of CVD. This suggests that increases in cytotoxic CD4+ T cells occur prior to the development of CVD and would be in keeping with the idea that an underlying factor, HCMV or otherwise, is involved in the expansion of this T-cell subset in these patients. The potential of other CD4+ T-cell subsets (as described in the first part of this article) contributing to outcome also cannot be ignored as functional effector memory CD4+ T-cells-exhibiting cytokine responses to recall antigens like tetanus toxoid are enriched within the peritoneal cavity of PD patients [40]. It has been reported that in the 21st century, chronic non-communicable disorders have overtaken infectious diseases as the major causes of morbidity and mortality in the world [41,42]. It remains to be seen whether infections like HCMV and human immunodeficiency virus infection, may be impacting on these statistics.

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**Conflict of interest statement.** None declared.

(See related article by Yadav et al. CD4+CD28null cells are expanded and exhibit a cytolytic profile in end-stage renal disease patients on peritoneal dialysis. *Nephrol Dial Transplant* 2011; 26: 1689–1694)

**References**


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**Fig. 1.** Overview of the differentiation of CD4+ T-cell subsets. Cytokine conditions required for generation of the subsets are shown with arrows. Intracellular transcription factors required for specific lineage commitments are shown in pale text within the cells. Signature cytokine release is shown in boxes. This should be considered only as a guide as there is continuing debate in the field and there are other CD4+ T cells that do not fall into these categories. There may also be significant differences when studying human versus murine cells.
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