Clinical & Translational Immunology

Australian and New Zealand Society for Immunology Inc.

Clinical & Translational Immunology 2022; e1427. doi: 10.1002/cti2.1427
www.wileyonlinelibrary.com/journal/cti

REVIEW

Immunosenescence: an unexplored role in glomerulonephritis

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Received 27 June 2022;
Revised 15 October 2022;
Accepted 16 October 2022

doi: 10.1002/cti2.1427

Clinical & Translational Immunology 2022; **11**: e1427

Abstract

Immunosenescence is a natural ageing phenomenon with alterations in innate and especially adaptive immunity and contributes to reduced antimicrobial defence and chronic low-grade inflammation. This is mostly reflected by an increase in organ-directed and/or circulating reactive and cytolytic terminally differentiated T cells that have lost their expression of the costimulatory receptor CD28. Apart from being induced by a genetic predisposition, ageing or viral infections (particularly cytomegalovirus infection), immunosenescence is accelerated in many inflammatory diseases and uraemia. This translates into an enhancement of vascular inflammation and cardiovascular disease varying from endothelial dysfunction to plaque rupture. Emerging data point to a mechanistic role of $CD28^{null}$ T cells in glomerulonephritis, where they initiate and propagate local inflammation in concordance with dendritic cells and macrophages. They are suitably equipped to escape immunological dampening by the absence of homing to lymph nodes, anti-apoptotic properties and resistance to suppression by regulatory T cells. Early accumulation of senescent $CD28^{null}$ T cells precedes glomerular or vascular injury, and targeting these cells could open avenues for early treatment interventions that aim at abrogating a detrimental vicious cycle.

Keywords: atherosclerosis, $CD28^{null}$ T cells, chemokines, cytomegalovirus, glomerulonephritis, inflammation

INTRODUCTION

Immunosenescence is characterised by age-related immunological alterations resulting in increased susceptibility to autoimmunity and endothelial dysfunction.[1] It involves innate and adaptive immune cells and includes thymic involution with peripheral loss of naïve T cells, telomere shortening, repertoire restriction with impaired T- and B-cell responses to newly encountered antigens and a skewed maturation phenotype with an increase in terminally differentiated senescent T cells that typically lack CD28.[1,2]

Senescent T cells contribute to a systemic chronic inflammatory state (inflammaging) and cardiovascular disease. A higher plasma fraction of $CD4^{+}CD28^{null}$ T cells was identified in patients with prevalent cardiovascular disease, acute

coronary syndrome and especially recurrent coronary events.[3] This increase was associated with worse cardiovascular outcomes in people with heart failure, end-stage kidney disease (ESKD) and also kidney transplant recipients (KTR).[4,5] *In vitro* and *in vivo* studies indicate that these pro-atherosclerotic $CD28^{null}$ T cells accumulate in unstable plaques and promote rupture.[6] This is mainly caused by their senescence-associated secretory phenotype (SASP) with increased tumor-necrosis factor (TNF)-α and interferon (IFN)-γ production, recruitment and activation of macrophages, and an endothelial tropism with direct killing of endothelial cells by high expression of cytolytic enzymes perforin and granzyme B.[6,7].

Similarly, emerging data highlight the central role of senescent T cells in the initiation and propagation of glomerulonephritis. In the next sections, we describe the characteristics and drivers of $CD28^{null}$ T cells. We outline how these immunosenescent T cells are perfectly suited to mediate endothelial damage in kidney disease. Finally, we speculate on potential therapies, which target these key culprits.

Characteristics of senescent T cells

Despite a nearly universal loss of the costimulatory molecule CD28 on their cell surface, these oligoclonal TCR-expressing cells are highly reactive. They contain exhausted ($PD1^+$) populations, are mostly late effector memory T cells ($CD45RA^-CCR7^-$ T_{EM} and especially $CD45RA^+CCR7^-$ T_{EMRA}) and no longer express CD27, preceding or following the loss of CD28 in $CD4^+$ and $CD8^+$ T cells, respectively.[2,6,8]

They are activated and proliferate upon interaction with antigen-presenting cells (APC) but also share many characteristics with NK cells. They are stimulated by classical antigens, such as heat-shock proteins (HSP), which contribute to atherosclerosis and immune-mediated glomerular disease (Figure 1).[9] Antigen-independent stimulation also occurs through binding to the highly expressed costimulatory receptors OX40 and 4-1BB.[10] Interleukin-15 (IL-15) enhances their proliferation via combined activities of STAT-5, Bcl-2 and mTORC1.[11] IL-7 and especially IL-15 are implicated in several autoimmune disorders and atherosclerosis, stimulate chemo-attraction and increase the cytotoxicity of senescent lymphocytes and NK cells both in healthy individuals and in people with acute coronary syndrome (Table 1).[12] $CD28^{null}$ T cells exert their cytotoxicity similarly to NK cells and $CD8^+$ T cells by releasing perforin and granzyme B.[9] This process occurs upon TCR ligation or by binding to NK activating receptors such as NKG2D and Killer Cell Immunoglobulin-like receptors (KIRs).[6,7] Exposure of $CD4^+CD28^{null}$ T cells to glomerular endothelial cells caused NKG2D-dependent endothelial damage independent of TCR ligation.[13]

Senescent T cells are well-equipped to initiate, as well as maintain, glomerular inflammation (Table 2). They have the potential to become long-lived and accumulate in kidneys over time. They are anti-apoptotic given their downregulation of Fas ligand and increased expression of Bcl-2 while escaping suppression by regulatory T cells (Tregs).[6,14,15] Their low-to-absent expression of CCR7 and CD62L prevents homing to regional lymph nodes and stimulates direct tissue invasion.[6,13] Moreover, high surface expression of CX3CR1 promotes binding to a variety of glomerular cells expressing its ligand, fractalkine (CX3CL1). This includes endothelial cells, mesangial cells and podocytes[16] (Figure 1). They are easily recruited to areas of inflammation because of a 25-fold increased activation of the adhesion molecule β_2 integrin upon stimulation.[17] In myocardial infarction, β_2 integrin-mediated migration is reactive oxygen species (ROS)-dependent and likely contributes to plaque destabilisation before rupture.[3,17] As compared with $CD28^+$ T cells, expression and activation of the β_2 integrin lymphocyte function-associated antigen-1 (LFA-1) and its subunits CD11a (integrin α_L) and CD18 next to integrin α_4 (CD49d) are notably increased in both $CD8^+$ and $CD4^+CD28^{null}$ T cells.[6,15,17] This is also relevant to many glomerular diseases where endothelial proteoglycans interact with selectins and β_2 integrin on lymphocytes.[18] Leukocyte infiltration into the kidney is especially driven by β_2 integrins binding to highly expressed ligands such as intercellular adhesion molecule-1 (ICAM-1) on renal endothelial, mesangial and epithelial cells across glomerulopathies including ANCA-associated vasculitis (AAV) and systemic lupus erythematosus (SLE).[18–20]

Loss of CD28 in senescent T cells

T-cell activation requires recognition of 'non-self' antigen by TCR and costimulatory pathway

Table 1. Shared mechanistic role of senescent T cells in glomerulonephritis and atherosclerosis

Senescent $CD4^+$ and/or $CD8^+$ lymphocytes	Glomerulonephritis	Atherosclerosis ($CD4^+ \geq CD8^+$)	References
Increased cytokine production (IFN-γ, TNF-α)	Glomerular and interstitial damage	Development of atherosclerosis	6,38,56,60
Endothelial toxicity (granzyme/perforin)	Glomerular endothelial cell lysis (CD4)	Endothelial damage- plaque rupture (CD4)	6,13,24,74
Activation of macrophages and monocytes	Glomerular and interstitial damage (CD4/CD8)	Development of atherosclerosis (CD4 > 8)	6,41,43,48–50,59
Oxidative-stress dependent activation of β2 integrin (LFA-1)	Binding on ICAM-1 on renal epithelial, mesangial, and endothelial cells	Binding on ICAM-1 on endothelial cells and promotion of plaque destabilisation	3,17,18
Increased expression of CX3CR1	The CX3CR1/fractalkine axis promotes glomerulonephritis	The CX3CR1/fractalkine axis promotes atherosclerosis	16,66,67,70,114
Enhancement of activation and proliferation by IL-15	IL-15 promotes glomerulonephritis	IL-15 promotes atherosclerosis in conjunction with fractalkine	11,12
Triggered by HSP	HSP activate innate and adaptive immunity in glomerulonephritis	HSP play an active role in atherosclerosis	9,51,115
Higher plasma concentration with HLA DRB1*04 genotype	HLA DRB1*04 predisposes to SLE nephritis	HLA DRB1*04 predisposes to cardiovascular disease	32–34
Increased protease production (especially T_{EMRA})	Proteases (MMP) promote glomerulonephritis	Active role proteases (MMP) in development and progression of atherosclerosis	2,116

HSP, heat-shock protein; ICAM-1, Intercellular Adhesion Molecule 1; IFN-γ, interferon-gamma; IL-15, interleukin-15; LFA-1, Lymphocyte function-associated antigen 1; MMP, matrix metalloproteinase; TNF-α, tumor-necrosis factor alpha.

stimulation (type 2 signalling). The costimulatory molecule CD28, the receptor for CD80/CD86 on APC, is constitutively expressed on naïve T cells and essential for immune homeostasis.[21] Although the homologous CTLA4 competes for the same ligands (with higher affinity), both molecules have opposing effects on T cells.[21] Upon binding to CD28, transcriptional, posttranslational and epigenetic modifications occur in these cells, stimulating survival, glycolytic rate, cytokine production (IL-4, IL-10, and especially IL-2) and clonal expansion.[21,22] The absence of CD28 can occur by various mechanisms (Figure 2). Most importantly, exposure to TNF-α downregulates the promotor of CD28 with a decline of nuclear protein binding motifs α and β. Accordingly, replicative stress because of recurrent or chronic infections leads to an exhausted lymphocyte phenotype in murine models with reduced expression of CD28.[23] Also, endogenous antigens such as HSP downregulate CD28 likely because of triggering of TNF-α release.[24] With sustained stimulation over time, loss of CD28 becomes permanent through transcriptional silencing.[25]

With ageing, the proportion of highly differentiated effector and memory $CD28^{null}$ T cells in plasma rises steadily and this occurs earlier and to a larger extent for $CD8^+$ T cells, which are more susceptible to replicative senescence.[2,25] Several factors promote the accumulation of these senescent T cells. With ageing, microbial dysbiosis with enrichment of pro-inflammatory commensals is more common.[1] This process is also cytokine (TNF-α)-driven and involved in inflammaging.[1] Cytomegalovirus (CMV) infection and resulting seropositivity are associated with an increase of the $CD4^+$ and $CD8^+CD28^{null}$ T cell fraction because of repeated antigenic triggering with decreased expression of CD27 and CD45RA than $CD28^{null}$ T cells from seronegative patients.[11,26] Chronic HIV and EBV infection also expands $CD8^+CD28^{null}$ T cells with a lower proportional expression of CD57 than CMV.[2,27] Recently, the hyperactive cytokine response in critically ill patients with acute COVID-19 infection was also associated with an increase in $CD4^+CD28^{null}CD57^+$ T cells.[28] The circulating fraction of $CD4^+CD28^{null}$ T cells is also increased in uraemia and autoimmune diseases such as SLE, rheumatoid arthritis (RA) and AAV, where it is closely linked to CMV seropositivity.[29,30] All these conditions share chronic inflammation and endothelial dysfunction[6,29,30] (Figure 2). A genetic predisposition also matters. The HLA DRB1*0301

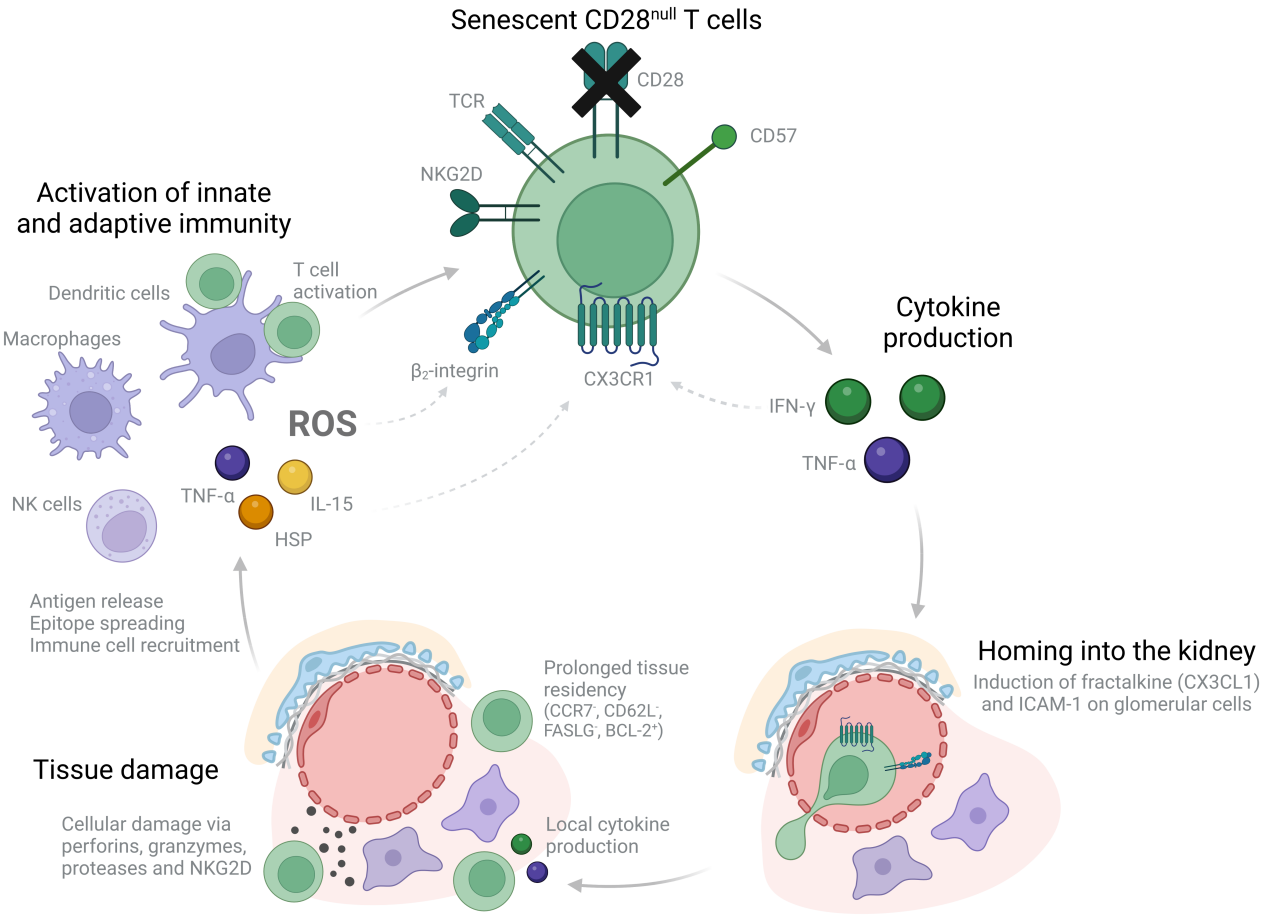

Figure 1. Role of senescent T cells in the pathogenesis of glomerulonephritis. Senescent CD28^{null} and CD57^{+} T cells have a secretory phenotype with enhanced excretion of TNF-α and IFN-γ, which induce the expression of ligands fractalkine and ICAM-1 in the kidney in various cells including podocytes, mesangial cells, epithelial cells and endothelial cells. This drives the homing of cytolytic CX3CR1^{+}CD28^{null} T cells with ROS-induced upregulated expression of β2 integrins into glomerulus and interstitium. The downregulation of CCR7 and CD62L impedes chemotaxis of these cells into lymph nodes. The invoked cellular damage through perforin, granzyme B and pro-inflammatory cytokines leads to release of HSP which further activates CD28^{null} T cells and increases their cytotoxicity. Cell death of nonimmune cells leads to epitope spreading and triggers innate and adaptive immunity which upon interaction with T cells stimulates T cell senescence but also contributes to ongoing glomerular and interstitial damage. TNF-α and IFN-γ up-regulate IL-15 production. IL-15 increases the survival and proliferation of senescent CD28^{null}, induces the expression of integrins and the NK cell activating receptor NKG2D and drives the activation of monocytes into M1-macrophages which further produce pro-inflammatory cytokines with the potential of downregulating CD28 expression in T cells. BCL-2, B-cell lymphoma 2; CCR7, C-C chemokine receptor type 7; DC, dendritic cells; FASLG, Fas ligand; HSP, heat-shock protein; ICAM-1, intercellular adhesion molecule 1; IFN-γ, interferon-gamma; IL-15, interleukin-15; NK cell, natural killer cells; NKG2D, natural killer group 2D; ROS, reactive oxygen species; TNF-α, tumor-necrosis factor alpha.

allele was associated both with less severity of RA and fewer circulating CD4^{+}CD28^{null} T cells.[31] This is in sharp contrast to HLA DR4 alleles (particularly HLA DRB1*0401 and DRB1*0404), which are associated with a higher concentration of these lymphocytes, enhanced cytokine production, more development and severity of autoimmune disease including SLE, RA and IgA vasculitis as well as cardiovascular disease.[29,32–34] Likewise, inflammatory conditions such as type 2 diabetes and obesity have been associated with an increase in CD4^{+}CD28^{null} T cells.[6,35] Plasma of obese individuals induces the loss of CD28 expression in peripheral blood mononuclear cells (PBMC) from healthy lean individuals.[36]

Glomerulonephritis and the role of senescent T cells

T cells are key players in glomerulonephritis, even in 'classical' antibody-mediated glomerular disease such as anti-GBM disease and SLE. Recent wide-

Table 2. Involvement of senescent T cells in perpetuation of *chronic* glomerular disease

Directed homing towards areas of inflammation (via CX3CR1, β2 integrin)
Absence of homing receptors which promote dissipation into lymph nodes (CD62L)
Oligoclonal TCR-repertoire
Relatively high proliferation rate, despite absence of type 2 signalling
Anti-apoptotic properties
Antigen-independent stimulation by IL-15 in inflammatory milieu
Resistance to Tregs
Triggered by ongoing damage and exposure to HSP
Vicious circle by TNF-α which downregulates CD28 expression at the transcriptional level while $CD28^{null}$ T cells increase TNF-α production.

HSP, heat-shock protein; IL-15, interleukin-15; TCR, T-cell receptor; TNF-α, tumor-necrosis factor alpha; Tregs, regulatory T cells.

scale transcriptomic analyses confirmed the prime involvement of T cells with IFN signature in human SLE glomerulonephritis next to mononuclear phagocytes, NK cells and dendritic cells (DC) particularly of the conventional DC type 2 (cDC2) phenotype.[37,38] Infiltration of glomerular and/or interstitial T cells defined the outcome of childhood IgAN.[39] Their role was also confirmed in diabetic nephropathy where a transcriptomics approach revealed an eightfold increase in leukocytes (half of which were T cells) in biopsy samples than in controls.[40] Depletion of $CD4^+$ T cells in rats prevented progression of glomerulonephritis because of reduced glomerular accumulation of $CD8^+$ T cells and activated macrophages with decreased expression of IFN-γ.[41] The exact role and phenotype of these cells and their modifiers such as age and CMV status in the course of glomerulonephritis largely remain unexplored. A major drawback hampering the development of hypothesis-generating murine models is that the loss of CD28 in circulating T cells is mainly observed in humans and primates.[6] Other markers of immune-senescence could be helpful here. In murine models of acute kidney injury (AKI), cellular senescence of resident and infiltrating immune cells likely explained the more severe phenotype in older mice.[42]

A relevant question is whether an increased concentration of circulating peripheral cytotoxic $CD28^-$ and especially $CD4^+$ T cells corresponds

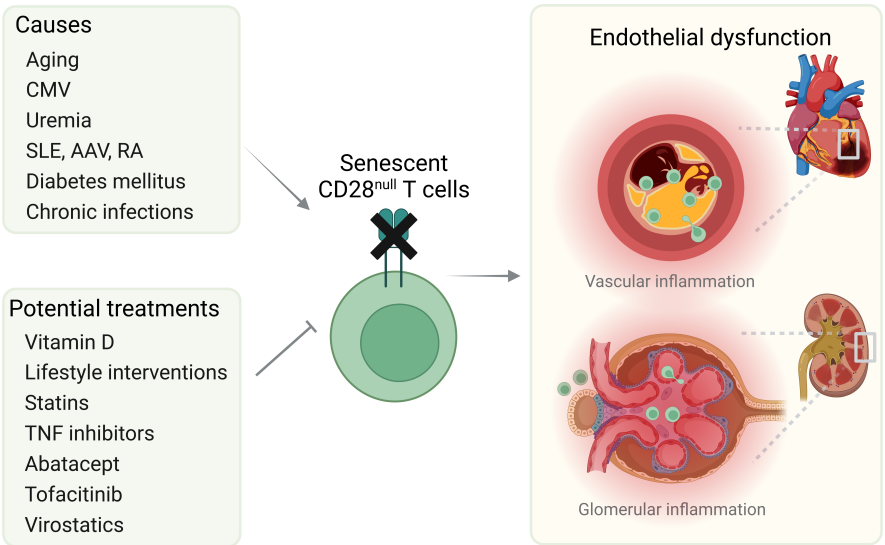

Figure 2. Causal factors in downregulation of CD28 in T cells and possible treatment options. Depicted on the left are mechanisms which lead to downregulation of CD28 in $CD4^+$ and $CD8^+$ T cells. TNF-α is a central molecule which exerts its effect at the transcriptional level with sustained stimulation over time leading to permanent CD28 loss. Other important factors are ageing and CMV infection which have a tropism for downregulation of CD28 respectively in $CD8^+$ and $CD4^+$ T cells. Other conditions depicted are associated with but with less certain causality, considering the increased concentration of TNF-α in for instance SLE, RA, AAV, in obesity or diabetes mellitus, and in viral and bacterial infections. Uraemia can also have both direct and indirect effects on CD28 downregulation. All inflammatory conditions which are associated with higher amounts of circulating $CD28^{null}$ T cells share endothelial dysfunction and cardiovascular disease. Depicted on the left are treatment options which have demonstrated to decrease circulating $CD28^{null}$ T cells (and at the same time to counteract vascular inflammation). A potential role of anti-oxidants which suppress IL-15 can be suspected but remains elusive. AAV, ANCA-associated vasculitis; HIV, human immune-deficiency virus; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; TNF-α, tumor-necrosis factor alpha.

with higher tissue (interstitial or glomerular) concentrations. In an OVA transgenic glomerulonephritis mouse model, the addition of *ex-vivo* activated cytotoxic T lymphocytes (CTL) led to accumulation of periglomerular infiltrates in the absence of immune complexes.[43] Multiple examples from autoimmune diseases support this.[44] In parallel with an increased serum concentration and enhanced expression of TNF-α and IFN-γ, the *in situ* concentration of $CD4^+$ $CD28^-$ T cells was increased in synovial fluid in RA, in the small airways in bronchiolitis obliterans, in thyroid and orbital tissue in Graves' disease, and in hepatic tissue in primary sclerosing cholangitis.[15,44–46] Also, and in parallel with peripheral expansion of β2 integrin expressing $CD4^+CD28^{null}$ T cells in granulomatosis with polyangiitis (GPA), immunostaining revealed their abundancy in granulomatous lesions.[47] In Immunoglobulin G4-related disease, circulating $CD28^{null}CD27^{null}CD57^+CD4^+$ T cells were the dominant effector subset with transcripts of activation, cytotoxicity and tissue migration, and the T_{EMRA} fraction particularly correlated with disease severity.[48] T_{EMRA} have increased production of proteases including metalloproteases which also affect cellular adhesion and migration.[2]

CX3CR1 positivity of infiltrating $CD4^+$ and $CD8^+$ $CD28^{null}$ T cells promotes their migration from peripheral blood[44] (Figure 1). The local micro-environment propagates the terminal differentiation and accumulation of cytotoxic cells by paracrine secretion of cytokines, chemokines and increased expression of adhesion molecules. The invoked tissue damage with apoptosis of nonimmune cells then causes epitope spreading with presentation of glomerular antigens by resident DC and monocytes or macrophages to $CD4^+$ T cells and recruitment and activation of CTL and macrophages.[43,48–50] Also, HSP-60 directly activates $CD28^{null}$ T cells and can aggravate glomerulonephritis after extracellular release from the kidney upon injury[51] (Figure 1). Exposure of $CD4^+CD28^{null}$ T cells of people with CKD to HSP-60 and -70 significantly increased their cytotoxicity.[24]

The immunological role of sex in glomerulonephritis

Of relevance but largely unexplored, sex modifies the origin, course and outcome of glomerular disease with a mostly male bias where SLE nephritis is the sole exception with a strong female predominance. Apart from variation in occupational hazards, smoking and drugs, of which determine the renal phenotype and prognosis, sex-based immunological differences are also essential.[52] Women in general have a stronger innate and adaptive immune response but are also more predisposed to develop autoimmune disease. Next to relevant X-linked genes, sex hormones also exert relevant and age-varying immunological effects, which could modify the role of immunosenescence in glomerulonephritis. In single-cell analyses of immune cells, increased IFN-γ-mediated signalling in males was observed in line with a higher expression of pro-inflammatory genes and with enhanced intercellular communication patterns.[53] The age-related decline of $CD8^+CD28^+$ T cells was more pronounced in Japanese men than in women.[54] Of note, animal studies mostly use male species although SLE murine models have also been designed where female animals have a more severe phenotype in most cases, but this is inconsistent,[55] and sex is not always disclosed.[56,57] Analyses in people with SLE are mostly being performed in females but generally without *a priori* exclusion of males.[14,58–61]

Systemic lupus erythematosus nephritis and T-cell-mediated damage

Accruing data have demonstrated an essential role of T cells in the pathogenesis of SLE, classically defined as B-lymphocyte-driven. High concentrations of circulating $CD4^+CD28^{null}$ T cells correlate with measures of disease severity such as SLEDAI index and serum concentration of IFN-γ, especially in patients with coexisting cardiovascular disease.[14,62] The risk of premature cardiovascular disease and atherosclerosis in SLE is well-established. Effector $CD4^+$ T cells from SLE-susceptible mice had accelerated atherosclerosis partially from resistance to Treg suppression and enhanced secretion of IL-17.[63] Renal arteriosclerosis in patients with SLE correlated with echocardiographic indices,[64] alluding to a continuum of vascular inflammation at the renal and extrarenal level.

When comparing patients with and without SLE nephritis, those with also have higher serum concentrations of TNF-α, IL-17, IL-10 and IL-15.[58] IL-15 increases the survival and proliferation of $CD28^{null}CX3CR1^+$ cytolytic effector memory T cells

resulting in enhanced trafficking to inflamed tissues.[11,12]

The fractalkine/CX3CR1 axis is involved in the pathogenesis of SLE nephritis. In murine SLE models, many exhausted T cells and glomerulus-infiltrating activated NK cells were already observed in the preclinical phase with high renal expression of fractalkine and of NKG2D ligand MICA.[56] Antagonists of fractalkine were reno-protective in another murine SLE model by reducing glomerular hypercellularity and macrophage infiltration.[57] In humans with class III and IV nephritis, glomerular fractalkine expression was increased.[59] In single-cell RNA analysis of human samples of lupus nephritis, most samples shared an enhanced NK cell activity and exhausted IFN-γ signature with increased expression of CX3CR1 in peripheral cells, but the overall composition and level of exhaustion of circulating T cells differed from the kidney population.[38,56,60] Caielli and co-workers nevertheless observed a congruent expansion of both circulating and infiltrating tubulo-interstitial $CX3CR1^{+}CD4^{+}$ T cells in patients with proliferative SLE nephritis.[65] TCR sequencing of kidney biopsies of patients with SLE nephritis demonstrated tubular and to a lesser extent glomerular infiltration with mostly oligoclonal $CD8^{+}CD28^{null}$ memory effector T cells.[61] Especially, the periglomerular $CD8^{+}$ T cell fraction correlates both with histological severity and treatment response in humans with SLE nephritis.[59,61] The absence of CD28 was not verified in these analyses.[59,61]

The chronicity of glomerular lesions in SLE nephritis and other aetiologies of glomerulonephritis is determined by the phenotype of the infiltrating immune cells. Activated lymphocytes invade the kidney in a manner dependent on type I IFN, but independent of class II MHC.[59,61] In a second phase, an adaptive immune response occurs through activation, clonal expansion of $CD4^{+}$ T cells and terminal differentiation of memory effector $CD8^{+}$ T cells, which are adherent to periglomerular or tubular epithelium.[61] Analysis of homing receptors confirmed these noncirculatory and mostly $CD28^{null}$ $CD8^{+}$ T cells in multiple sites of inflamed kidney tissue to persist for years.[61] Resident memory T cells are long-lived and maladaptive lymphocytes with pathogenic role in numerous diseases including kidney disease.

Recruitment of senescent T cells via the CX3CR1-fractalkine axis

Decreased levels of DNA methyl transferases in senescent $CD4^{+}CD28^{null}$ T cells cause overexpression of CX3CR1. This receptor binds with its sole ligand, fractalkine, in both soluble or (membrane)-bound forms, and plays a crucial role in human pathophysiology as a chemokine and adhesion molecule.[66] It is involved in the early phase of vascular inflammation, chronic inflammatory diseases such as RA but also has regulatory functions.[16] Upregulation of this axis by angiotensin-II (AT-II) in the aorta and vascular smooth muscle cells of uremic mice promotes homing of T cells.[67] CX3CR1 was upregulated in arterial segments of patients with ESKD and binds to endothelial fractalkine, whose expression is increased upon exposure to monocytes, preconditioned with the uremic retention solute indoxyl sulphate.[68] Higher monocyte expression of CX3CR1 in patients with CKD predicts cardiovascular events.[69]

The fractalkine/CX3CR1 axis is central in the pathogenesis of glomerulopathies.[16,70] Fractalkine is produced in mostly endothelial and tubular epithelial cells but also mesangial cells and podocytes in response to pro-inflammatory cytokines, such as TNF-α, IL-1β, MCP-1 and IFN-γ through multiple intracellular signalling pathways encompassing NF-κB and JAK–STAT.[16,49,70,71] The high expression of CX3CR1 in senescent $CD28^{null}$ $CD4^{+}$ lymphocytes stimulates homing of these cells into the inflamed kidney perpetuating a positive feedback loop.[66] This property is shared with $CD8^{+}$ T cells, NK and iNKT cells, γδ T cells and mononuclear phagocytes such as activated macrophages and monocytes while B cells lack CX3CR1.[66] Recent data disclosed its role as kidney-specific homing-receptor for cDC2, which recruit and regulate immune cells in glomerulonephritis.[71,72] The proportion of CX3CR1 expressing T cells and serum concentration of fractalkine is increased in CKD.[66] This could amplify the disease phenotype with declining kidney function, bearing in mind the role of pro-inflammatory uremic retention solutes. Antibodies against CX3CR1 blocked the glomerular infiltration of leukocytes and DCs resulting in decreased crescent formation in a rat model.[73]

A role of CX3CR1 in glomerulonephritis is also supported by clinical data from patients with

IgAN and SLE. Micro-array analysis in patients with IgAN and gross haematuria demonstrated an increased CX3CR1 expression in PBMC and CTL promoting their transendothelial migration.[70] Kidney biopsies of patients with IgA vasculitis and IgAN were characterised by upregulation of glomerular fractalkine in parallel with upregulation of HLA-DR and CX3CR1 in circulating NK cells and CTL.[74] An increased serum fractalkine concentration corresponds with more aggressive disease with pronounced lymphocyte infiltration in patients with IgAN.[75]

Cytomegalovirus and immunosenescence

Cytomegalovirus is a widespread virus characterised by lifelong endothelial latency. Infection leads to repeated T lymphocyte activation and effector memory inflation with accumulation of CMV-specific T cells and attrition of the naïve T cell pool by 20 years.[76] This premature senescence correlates with an upregulation of CD57 synergistically with age with an estimated acceleration of epigenetic ageing by 5 years.[77] Accrual of $CD28^{null}CX3CR1^{+}$ memory T cells correlates with increased vascular inflammation in seropositive people with AAV and healthy volunteers > 60 years.[77–79] Ganciclovir decreased the concentration of circulating $CD4^{+}CD28^{null}$ T cells in people with AAV.[80] Repeated CMV infection because of impaired immunity further expands this fraction by TCR-mediated antigenic triggering.[26]

There is broad support of a direct (by the presence of viral antigen and DNA in diseased endothelial and vascular smooth muscle cells) and indirect role (through accelerated immune-senescence) of CMV in the development of cardiovascular disease. Cytokine serum concentrations are higher in CMV seropositive patients with chronic heart failure than in their seronegative counterparts and correlate with anti-CMV antibody titers.[81] A meta-analysis of community-based prospective observational studies demonstrated an association between CMV infection and later development of cardiovascular disease.[82]

In KTR, previous CMV infection predicts inferior cardiovascular outcome and CMV D+/R- status is associated with a higher mortality and more graft loss according to OPTN data.[83] CMV prophylaxis is associated with better cardiovascular outcome in KTR according to registry data.[84] The not-uncommon presence of CMV (antigen/DNA) in especially the renal graft cortex was associated with intimal thickening of small arterioles on KTR protocol biopsies.[85] High viral loads of CMV and serostatus were associated with a faster decline of kidney graft function.[86–88] In KTR, CMV infection was associated with an incremental increase in $CD28^{null}$ T cells, with a very high expression of CX3CR1 and NKG2D in $CD27^{null}$ T cells.[13] Their concentration in lymph nodes remained low suggesting directed recruitment.[89] *In vitro*, they proliferated in response to PBMC previously exposed to CMV-derived but not HLA-derived antigens.[13] Endothelial damage by CMV is caused by induction of endothelial fractalkine and ensuing recruitment of CX3CR1- and NKG2D-positive immune cells including senescent $CD4^{+}$ T cells.[90]

Cytomegalovirus can aggravate autoimmune-mediated inflammation.[26] In murine models of multiple sclerosis, exposure to CMV increased the peripheral fraction of $CD4^{+}CD28^{null}$ T cells followed by recruitment into the spinal cord and increased demyelinisation.[26] In RA, CMV positivity increases circulating $CX3CR1^{+}CD28^{null}$ T cells, which correlated with intima-media thickness.[91] Whether a CMV-induced rise in $CX3CR1^{+}CD28^{null}$ cells could potentiate microvascular inflammation in the glomeruli and periglomerular areas should be further explored.

Immunosenescence and uraemia

Uraemia is characterised by Th1 predominance and also by premature senescence of lymphocytes likely contributing to its inflammatory state and ensuing cardiovascular disease.[92] $CD4^{+}$ but also $CD8^{+}CD28^{null}CD57^{+}$ T cells are increased in people with ESKD, especially in CMV seropositive patients, correlating with inflammation and cardiovascular events.[92,93] In patients with CKD, circulating $CD4^{+}CD28^{null}$ T cell concentrations correlate with serum TNF-α concentration, IMT and vascular calcification status.[94] In HD patients, concentrations of circulating $CD4^{+}$ and $CD8^{+}$ $CD28^{null}$ T cells are associated with erythropoietin resistance in CMV seropositive patients and the degree of CX3CR1 expression correlates with impairment of flow-mediated dilatation and increased IMT.[93,95] These senescent changes, which include telomere shortening, also occur in children with CKD and strikingly in those with previous exposure to immunosuppression.[8,30] Of

relevance, adolescents and young adults with ESKD because of glomerulonephritis had higher risk of cardiovascular disease in a large USRDS-based observational study.[96] Recent registry data indicate that adults with primary glomerular disease have a 2.5 times higher risk of cardiovascular disease than the general population.[97]

A specific uremic retention solute with an established role in immunosenescence is the protein-bound molecule indoxyl sulphate. This ligand of the acyl hydrocarbon receptor (AhR) downregulates the lymphocyte expression of CD28 at the transcriptional level.[98] AhR is a major player in B- and T-cell physiology, expressed on many T-cell subtypes but especially Th17 cells which regulates IL-22 production.[98] In ESKD, indoxyl sulphate binds to AhR on monocytes leading to increased production of TNF-α.[99] Age and poor kidney function are classically associated with worse renal outcome in patients with glomerulonephritis. Both conditions are characterised by increased concentrations of TNF-α, which downregulates the transcription of CD28 at the promotor level. Podocytes express AhR, which are activated upon exposure to indoxyl sulphate in the uremic state.[100] This results in a pro-inflammatory phenotype in both human and murine immortalised podocytes with foot effacement, cytoplasmic vacuoles and decreased mRNA expression of podocyte-specific proteins with abnormal granular and wrinkled patterns of podocin and synaptopodin.[100] Mice exposed to indoxyl sulphate for 8 weeks exhibited prominent renal and vascular damage including tubulo-interstitial lesions, ischaemic changes and mesangiolysis.[100] This suggests that uraemia could initiate and aggravate podocyte damage both directly or indirectly by creating a pro-inflammatory milieu.

Targeting $CD28^{null}$ T cells

$CD28^{null}$ status of T cells is not only a biomarker of immunosenescence but also a potential therapeutic target. Restoration of its expression in chronically activated human $CD8^+$ T cells via gene transduction attenuated replicative senescence via increased telomerase activity, more proliferative potential and a lower production and secretion of pro-inflammatory cytokines.[101] Also, supplementation of active vitamin D, which has established immunological effects on adaptive and innate immunity, increases the expression of CD28 in $CD4^+$ T cells from liver tissue of people with primary sclerosing cholangitis (PSC) even in the presence of TNF-α.[46] Patients with PSC and vitamin D deficiency had lower levels of circulating $CD4^+CD28^{null}$ T cells after repletion.[46]

Lifestyle measures also seem to be beneficial for counteracting immunosenescence. A 4-week regimen of hypoxic exercise upregulated the CD28 expression in circulating T cells at baseline and after strenuous exercise, most likely because of improvement of oxidative stress and lowering of pro-inflammatory cytokines.[102] A systematic review of studies including RCT demonstrated a beneficial effect of repeated aerobic exercise or endurance resistance training on CD28 expression of $CD8^+$ T cells irrespective of age or level of sedentarism.[103] This occurred despite a temporary increase in senescent $CD8^+CD28^{null}$ T cells immediately postexercise.[103] Cardioprotective drugs such as lipid-lowering statins have pleiotropic effects, which include a lowering of circulating $CD4^+CD28^{null}$ T cells.[6,29] This is likely related to anti-inflammatory properties and pro-apoptotic effects on senescent T cells.[6,29]

Considering the role of TNF-α in the downregulation of CD28, a potential beneficial role of TNF-α inhibitors can be speculated. Both *in vivo* and *in vitro* data demonstrated a dose-dependent decrease in $CD4^+CD28^{null}$ T cells by infliximab in patients with RA or unstable angina.[104,105] In people with RA, these drugs exerted beneficial effects on cardiovascular events and mortality.[106] In the same study population, 48 weeks of abatacept treatment, of which is a fusion protein containing CTLA-4 that binds ligands CD80 and 86, also decreased both circulating $CD4^+$ and $CD8^+CD28^{null}$ T cells in parallel with clinical recovery.[107] In parallel with TNF-α inhibitors, patients with RA on abatacept had a better cardiovascular outcome than conventional synthetic disease-modifying antirheumatic drugs.[108] Its role as a potential treatment in glomerulonephritis and AAV remains yet unestablished.

Finally, tofacitinib, a selective JAK1/JAK3 inhibitor, blocks IL-7/IL-15-signalling, thereby preventing the expansion of $CD4^+CD28^{null}$ (but not $CD28^+$) T cells.[109] In a recent phase I trial, tofacitinib attenuated the type I IFN response in patients with SLE with ensuing improvement of cardiometabolic parameters, endothelial function and vascular stiffness.[110] In a MRL/lpr SLE mouse

model, tofacitinib decreased the proliferation of tissue-resident memory T cells leading to improved preservation of kidney function.[111] Current evidence supports a net cardiovascular benefit of JAK–STAT inhibitors because of anti-atherosclerotic effects, although potentially prothrombotic effects with high-dose treatment were reported.[112] Also, patients with RA allocated to tofacitinib versus TNF-blockers had more serious adverse cardiac events.[113]

FUTURE PROSPECTS

Recent studies including transcriptomics data demonstrate an emerging role of immunosenescence in the pathophysiology of both glomerulonephritis and vascular inflammation. The role of terminally differentiated and cytotoxic $CD28^{null}$ T cells, however, has not been clarified. A direct causal link between a provoked increase in these circulating immunosenescent T cells and ensuing intrarenal accumulation should be demonstrated. Both experimental animal models or kidney biopsies of humans with glomerular disease and longitudinal follow-up of T cells could contribute to a better recognition of the dynamics of this T-cell subpopulation. Considering the loss of CD28 in circulating T cells is mainly observed in humans and primates, other markers of immunosenescence should also be included in animal experiments.

Cytomegalovirus serostatus could modify the course of glomerulonephritis by increasing these terminally differentiated lymphocytes, which express specialised homing receptors, such as CX3CR1. Whether a CMV-induced increase in $CX3CR1^{+}CD28^{null}$ cells could potentiate microvascular inflammation in the glomeruli and periglomerular areas should be further explored. Also, intrinsic effects of ageing or uraemia on glomerular inflammation or podocyte toxicity in animal and human models should be further deciphered. A potential synergism between CMV and uremic toxins in microvascular inflammation is an attractive hypothesis with potential relevance for biomedical research, bearing in mind that CMV-directed treatment including antiviral drugs and vaccines could prove beneficial.

Shared mechanistic pathways between vascular and glomerular inflammation highlight the links between cardiovascular risk, systemic autoimmune diseases, such as SLE or AAV and CKD. Importantly, early T-cell accumulation precedes glomerular or vascular injury and as such could open avenues for early and successful treatment interventions, which include chemokine-driven strategies.

ACKNOWLEDGMENT

The authors thank Dr Andrew S Brown for linguistic review of the manuscript.

AUTHOR CONTRIBUTIONS

Steven Van Laecke: Conceptualization; writing – original draft; writing – review and editing. **Karel Van Damme:** Writing – original draft; writing – review and editing. **Amélie Dendooven:** Writing – original draft; writing – review and editing.

CONFLICT OF INTEREST

Steven Van Laecke has served in the advisory board of Hansa and GSK. The others authors declare no conflict of interest.

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Graphical Abstract

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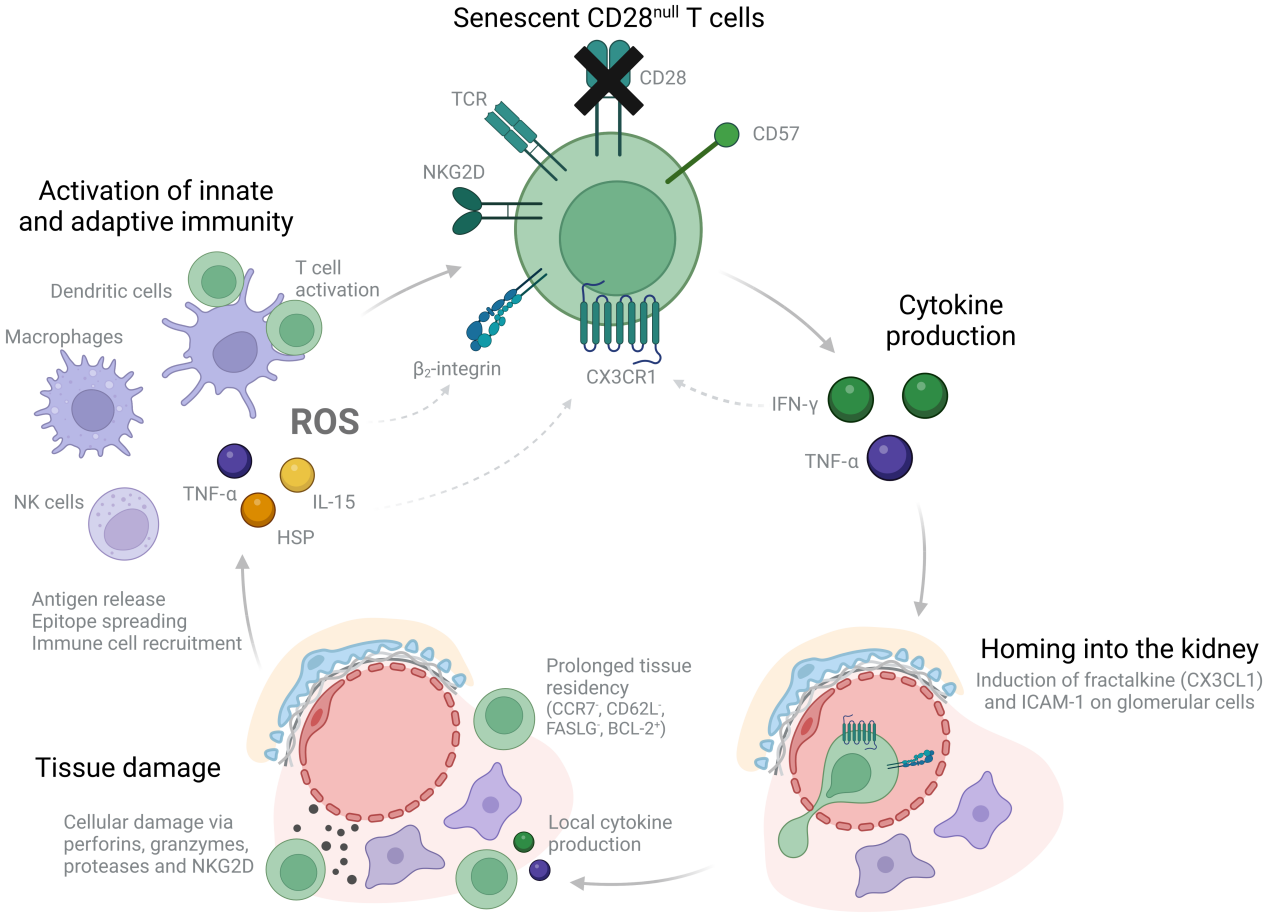

In this article, we discuss the role of immunosenescence in the ethiopathogenesis and course of glomerulonephritis. We integrate an overview of (non) modifiable risk factors with potential relevance for treatment. We also describe the strikingly similar role of senescent lymphocytes and its mediators such as pro-inflammatory cytokines, chemokines and integrins in the development of atherosclerotic disease.