Unconventional T-cells and kidney disease

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ABSTRACT

Unconventional T-cells are a diverse and until recently underappreciated group of relatively rare lymphocytes that are distinct from conventional $CD4^+$ and $CD8^+$ T-cells, and that at large recognise antigens in the absence of classical restriction through the major histocompatibility complex (MHC). These non-MHC-restricted T-cells include mucosal-associated invariant T (MAIT) cells, natural killer T (NKT) cells, gamma/delta (γδ) T-cells and further, often rather ill-defined, subsets of T-cells. Depending on the physiological context, such unconventional T-cells may assume either protective or pathogenic roles in a range of inflammatory and autoimmune scenarios related to acute and chronic kidney disease and to kidney replacement therapy-associated conditions. As consequence, experimental models and clinical studies have revealed the potential of certain unconventional T-cells as targets for therapeutic interventions and as prognostic and diagnostic biomarkers. This includes the responsiveness of human Vγ9/Vδ2 T-cells and MAIT cells to many microbial pathogens, with implications for early diagnosis, risk stratification and targeted treatment of peritoneal dialysis-related peritonitis. The expansion of other, non-Vγ9/Vδ2 γδ T-cells during CMV infection and their contribution to viral clearance suggest that these cells can be harnessed for immune monitoring and adoptive immunotherapy in kidney transplant recipients. In addition, populations of NKT, MAIT or γδ T-cells are involved in the immunopathology of IgA nephropathy and in models of glomerulonephritis, ischaemia-reperfusion injury and kidney transplantation.

INTRODUCTION

The immune system has evolved to provide optimal defence against a myriad of hazards. In anticipation of the fact that each pathogen is different from one another in expressing a distinct antigenic signature, the body harbours billions of individual T-lymphocytes, each one with unique specificity. Upon encountering their target through the T-cell receptor (TCR), such specific T-cells will undergo clonal expansion and turn into effector T-cells to help orchestrate an effective immune response and clear the insult on the body. Some will also differentiate into **memory T-cells** that confer protection from re-infection by the exact same organism over years to come, often for life – a hallmark of **adaptive immunity** and the basis of successful vaccines.

Phenotypically and functionally, T-cells are defined by their surface expression of CD4 or CD8. $CD4^+$ T-cells recognise antigenic peptides presented by major histocompatibility complex (MHC) class II molecules. These peptides are typically derived from exogenous sources such as microbes and allergens upon endocytosis by cells specialised in **antigen presentation** like dendritic cells (DCs) and macrophages, or, in rarer cases, upon autophagy of intracellular material by such antigen presenting cells (APCs). $CD4^+$ T-cells can assume a multitude of effector functions, with the best-known examples comprising T helper cells polarised towards IFN-γ (Th1), IL-4 (Th2) and IL-17A (Th17) production, T regulatory (Treg) cells with an immunosuppressive role, and T follicular helper cells (Tfh) that orchestrate B-cell responses in lymph nodes and spleen [1].

$CD8^+$ T-cells recognise antigenic peptides presented by most cell types in the body, in the context of MHC class I molecules, and can exert direct cytotoxicity towards those targets. Here, peptides typically originate from intracellular proteins after degradation by the proteasome and are especially relevant in anti-viral and anti-tumour immunity, but can also derive from exogenous proteins in a process known as antigen cross-presentation. While not considered as plastic in their

phenotype as $CD4^+$ T-cells and typically having a pro-inflammatory function, $CD8^+$ T-cells may also assume cytokine profiles reminiscent of Th2, Th17, Treg and Tfh cells [2].

The past years have seen a wealth of new findings concerning the biology of 'unconventional' T-cells, a hitherto underappreciated group of relatively rare T-cells that escape the common classification into 'helper', 'cytotoxic' or 'regulatory' T-cells, and that at large are not restricted by classical MHC molecules [3,4]. Some unconventional T-cells are similar to classical $CD4^+$ and $CD8^+$ T-cells in that they express a T-cell receptor (TCR) composed of TCRα and TCRβ chains, including mucosal-associated invariant T (MAIT) cells and invariant natural killer T (iNKT) cells. Other unconventional T-cells express an entirely distinct type of TCR and are referred to as γδ T-cells. More often than not, the antigenic structures unconventional T-cells respond to remain elusive, and our understanding of what these cells do, and when, is limited. This knowledge gap is amplified by the fact that many unconventional T-cell subsets are unique to humans, and thus notoriously challenging to study.

Major recent breakthroughs in the field relate to the discovery of butyrophilins (BTNs) as key regulators of γδ T-cells [5,6] and of vitamin B2 metabolites as cognate ligands for MAIT cells [7,8], the characterisation of T-cells that respond to self and non-self lipids presented by members of the MHC-related CD1 family [9,10], and the elucidation of distinct TCR repertoires that define functional T-cell subsets [11,12]. Meanwhile in the clinic, unconventional T-cells are increasingly being exploited for novel immunotherapies, with promising potential [13,14]. In the context of nephrology, unconventional T-cells have been implicated in conditions such as glomerulonephritis [15,16], peritoneal dialysis-related peritonitis [17] and during cytomegalovirus (CMV) infection in kidney transplant patients [18].

In this Review, we provide a timely update of progress in basic and clinical research related to the role of unconventional T-cells in the immunopathology of kidney disease and kidney

replacement therapy-associated conditions, and discuss their potential as targets for therapeutic interventions and as prognostic and diagnostic biomarkers. In the majority of cases, we focus on unconventional T-cells in humans but, where appropriate, also draw on knowledge gained from animal models. In order to avoid confusion, we use the Lefranc & Rabbits nomenclature for human γδ T-cells [19] and the Heilig & Tonegawa nomenclature for murine γδ T-cells [20] throughout this review.

SOME T-CELLS ARE NOT CONVENTIONAL

Unconventional T-cells are different from classical $CD4^+$ T-cells and $CD8^+$ T-cells (**Table 1**) and can be distinguished by their TCR usage, the antigen presenting molecules used, the often unconventional nature of the ligands they recognise, and/or their functions which may integrate features of adaptive and **innate immunity**, leading to their description as 'innate-like T-cells' or 'donor-unrestricted T-cells' in the literature.

While some unconventional T-cells only represent small populations [3,9], human γδ T-cells in healthy blood constitute 1-5% of all T-cells in the circulation, at times even much higher [21]. In contrast, γδ T-cells are scarce in healthy kidney tissues [22,23]. γδ T-cells can be distinguished based on their TCR usage and are typically divided into Vγ9/Vδ2 T-cells, the dominant population in human blood, and other γδ T-cells that are mainly found in tissues. Among these, three subsets are of particular interest here: $V\delta2^{neg}$ γδ T-cells (which may or may not co-express Vγ9) and $V\gamma9^-$ $V\delta2^+$ γδ T-cells (where the Vδ2 chain pairs with a TCRγ chain other than Vγ9), and Vγ4/Vδ1 γδ T-cells that populate the human intestine (**Figure 1**). For better readability, especially for a non-specialist audience, we will refer to these three subsets combined as 'non-Vγ9/Vδ2 γδ T-cells' for most parts of this review.

MAIT cells comprise another 1-10% of blood T-cells in humans and are enriched further in mucosal tissues, for instance in the intestine and in the liver [24,25], but not in the human kidney [26] – although tissue-resident MAIT cells in the kidney display phenotypically distinct features compared to their counterparts in human blood [26]. In contrast to the relatively prominent γδ T-cell and MAIT cell populations, iNKT cells make up only 0.01-1%, germline-encoded mycolyl lipid-reactive (GEM) T-cells barely 0.001-0.1% of blood T-cells in healthy donors [3,9,27].

It is noteworthy that T-cells with a γδ TCR are present in most jawed vertebrates (with the possible exception of scaled reptiles such as lizards and snakes [28]), suggesting a clear evolutionary benefit from the conservation of unconventional T-cells alongside classical T-cells. However, whereas many aspects of the immune system are fairly conserved between humans and animals, including the concept of MHC restriction of classical T-cells [29], the unconventional human T-cell compartment is only poorly reflected in other species, thereby hampering studies in experimental models. For instance, while NKT cells and their restricting element CD1d exist in most mammals, the antigen presenting molecules CD1a, CD1b and CD1c are all absent in mice [3,9]. Similarly, human and mouse γδ T-cell subsets do not correspond to each other in function or TCR usage [30]. In particular, mice do not possess the γδ T-cell restricting elements BTN2A1, BTN3A1, BTNL3 and BTNL8, where other butyrophilin family members play mechanistically similar but physiologically distinct roles [6]. On a functional level, the dominant γδ T-cell subset in human blood, characterised by a Vγ9/Vδ2 TCR and an unusual responsiveness to 'phosphoantigens', is limited to primates and – curiously – to alpacas but it does not exist in other animals studied so far [31]. Yet, despite these extensive differences between species, the general (and perhaps oversimplified) concept prevails of a tripartite labour division between $CD4^+$ T-cells that monitor the microenvironment for proteins indicating exogenous hazards, $CD8^+$ T-cells that screen the cells of the body for aberrant proteins resulting from infection or malignant

transformation, and unconventional T-cells that survey and regulate tissue integrity and sense stress in a non-MHC-restricted manner [3,28,29].

Unconventional ligands for unconventional lymphocytes

The plethora of structures recognised by unconventional human T-cells, together with the presenting and costimulatory molecules involved in this recognition, has been expertly reviewed [8,9,32,33,34]. A selection of ligands, spanning surface markers upregulated on stressed cells, self and non-self lipids and microbial metabolites, is depicted in **Figure 1**. Broadly speaking, unconventional T-cells recognise three categories of ligands: non-self molecules derived from pathogens, commensals and the environment, self ligands that are upregulated upon cellular stress, and structures that are constitutively expressed in healthy tissues and define normal physiological conditions. In many cases, these ligands are non-proteinaceous and depend on presentation molecules such as MR1 and members of the CD1 family. In other cases, cell surface-bound or soluble ligands may be recognised directly by the TCR, in the absence of any apparent presentation.

'Phosphoantigens': phosphorylated isoprenoid precursors

Among the best characterised microbial activators are the metabolites (*E*)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate (HMB-PP) that acts specifically on Vγ9/Vδ2 T-cells [35], and 5-(2-oxopropylideneamino)-6-D-ribitylaminouracil (5-OP-RU) that is recognised by MAIT cells [36]. HMB-PP is an intermediate of the microbial non-mevalonate pathway of isoprenoid biosynthesis utilised by the majority of pathogenic and commensal Gram-negative bacteria and by Gram-positive bacteria like *Corynebacterium*, *Mycobacterium* and *Clostridium* [37,38]. It binds to the intracellular B30.2 domain of butyrophilin BTN3A1 and is thought to induce a conformation change that allows recognition of the related molecule BTN2A1 by the Vγ9/Vδ2 TCR

[39,40,41,42]. As such, HMB-PP is not a TCR ligand itself but is critical for Vγ9/Vδ2 T-cell responses toward microbes. The end product of both the non-mevalonate pathway in microbes and the upper part of the classical, mevalonate pathway of isoprenoid biosynthesis in human cells is isopentenyl pyrophosphate (IPP). Free IPP is far less potent than HMB-PP but binds similarly to BTN3A1, and may be involved in flagging metabolic stress upon malignancy or pharmacological intervention. As a result, Vγ9/Vδ2 T-cells readily respond to target cells treated with downstream inhibitors of the mevalonate pathway, such as the anti-bone resorption drug zoledronate, that lead to intracellular accumulation of IPP [42,44]. The contribution of TCR affinity and diversity to the BTN2A1/BTN3A1 and phosphoantigen-dependent activation of Vγ9/Vδ2 T-cells is only beginning to be understood, with a likely contribution of additional, yet unknown, molecules fine-tuning the response [41,45].

Vitamins and more

The molecule 5-OP-RU represents the most potent MAIT cell agonist identified to date and is a derivative from the microbial riboflavin (vitamin B2) biosynthesis that is stabilised upon binding MR1 [7]. Of note, the majority of bacteria and fungi synthesise vitamin B2, including most species of the intestinal microbiota, with the prominent exception of streptococci and enterococci. As both the non-mevalonate and riboflavin pathways are absent from humans, recognition of HMB-PP and 5-OP-RU allows the human immune system to quickly and uniformly sense metabolites shared by a large range of microbes [48]; comprehensive lists of clinically relevant bacterial pathogens and their capacity to activate Vγ9/Vδ2 T-cells and/or MAIT cells have been compiled elsewhere [48,49]. Although they only constitute relatively small subpopulations within the total T-cell pool, cell types such as Vγ9/Vδ2 T-cells and MAIT cells represent in fact the most abundant 'antigen-specific' T-cells in the human body, far more frequent than $CD4^+$ or $CD8^+$ T-cells recognising common viral or bacterial antigens [3]. Given their overlapping

recognition of micro-organisms it is conceivable that these two unconventional T-cell types may even compensate each other's role, based on findings in a patient with no functional MR1 as result of a rare genetic mutation who lacked circulating MAIT cells but instead had elevated levels of Vγ9/Vδ2 T-cells [50]. Besides 5-OP-RU, related metabolites may also be recognised by MAIT cells, some of which even in an inhibitory fashion. In fact, the emerging potential of MR1 to present not only riboflavin derivatives but also folic acid (vitamin B9) metabolites and unrelated compounds including drugs such as diclofenac has given rise to the notion of a far greater diversity of MAIT cells and MAIT-like cells than originally envisaged [8,46,47] (**Table 1**).

Self and non-self lipids

Other exogenous ligands recognised by unconventional T-cells include α-glycosylceramides, glycosphingolipids and glycodiacylglycerols from a range of organisms that can induce CD1d-dependent activation of iNKT cells [51], with α-galactosylceramide (α-GalCer) from the marine sponge *Agelas mauritianus* representing the prototypical and best studied iNKT cell ligand [52]. In addition, mycobacterial glucose-6-*O*-monomycolate and free mycolic acid are recognised by GEM T-cells in the context of CD1b [53]; and mycobacterial mannosyl-β1-phosphomycoketide actives CD1c-restricted T-cells [54]. The mycobacterial lipopeptide dideoxymycobactin-838 is the best characterised foreign ligand presented by CD1a [55]. However, many unconventional T-cells are also capable of recognising self antigens bound to CD1a, CD1b, CD1c or CD1d, and even the empty presentation molecules themselves, thereby blurring the line between sensing microbial infection and surveying healthy or stressed self [3,9,10,32,33,34] (**Table 1**). In this respect it is worth noting that while iNKT cells express a CD1d-restricted semi-invariant TCR ($V\alpha24^+$ in humans; $V\alpha14^+$ in mice) and recognise α-GalCer, another population of so-called type II NKT cells is similarly restricted by CD1d but uses variable TCRs and does not respond to α-GalCer [56,57].

Lymphoid stress surveillance

The role of unconventional T-cells in immune surveillance is best exemplified by certain subsets that are not restricted by known antigen presentation molecules. Amongst these, human non-Vγ9/Vδ2 γδ T-cells are associated with the response to **cytomegalovirus (CMV) infection** [58,59,60]. Their contribution to antiviral immunity nothwithstanding, all ligands identified so far for CMV-reactive γδ T-cells represent stress-related self proteins expressed by CMV-infected tissues (and often also by tumour cells), rather than viral proteins. These molecules include endothelial protein C receptor (EPCR) [61], annexin A2 [62], ephrin receptor A2 and HLA class I free heavy chain [63,64]. Similarly, many $V\gamma4^+$ γδ T-cells in the human intestine appear to recognise the constitutively expressed butyrophilin-like molecules BTNL3 and BTNL8, with local inflammation leading to downregulation of BTNL8 on the gut epithelium and loss of intraepithelial $V\gamma4^+$ γδ T-cells [65,66].

Bacterial superantigens

Some micro-organisms produce so-called 'superantigens' with the ability to bypass the TCR specificity and activate T-cells directly by crosslinking their TCR with MHC class II molecules on APCs. These proteinaceous superantigens include the staphylococcal enterotoxins SEA, SEB and toxic shock syndrome toxin-1 (TSST-1), and streptococcal pyrogenic exotoxins (Spe), which all have been shown to act on subsets of human γδ T-cells, MAIT cells and/or iNKT cells [67,68].

TCR-independent target recognition

In addition to self and non-self structures recognised via the TCR, many unconventional T-cells are equipped with an arsenal of activating and/or inhibitory receptors capable of sensing physiological stress, injury, infection and malignancy. These may include proteins usually associated with natural killer (NK) cells like the natural cytotoxicity receptors NKp30 and NKp44

and other activating receptors like natural killer group 2D (NKG2D) and DNAX accessory molecule-1 (DNAM-1), as well as killer cell immunoglobulin-like receptors, antibody receptors like the high affinity Fc receptor for IgG, FcγRIII (CD16), and pathogen recognition receptors including Toll-like receptors [69,70,71,72]. In addition, many unconventional T-cells express the β1 subunit of the IL-12 receptor, the IFN-α receptor and the IL-18 receptor β chain, and can be activated directly by the corresponding cytokines [11,73]. An appropriate microenvironment appears thus necessary for fine-tuning unconventional T-cell responses to a multiplicity of stimulatory signals, with non-TCR related functions complementing the TCR ligand-specific responsiveness and allowing unconventional T-cells to engage in a wide range of immunopathological scenarios, by sensing multimolecular stress signatures [11,74].

Unconventional functions of unconventional lymphocytes

The function of unconventional T-cells cannot be generalised. As diverse as the ligands they recognise, and the TCRs and accessory molecules involved in this recognition, is the variety of functional outcomes [3,6,7,10,73,75]. Some unconventional T-cell responses match comparable responses by $CD4^+$ and $CD8^+$ T-cells, such as the frequent acquisition of a pro-inflammatory and/or cytotoxic role akin to Th1 cells and cytotoxic T lymphocytes. Also well described is the potential of unconventional T-cells to provide B-cell help akin to Th2 or Tfh cells and to induce maturation of DCs [75], and to amplify inflammatory, angiogenic and pro-tumorigenic responses in a Th17-like manner [76,77]. Other functions are more reminiscent of those of NK cells, such as the capacity to survey healthy and stress tissues via activating and inhibitory NK receptors, exert **antibody-dependent cellular cytotoxicity (ADCC)** towards opsonised targets, and respond to stimulation by cytokines such as IFN-α, IL-12 or IL-18 [7,11,77,78,79]. Human Vγ9/Vδ2 T-cells in particular have also been reported to act as professional APCs for $CD4^+$ and $CD8^+$ T-cells [75,80], and even to phagocytose bacteria and malaria parasites [81,82]. Further

and rather unexpected functions of unconventional T-cells, especially in mouse models, include roles in wound healing, body temperature regulation and nutrient sensing [83,84,85]. It is this wide plasticity that has led to their categorisation as 'unconventional' T-cells that 'bridge innate and adaptive immunity', for the lack of a better term.

Private and public profiles

During T-cell development in the thymus, the genes encoding the two chains of the TCR undergo extensive somatic rearrangement through V(D)J recombination of variable (V), diversity (D) and joining (J) segments, a process yielding highly diverse **TCR repertoires** for both αβ and γδ T-cells [86]. Recent technological advances have allowed the determination of these TCR sequence profiles in experimental and clinical scenarios, and revealed that most unconventional T-cell populations are actually oligoclonal in nature, with a restricted repertoire skewed towards certain TCR rearrangements, as opposed to classical $CD4^+$ and $CD8^+$ T-cells that are largely polyclonal and 'unfocused', with each TCR at low frequency [3,4,7,8,9,10,11,12]. While the oligoclonal repertoires of unconventional T-cells are often 'private' – unique to each individual and not found in another person – some T-cells stand out as having 'public' TCRs, shared between people and often based on germline-encoded sequences. Examples of such public TCRs include Vγ9/Vδ2 T-cells that carry a semi-invariant Vγ9 chain, and the invariant Vα chains of MAIT cells, iNKT cells and GEM T-cells (**Table 1**). These restricted repertoires explain how whole populations of unconventional T-cells can respond to the same stimulus, in contrast to $CD4^+$ and $CD8^+$ T-cells where each individual cell has its own distinct and unique antigen specificity.

Innate and adaptive subsets

Recent research on γδ T-cells has shown how TCR repertoires change during ontogeny and in response to antigenic challenges, giving rise to the concept of innate-like and adaptive-like T-cell

subsets, elegantly integrating earlier and at times contradictory observations about the nature of γδ T-cell responses [11,12,87]. Accordingly, innate-like γδ T-cell subsets are characterised by relatively stable and oligoclonal TCR repertoires that do not change with time and that allow those cells to respond rapidly and uniformly to a given stimulus, similar to responses of the innate immune system via pathogen recognition receptors or NK receptors. The prime example of such innate-like γδ T-cells are phosphoantigen-reactive and BTN2A1/BTN3A1-dependent Vγ9/Vδ2 T-cells [88,89,90]. Other γδ T-cells respond more in an adaptive-like manner, with certain TCR sequences becoming enriched through expansion of the corresponding clones and with the potential to establish long-lived memory, such as CMV-reactive non-Vγ9/Vδ2 γδ T-cells [91,92]. Whether unconventional T-cells other than γδ T-cells conform to this model in a similar manner and harbour innate-like and adaptive-live subsets is subject to current investigation.

Protection versus pathogenesis

Despite constituting only relatively minor populations of immune cells, there is mounting evidence for a key involvement of unconventional T-cells in the immunopathology of many infectious, inflammatory and autoimmune scenarios, where they may be initiating, amplifying or dampening disease processes [74,75,76,93]. In the following, we will be reviewing the protective and pathogenic roles of unconventional T-cells in a variety of kidney-related pathologies including acute kidney injury, glomerulonephritis, fibrosis, dialysis and transplantation.

ACUTE KIDNEY INJURY

Acute kidney injury refers to an abrupt decrease in kidney function, resulting in the retention of urea and other waste products and in the dysregulation of extracellular volume and electrolytes. As a broad clinical syndrome, it encompasses kidney-specific conditions such as acute glomerular

disease, and non-specific conditions such as **ischaemia reperfusion injury (IRI)** and toxic injury. Kidney IRI is characterised by tubular cell necrosis and an interstitial infiltration of neutrophils, macrophages, and T-cells, and associated with increased mortality in patients with acute kidney failure and poorer graft survival in kidney transplant recipients. After IRI of the kidneys, declines in blood γδ T-cell frequencies are more pronounced in patients with elevated urinary cell stress biomarkers such as tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP-7), suggesting that γδ T-cells home from blood to the affected kidneys [94]. In support, a mouse model of tubular cell injury induced by calcium oxalate saw an increase in kidney-infiltrating activated γδ T-cells, alongside enhanced IL-17A levels [95]. As clear indication of an exacerbating role for γδ T-cells in the immunopathology, γδ T-cell deficient mice exhibit decreased tubular necrosis after IRI, a better glomerular filtration rate and reduced mortality, compared to wild-type mice [96,97]. Although γδ T-cells do not appear to regulate neutrophil and macrophage infiltration in this scenario [96], they may facilitate and amplify the development of kidney lesions after IRI by recruiting adaptive T-cells [97].

IRI events can result in profound tissue hypoxia, which disturbs the physiological balance in the tissue and disrupts the energy supply. One of those consequences is the local accumulation of metabolites like adenosine at sites of ischaemic damage. Extracellular adenosine binds to receptors such as adenosine 2A receptor (A2AR), which was shown to suppress murine CD1d-dependent iNKT cell activation and thereby limit tissue damage during hepatic ischaemia reperfusion [99]. This adenosine/A2AR axis also confers protection against ischaemic damage of the kidneys, by blocking the production of IFN-γ by iNKT cells [100,101]. Administration of DCs loaded with α-GalCer and tolerised using A2AR agonists can inhibit the pro-inflammatory function of iNKT cells in mouse kidneys and protect them from induced IRI [101].

In contrast to the exacerbating role of iNKT cells during IRI, murine type II NKT cells appear to protect kidneys from tissue damage, by decreasing the levels of pro-inflammatory cytokines such as IFN-γ and IL-6, and by enhancing regulatory cytokines such as IL-4 and IL-10 [102]. Human type II NKT cells activated by sulfatide can restore hypoxic tubular epithelial cell proliferation and prevent apoptosis *in vitro* via expression of HIF-1α and IL-10. In biopsies from patients with acute tubular necrosis, the number of type II NKT cells in kidney tissue correlates negatively with the severity of the disease [102]. As therapeutic option, rapamycin treatment increases the recruitment of NKT cells (identified as $CD3^+$ $NK1.1^+$ cells) to the kidneys in a mouse model of IRI, and improves kidney function and histological lesions [103].

GLOMERULONEPHRITIS

Glomerulonephritis encompasses all inflammatory and non-inflammatory kidney diseases affecting the glomerular structure, in particular the capillaries, mesangial and epithelial compartments. While genetic risk factors together with environmental factors are the basis of a profound dysregulation of the humoral response in patients suffering from glomerulonephritis, the role of unconventional T-cells in the pathophysiology of these diseases has been widely overlooked. However, with the increasing availability of experimental models, this knowledge gap is now being addressed *in vivo*, especially in mice and rats. Intriguingly, unconventional T-cells can have multiple, and sometimes even opposite, functions according to the model used. Meanwhile, data from human studies are often scarce or need to be corroborated by using state-of-the-art experimental techniques (**Table 2**).

IgA nephropathy

The clinical phenomenon of **immunoglobulin A (IgA) nephropathy** is characterised by an increase of circulatory IgA1 antibodies with aberrant glycosylation, which promote the formation of immune complexes depositing in the kidneys, ultimately leading to glomerular damage [104]. As IgA1 is mainly produced in mucosal tissues, a primary abnormality within the mucosal immune system may underly the pathogenesis of the disease. In this regard, the gut mucosal γδ T-cell repertoire in patients with IgA nephropathy undergoes striking changes in their TCR repertoire compared to healthy controls [105], which is also observed in the bone marrow [106]. In parallel, the number of $V\gamma9^+$ γδ T-cells is increased in the peripheral blood of IgA nephropathy patients and correlates with serum IgA levels and the number of IgA^+ B-cells [107]. Whether this oligoclonal expansion of $V\gamma9^+$ γδ T-cells is a response to self or non-self ligands remains unanswered. In the kidneys of patients with IgA nephropathy, T-cells infiltrate the kidney interstitium. However, while αβ T-cells are found in both stable and progressive disease, γδ T-cells are only associated with progressive IgA nephropathy [22]. Spectratyping studies revealed that kidney-infiltrating γδ T-cells use a restricted TCR repertoire dominated by Vδ1 transcripts, again indicating an adaptive-like oligoclonal expansion (**Figure 2A**) [108]. While the target structures are not known it is thinkable that these γδ T-cells may expand to stress markers at the site of inflammation and subsequently induce IgA class switching in B-cells [107]. More research is clearly needed to reconcile these γδ T-cell responses in blood, mucosa and kidneys of patients with IgA nephropathy, and their relevance in the disease process.

ANCA-associated vasculitis and crescentic glomerulonephritis

The clinical presentation of **anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis** includes three pathologies: microscopic polyangiitis, granulomatosis with polyangiitis, and eosinophilic granulomatosis with polyangiitis. The major antigens recognised by these

ANCAs are myeloperoxidase (MPO) and proteinase 3 (PR3), enzymes that are usually stored inside neutrophils and released during inflammatory events [109]. ANCAs bind target antigens on the neutrophil surface, which in turn release reactive oxygen species and lytic enzymes that injure vascular endothelial cells [109]. In mouse models, ANCA-associated glomerulonephritis is also characterised by a high frequency of Th17 cells in the kidneys, which contribute to crescent formation and kidney impairment by inducing the expression of chemokines in mesangial cells and recruiting T-cells and monocytes [110].

In human ANCA-associated glomerulonephritis, γδ T-cell levels are normal in peripheral blood [111], but γδ T-cells expressing NKG2D infiltrate the periphery of tubular and glomerular capillaries in the kidneys [112]. In an experimental model of crescentic glomerulonephritis, γδ T-cell deficient mice have fewer $CD8^+$ T-cells and macrophages in their kidneys than wildtype animals, suggesting that γδ T-cells recruit T-cells and macrophages to the kidney interstitium [113]. More recently, resident murine γδ T-cells expressing the chemokine receptor CCR6 were found to be a major cellular source of IL-17A at the early phase of crescentic glomerulonephritis, whereas $CD4^+$ T-cells coming from the gut via the CCL20/CCR6 axis are the major source of IL-17A later on [15,114]. IL-17A production in kidney-resident γδ T-cells depends on IL-23 produced by kidney DCs [15], driving the further recruitment of neutrophils and macrophages, and promoting the development of MPO-specific $CD4^+$ T-cells [115]. This pro-inflammatory action of IL-17A producing murine γδ T-cells appears to be critical in the pathogenesis of crescentic glomerulonephritis and the injury of the kidney (**Figure 2B**). Whether similar mechanisms operate in human patients remains to be confirmed.

With regard to other unconventional T-cells, mouse models show that the lack or the reduction of iNKT cells accelerate the course of crescentic glomerulonephritis, and that the pathology can be rescued by adoptive transfer of iNKT cells [116]. iNKT cells have been associated with intraglomerular downregulation of TGF-β1 and IFN-γ expression, NF-κB

phosphorylation and complement deposit; and staining of iNKT cells shows their localisation to sites of glomerular damage. Experimental activation of iNKT cells using α-GalCer has a protective role through induction of IL-4 and IL-10 expression, resulting in less severe lesions [116]. Conversely, another model showed that TGF-β mRNA is decreased in iNKT deficient Jα18$^{-/-}$ mice compared to wild-type animals, and that neutralising TGF-β antibodies significantly enhance the severity of crescentic glomerulonephritis [117]. A direct immunosuppressive effect of murine iNKT cells is evident from their inhibition of mesangial cell proliferation in response to lipopolysaccharide. Those protective iNKT cells express CXCR6 and are attracted to sites of glomerular damage through CXCL16, which is produced by DCs at the early stage of crescentic glomerulonephritis [118].

Lupus nephritis

Systemic lupus erythematosus is a multisystemic disease characterised by genetic susceptibility and environmental factors, which promote the loss of immune tolerance and the development of an autoimmune response against nuclear antigens. The interplay between glomerular immune complex deposition and kidney-infiltrating immune cells ultimately leads to glomerulonephritis.

In patients with systemic lupus erythematosus, circulating γδ T-cell levels are reduced and inversely correlated with the disease activity, suggesting these cells migrate from blood to lymph nodes or tissues [119,120]. γδ T-cells may have at least three different roles during the pathophysiology of lupus nephritis (**Figure 2C**). In patients, central memory Vδ1^{+} γδ T-cell subset may modulate the activity on CD4^{+} T-cells [120]. In line with this observation, γδ T-cell deficient MRL/lpr mice exhibit exacerbated glomerulonephritis, suggesting that γδ T-cells may be involved in the regulation of systemic autoimmunity [121]. In addition, γδ T-cell lines derived from patients with lupus nephritis were shown to provide non-MHC-restricted help for the production of anti-DNA IgG by B-cells [122]. In a pristane-induced lupus mouse model, which

is achieved by intraperitoneal injection of the mineral oil pristane leading to lupus-like disease with immune complex glomerulonephritis, $CXCR5^+$ but not $CXCR5^-$ γδ T-cells possess APC-like properties and induce Tfh cell differentiation, enhancing production of auto-antibodies and promoting lupus nephritis [123]. As antigen-presenting γδ T-cells are well characterised in humans [75,80], similar mechanisms may operate in lupus patients. In the same mouse model of pristane-induced lupus nephritis, kidney γδ T-cells express IL-17F, which promotes glomerulonephritis by recruiting tissue-destructive neutrophils [124]. However, further studies are required to confirm these findings in humans.

Administration of α-GalCer induces a decrease in the proportion of iNKT cells and suppresses Th2 responses while slowing down lupus nephritis progression in mice [16]. Of note, opposite results are observed with a brief α-GalCer perfusion versus repeated injection [125]. The improvement in disease severity upon α-GalCer treatment is associated with reduced IL-10 production and delayed onset of murine lupus, whereas repeated treatment induces marked iNKT cell hyporesponsiveness and does not affect the disease outcome. Deletion of CD1d in lupus-susceptible BFWF1 mice exacerbates the severity of nephritis [126], implying a regulatory role of iNKT cells during the development of disease, opposite results of NKT cell activation by α-GalCer are observed in pristane-induced lupus-like autoimmunity in BALB/c and SJL mice [125], suggesting that iNKT cell activation can both suppress and promote the pathology, in a strain dependent manner.

Adriamycin-induced progressive glomerulosclerosis

Adriamycin-induced progressive glomerulosclerosis is a mouse model of chronic progressive glomerular disease, characterised by a rapid onset of glomerular podocyte damage, which progresses to segmental glomerular sclerosis and mirrors human primary focal segmental glomerulosclerosis. In this model, γδ T-cells significantly infiltrate the kidney interstitium,

express TGF-β, and correlate with levels of serum creatinine and the severity of glomerular sclerosis. They display invariant Vγ4/Vδ1 or Vγ6/Vδ1 TCRs, suggesting an antigen-driven stimulation [127,128]. However, the function of these cells is presently unclear. They were initially seen as innate cells regulating inflammation [128], but this finding has been challenged by others [129], and they may in fact contribute to fibrosis. Most importantly, these findings from adriamycin-induced disease in mouse models have yet to be translated to patients suffering from primary focal segmental glomerulosclerosis.

Heymann nephritis

Heymann nephritis is induced by injection of isolated proximal tubule brush border components into rats, leading to glomerular IgG deposition and mimicking membranous nephritis in patients. In this experimental model, there is an increase of interstitial γδ T-cells predominantly expressing an invariant Vγ6/Vδ1 TCR and the NK receptor NKG2D. These rat γδ T-cells have been found to express TGF-β, IL-4 and IL-5, yet their function is largely elusive [130]. Most importantly, these results have not been translated to patients with membranous nephropathy, in part because the autoantigenic target identified in this model (megalin) is not found in membranous nephritis immune deposits in humans.

KIDNEY FIBROSIS

Chronic kidney disease, including glomerulonephritis, often progresses toward tubulo-interstitial fibrosis, independently of the aetiology [131]. In a mouse model of unilateral ureteral obstruction, kidney γδ T-cells are an important source of IL-17A necessary for the recruitment of T-cells and macrophages and development of kidney fibrosis [132]. In humans, these findings are corroborated by the presence of elevated numbers of $V\delta1^+$ γδ T-cell expressing IL-17A in close

contact to proximal tubular epithelial cells at sites of interstitial fibrosis, suggesting that they participate in the disease progression [133]. The role of MAIT cells in experimental models of kidney disease is unknown because of their low prevalence in laboratory mouse strains, underlining the importance of investigating unconventional T-cells in clinical specimens from patients and healthy individuals. In this regard, tissue samples from human kidneys with tubulo-interstitial fibrosis show elevated numbers of MAIT cells with activated phenotype compared with healthy kidneys, and a positive correlation between MAIT numbers and glomerular filtration rate (GFR) reduction [134]. MAIT cell numbers also correlate with the histological degree of fibrosis, and those MAIT cells localise to the tubulo-interstitial compartment. In agreement with the fact that kidney hypoxia is an established driver of inflammation and fibrosis, human MAIT cells become readily activated under hypoxic conditions *in vitro* and induce necrosis in co-cultured proximal tubular epithelial cells [134]. Further research is needed to help define the physiological context leading to MAIT infiltration and activation to limit their detrimental effect contributing to kidney fibrosis.

KIDNEY REPLACEMENT THERAPIES

Kidney failure ultimately necessitates the commencement of kidney replacement therapy as life-saving treatment, with the options available comprising kidney transplantation, haemodialysis or peritoneal dialysis, depending on clinical circumstances, personal preference and the availability of donor organs. Of relevance for this review, unconventional T-cells have been implicated in all three kidney replacement therapy scenarios, particularly in the context of infection.

Haemodialysis

Haemodialysis (HD) is the most common form of dialysis, and describes the process of removing fluid and waste products from the blood and correcting electrolyte imbalances by means of an extracorporeal dialyser, with access via a central venous catheter or a fistula. Blood purification is performed by ultrafiltration and diffusion through a semipermeable dialysis membrane against a sterile fluid with normal ionic constitution [135]. The need to use permanent lines that are prone to exit site infections and biofilm colonisation, together with extracorporeal blood filtration and an enhanced risk of bloodstream infections by skin commensals and contaminants, make individuals receiving long-term HD a particularly vulnerable patient population [136].

Impaired cell-mediated immunity is common in uraemic patients and possibly contributes to their increased susceptibility and severity of microbial and viral infections, which remain major causes of morbidity and mortality in this population [137]. In addition to general anaemia, lymphopenia and T-cell anergy in HD patients [138,139], early studies found a depletion of γδ T-cells in the blood of adult and paediatric HD patients but not of individuals undergoing peritoneal dialysis, leading to speculations whether such a reduction in γδ T-cell levels may predispose HD patients further to infection [140,141]. Indeed, the functional response of γδ T-cells to stimulation with HMB-PP, fixed *E. coli* bacteria or pro-inflammatory cytokines appears to be compromised in HD patients, in particular those with latent tuberculosis [142]. Levels of iNKT and MAIT cells are similarly compromised in HD patients, indicating a general impairment of both unconventional and conventional T-cell populations [143,144]. While at least in the case of iNKT cells, this systemic loss appears to be a general phenomenon in all uraemic patients with kidney failure, even before the first dialysis session [145], there are conflicting data on whether kidney transplantation restores these depleted iNKT cell pools [143,145]. On a functional level, MAIT cells appear to be less affected in HD patients than their γδ T-cell counterparts in that their ability to respond to fixed *E. coli* is strongly impaired but not their response to cytokine stimulation, nor

are they impacted by the presence of latent tuberculosis [144]. Whether these differences between γδ T-cells and MAIT cells reflect different physiological sensitivities to stimulation and overlapping but different roles in microbial infections such as tuberculosis remains to be confirmed. It is also yet to be seen whether the loss of unconventional T-cells in the circulation of HD patients constitutes a systemic dysfunction as a result of uraemia, malnutrition and age, or rather a chemokine-guided recruitment of unconventional T-cells from the blood to sites of inflammation and infection such as the lung.

Peritoneal dialysis

Peritoneal dialysis (PD) represents an alternative to HD for patients with kidney failure and utilises the peritoneum, the natural lining of the abdomen, as semipermeable membrane through which waste products are removed from the blood by natural diffusion and osmosis. This involves the implantation of a permanent silicone tube, the Tenckhoff catheter, in the abdominal wall to allow infusion of the peritoneal cavity with fresh dialysis fluid and subsequent drainage of the waste effluent, in up to four cycles per day depending on the modality. PD may offer better quality of life and clinical benefits compared to HD, especially for paediatric patients and during the first years of kidney replacement therapy [146,147]. Yet, infection and inflammation-related fibrosis remain major causes of morbidity and ultimately, of treatment failure in PD patients. Early diagnosis of peritonitis and long-term preservation of the permeability of the peritoneal membrane are therefore amongst the foremost clinical priorities in this population [148].

While most studies in humans are restricted to blood, biopsies and surplus tissues after surgery, research into immune responses in PD patients is facilitated by the fact that the Tenckhoff catheter serves as a continuous window into local inflammatory events in real time and allows for convenient, non-invasive and repeated sampling directly from the peritoneal cavity [149,150]. The cellular compartment in the peritoneal effluent of stable PD patients is predominantly

comprised of monocytes/macrophages, T-cells and detached mesothelial cells, with other cells like DCs and eosinophils representing minor fractions [151,152]. γδ T-cells were identified in PD effluent 25 years ago as a small population within the peritoneal T-cell compartment [153] but their relevance for PD-related peritonitis was only addressed more recently [154,155]. Tissue-resident γδ T-cells have also been found within the submesothelial zone of the peritoneal membrane where they may express pro-inflammatory cytokines such as IL-17A and contribute to fibrosis and ultimately, ultrafiltration failure [156].

PD-related peritonitis

Acute peritonitis sees a marked influx of large numbers of immune cells into the peritoneal cavity, leading to the presentation with a 'cloudy bag' [148]. While this inflammatory infiltrate is dominated by neutrophils that can constitute >95% of all cells, other immune cells including T-cells increase in numbers as well even though their relative proportion is eclipsed by neutrophils [150,151]. Within this peritoneal T-cell population, Vγ9/Vδ2 T-cells are readily detectable in cloudy PD effluent and appear to be enriched locally when compared to levels in blood, and are increased during acute peritonitis when compared to levels in the PD effluent of stable, non-inflamed individuals [150]. This local accumulation is particularly apparent in infections caused by HMB-PP producing but not HMB-PP deficient organisms, suggesting an antigen-specific recruitment and/or expansion of Vγ9/Vδ2 T-cells at the site of infection [150]. The response of peritoneal Vγ9/Vδ2 T-cells may actually be distinct enough to allow an early discrimination between infections by HMB-PP positive (largely Gram-negative bacteria and coryneform Gram-positive species) and HMB-PP negative bacteria (mostly staphylococci, streptococci and enterococci) [154,157,158]. Given that infections by HMB-PP positive organisms are associated with higher hospital admission and technique failure rates and generally poorer clinical outcomes,

this correlation may have diagnostic and prognostic relevance and guide early patient management (**Table 3**) [150,155].

MAIT cells also appear to be enriched in the inflamed peritoneal cavity of PD patients compared to blood [150], similar to the situation in patients with decompensated liver cirrhosis [159,160]; their increased proportion within the peritoneal T-cell pool during episodes of acute PD-related peritonitis may be suggestive of local responses to microbes possessing the vitamin B2 biosynthesis pathway [150]. In contrast to these advances in our understanding of peritoneal γδ T-cell and MAIT cells responses, iNKT cells have not been studied in peritoneal effluent so far, only in the blood of PD patients [145]. Whether unconventional T-cells simply constitute potentially useful biomarkers or actually contribute to the immunopathology and to clinical outcomes remains to be shown. It is interesting to note that in cell culture Vγ9/Vδ2 T-cells and MAIT cells are both capable of orchestrating early inflammatory responses in a ligand dependent manner [49,155] and inducing release of inflammatory chemokines and cytokines as well as epithelial–mesenchymal transition of mesothelial cells [150], thereby potentially amplifying disease severity and contributing to peritoneal fibrosis (**Figure 3**). However, with suggestions that mesothelium-derived inhibitory factors like TGF-β may also dampen T-cell responses in the steady state [161], the crosstalk of unconventional T-cells with the local tissue before, during and after episodes of peritonitis clearly needs closer attention [150,156].

Kidney transplantation

Kidney transplantation is the treatment of choice for patients with kidney failure, because it associated with a better patient survival, a better quality of life and a lower cost [162]. However, this kidney replacement therapy requires the use of long-term potent immunosuppressive treatments, which ultimately lead to the emergence of opportunistic infections and cancers.

Moreover, in a significant proportion of patients, antibody-mediated rejection cannot be prevented by immunosuppressants and remains the leading cause of graft loss [163].

CMV infection

CMV infection is a common and severe complication affecting kidney transplant recipients [164], and is associated with rejection [165] and poor graft and overall survival [166,167]. Current anti-CMV therapies with ganciclovir or valganciclovir are unable to systematically prevent CMV infection in these patients, with CMV-seronegative recipients receiving an organ from a seropositive donor (D^+R^-) having the highest risk of developing disease [168,169]. A robust and persistent CMV-specific T-cell immune response is seen as essential to control the virus lifelong, but this response is suppressed in kidney transplant recipients [170]. In fact, there is now compelling evidence that γδ T-cells expand following CMV infection in kidney transplant recipients, possess a TCR repertoire and a phenotype compatible with an antigen-driven expansion, and are able to control CMV infection [92,171]. A role for other unconventional T-cells like MAIT cells and iNKT cells in CMV-infected individuals has yet to be demonstrated.

CMV-reactive γδ T-cells

Expansion of non-Vγ9/Vδ2 γδ T-cells upon CMV infection was first observed in the blood of kidney transplant recipients [58,59], and was later confirmed in other immunocompromised patients [92,166,172,173], newborns [60] and healthy adults [174], demonstrating that their involvement during CMV infection is universal and not specific of a certain pathology. Among non-Vγ9/Vδ2 γδ T-cells in the blood, a sizable population of $Vγ9^-$ $Vδ2^+$ γδ T cells is reactive against CMV, similarly to the earlier described CMV-reactive $Vδ2^{neg}$ γδ T cells [88,175]. This $Vγ9^-$ $Vδ2^+$ γδ T-cells subset is specifically expanded during severe CMV infection [175]. The CMV-induced expansion of non-Vγ9/Vδ2 γδ T-cells correlates with viral clearance and occurs at

an average of 50 days after CMV infection [176,177], following a kinetic similar to that of CMV-specific $CD8^+$ T-cells [171]. Importantly, no other viruses such as herpes simplex virus, varicella zoster virus, Epstein-Barr virus, or influenza virus could be associated with this non-Vγ9/Vδ2 γδ T-cell response [58,178]. While a large majority of non-Vγ9/Vδ2 γδ T-cells have a naïve resting phenotype in seronegative patients, there is an increase after CMV infection in the proportion of activated and terminally differentiated effector memory cells that often express cytotoxic molecules, NK receptors and CD16 [60,175,171,179]. The long-lasting nature of the CMV driven expansion of non-Vγ9/Vδ2 γδ T-cells supports an adaptive and antigen-specific response (**Figure 4A**) [88,92]. However, with only few ligands for non-Vγ9/Vδ2 γδ T-cells identified so far, the underlying molecular mechanism remains obscure. As the number of circulating non-Vγ9/Vδ2 γδ T-cells recognising molecules such as EPCR and annexin A2 appears to be insignificant *in vivo* [61,62], other as yet unknown ligands are likely to be involved.

Non-Vγ9/Vδ2 γδ T-cell lines or clones are able to inhibit CMV spread *in vitro* and kill CMV-infected cells [179,180]. In accordance, mouse γδ T-cells can protect from murine CMV infection [181,182] and kidney transplant recipients from CMV recurrence [176] (**Figure 4B**). Non-Vγ9/Vδ2 γδ T-cells from CMV-seropositive donors also inhibit viral spread through antibody-dependent cell-mediated inhibition via CD16 (**Figure 4C**) [179]. In addition to the direct recognition of CMV-infected cells, non-Vγ9/Vδ2 γδ T-cell effector functions are modulated by the microenvironment. During the course of CMV infection, myeloid cells like monocytes, macrophages and DCs produce pro-inflammatory cytokines like type I IFNs and IL-12 [183], which in turn enhance the CD16-induced IFN-γ production by non-Vγ9/Vδ2 γδ T-cells and the subsequent control of CMV replication *in vitro* [179]. Likewise, IL-18 secreted by CMV-infected endothelial cells can potentiate the IFN-γ production induced by TCR stimulation [184, suggesting that non-Vγ9/Vδ2 γδ T-cell activation is under the control of the cytokine milieu induced by CMV infection. Finally, CMV-induced non-Vγ9/Vδ2 γδ T-cells may also help initiate

protective immunity by inducing the maturation of DCs [172]. These findings support the view that non-Vγ9/Vδ2 γδ T-cells complement the role of CMV-specific $CD8^+$ T-cells and contribute to a life-long control of the virus.

Transplant rejection

After organ transplantation, there are two pathways of allorecognition that are closely associated with two types of **T-cell mediated rejection** of the graft – a direct one where recipient T-cells recognise mismatched donor HLA molecules on donor APCs, leading to graft infiltration by recipient cytotoxic $CD8^+$ T-cells; and an indirect pathway where recipient $CD4^+$ T-cells recognise peptides from donor HLA molecules presented by recipient APCs [185]. In addition to T-cells, recipient B-cells can recognise donor HLA antigens through their B-cell receptors, internalise and present the alloantigen to cognate Tfh cells, which then help mature recipient B-cells mature into donor-specific antibody (DSA)-producing plasma cells [186]. This allorecognition leads to **antibody-mediated rejection** of transplants, characterised by DSA-mediated lesions which encompass direct DSA-mediated apoptosis [187], complement-binding cell lysis [188,189], and ADCC [190,191].

Unconventional T-cells are usually viewed as non-alloreactive because they are not MHC-restricted. In support of this concept, γδ T-cells are unable to induce graft versus host disease in lethally irradiated mice grafted with MHC-incompatible donor marrow [192]. However, RNA sequencing analyses identified four long noncoding RNAs as potential biomarkers of human allograft rejection and correlated their expression with the presence of γδ T-cells [193], suggesting that human γδ T-cells are in fact involved during rejection, despite their apparent inability to recognise donor MHC molecules. A direct role for γδ T-cells during T-cell mediated rejection has so far only been demonstrated in mouse models and has mainly been attributed to their production of IL-17A, which accelerates rejection by inhibiting Treg cell expansion [194]. IL-

17A producing γδ T-cells may also promote the accumulation of mature DCs in draining lymph nodes to subsequently regulate αβ T-cell function [195], and favour cross-priming of $CD8^+$ T-cells [196] (**Figure 5A**). Whether these findings apply to human transplant recipients during T-cell mediated rejection is unknown at present.

During antibody-mediated rejection, microvascular inflammation (glomerulitis and peritubular capillaritis) – defined by an accumulation of polymorphonuclear cells, macrophages, and lymphocytes around capillaries – is now recognised as the main factor of antibody-mediated rejection [197]. Amongst this inflammatory infiltrate, NK cells are found in lesions of the kidney microcirculation, suggestive of ADCC through DSA interaction with CD16 [190]. Of note, CMV infection reshapes the $CD16^+$ lymphocyte compartment composition in CMV seropositive kidney transplant recipients who exhibit an equal number of $CD16^+$ NK cells and $CD16^+$ γδ T-cells [179]. In cell culture, CMV-induced $CD16^+$ γδ T-cells readily perform ADCC against endothelial cells coated with DSA. In the grafts, γδ T-cells are present within the microvascular inflammation in CMV-experienced patients and correlate with poor graft outcome in recipients with DSA, supporting the notion that CMV-induced $CD16^+$ γδ T-cells contribute to DSA-mediated transplant rejection [198] (**Figure 5B**).

Transplant tolerance

Emerging evidence suggests that unconventional T-cells may also contribute to graft survival. While human $V\delta1^+$ γδ T-cells were originally postulated to mediate operational tolerance in liver transplantation [199,200], these alterations in the γδ T-cell compartment are in fact associated with CMV infection and not restricted to tolerant liver recipients [201]. iNKT cells have been implicated in allograft tolerance, in synergy with Treg cells. For instance, in a mouse model of bone marrow transplantation, recipient iNKT cells induce donor Treg expansion and enhance their potential to secrete IL-10 [202,203], while at the same time suppressing IFN-γ production

by donor $CD4^+$ T-cells [203]. Such mechanisms are likely to contribute to the prevention of graft versus host reactions. In addition to modulating T-cell responses, recipient iNKT cells also favour tolerogenic DCs, as shown in mice after a combined transplantation of heart and bone marrow [203,204]. However, the involvement of iNKT cells in tolerance induction after solid organ transplantation alone, and in particular kidney transplantation, remains to be investigated.

Post-transplant malignancies

The risk of cancer in kidney transplant recipients is much greater than in the general population. The most common type of malignancy in this patient group is non-melanoma skin cancer, followed by lymphoma and kidney cancers [205,206], with immunosuppressants having direct effects on tumour growth, activating oncogenic viruses and suppressing cancer immunosurveillance. Among the cells involved in anti-tumour immunity, γδ T-cells play a key role [14]. In humans, γδ T-cells infiltrate many carcinomas and have a strong reactivity against tumour cells, leading to promising attempts to exploit this potential in immunotherapy trials [44,207]. However, other studies also reported pro-tumoral functions of γδ T-cells suggesting that different subsets of γδ T-cells exert opposite functions in tumour surveillance [14], and high levels of circulating BTN2A1 may be an indicator of Vγ9/Vδ2 T-cell exhaustion and facilitate tumour immune escape in renal cell carcinoma patients [208]. Surprisingly, immunity to tumours can be acquired during previous infections [209]. In line with this observation, CMV-induced γδ T-cells have a TCR-dependent cross-reactivity against CMV-infected cells and tumour cells [172,180] and can inhibit tumour growth in mouse models [210]. In kidney transplant recipients, CMV-induced γδ T-cell counts are correlated with reduced cancer occurrence [211]. This shared reactivity against CMV-infected and tumour cells has also been observed after allogeneic stem cell transplantation [172], where CMV infection and γδ T-cell expansion are associated with a decreased risk of acute myeloid leukaemia relapse [212,213]. The potential protective role of

CMV against cancer in transplant recipients might be due to the fact that CMV-infected cells and tumour cells share stress-induced molecules recognised by γδ TCRs [33,62], resulting in the selection of common effector cells amongst which γδ T-cells take an important part.

OUTLOOK

We here attempted to summarise research from over the past years that has highlighted crucial contributions of unconventional T-cell to the immunopathology of kidney disease, and the progress being made in translating this knowledge towards clinical interventions and novel tests. Yet, a number of key unresolved questions remain in the field. Most pertinently, there is a need to discover further ligands for unconventional T-cells, certainly so for the majority of non-Vγ9/Vδ2 γδ T-cells but also for many CD1-restricted αβ T-cells, and to better define the underlying molecular and cellular mechanisms of antigen presentation and recognition. However, a deeper understanding of unconventional T-cells and the physiological context of their responses can only come with access to appropriate experimental models and patient cohorts, analyses of relevant tissues and corresponding clinical data, and the availability of molecular tools and state-of-the-art technological platforms. This is particularly valid for the translation of preliminary findings in mouse models to patients with IgA, crescentic and lupus nephritis.

Infection diagnosis

Monitoring microbe-responsive Vγ9/Vδ2 T-cells in individuals presenting with PD-related peritonitis or CMV-reactive non-Vγ9/Vδ2 γδ T-cells after transplantation are promising examples that may have direct clinical use with respect to diagnosis, prognosis and risk stratification of kidney patients (**Table 3**). In particular, early prediction of the presence of HMB-PP producing bacteria (or ruling them out) in PD patients presenting with symptoms of acute peritonitis might

help guide patient management, advance antibiotic stewardship and improve clinical outcomes [17]. MAIT cells may have additional diagnostic value when combined with an assessment of peritoneal Vγ9/Vδ2 T-cells [150]. Monitoring non-Vγ9/Vδ2 γδ T-cells in CMV-infected kidney transplant recipients is likely to help personalise the duration of CMV treatment [92,175,176]. Individuals displaying expansion of non-Vγ9/Vδ2 γδ T-cell as indication of rapid CMV clearance may benefit from early cessation of anti-CMV therapy to limit treatment-related adverse events; in patients with no such expansion, CMV treatment would be continued to avoid recurrence (**Figure 4D**). This strategy is currently being trialled at the University Hospital in Bordeaux, France [214].

Drug development

Abrogation of Vγ9/Vδ2 T-cell responses can be achieved experimentally using inhibitory antibodies against BTN2 or BTN3 [39,42], and MAIT cell responses can be blocked using antibodies against MR1 [215], opening up possibilities in the clinic to specifically suppress overshooting unconventional T-cell responses and limit inflammation-induced tissue damage in particularly vulnerable individuals [155]. The responsiveness of Vγ9/Vδ2 T-cells toward HMB-PP producing bacteria also allows for the treatment of bacterial infections using new 'immuno-antibiotics' targeting the non-mevalonate pathway in those organisms and thereby indirectly affecting γδ T-cell responses [216] – inhibitors upstream of HMB-PP abrogate the production of this immunogenic metabolite and as a result silence anti-microbial γδ T-cell responses [155], while downstream inhibition leads to HMB-PP accumulation and thus a more pronounced γδ T-cell activation [217]. A similar targeting of the microbial riboflavin biosynthesis may result in a corresponding manipulation of anti-microbial MAIT cell responses [216].

Novel immunotherapies

Targeted manipulation of unconventional T-cells in the clinic is less advanced for kidney patients. Administration of the HMB-PP analogue Phosphostim as well as of free α-GalCer or α-GalCer pulsed DCs to stimulate Vγ9/Vδ2 T-cells and iNKT cells, respectively, has been tested successfully in cancer patients and is considered safe [13,14,44]; other formulations such as agonistic BTN3 antibodies that directly activate Vγ9/Vδ2 T-cells are in preclinical development [218]. The potential of aminobisphosphonates like zoledronate to trigger a Vγ9/Vδ2 T-cell mediated cytotoxic response has been exploited in cancer trials [13,14,44] but may also be relevant to boost the immune system in immunocompromised patients [219]. Equally, adoptively transferred γδ T-cells and iNKT cells have good safety profiles and show promising efficacies in a range of malignancies incuding renal cell carcinoma [44,207]. However, whether and how these findings translate to a nephrological context remains to be seen. In this respect, adoptive transfer of CMV-reactive T-cells represents an attractive approach for treating refractory or resistant CMV infections in kidney transplant recipients. A recent phase I clinical trial using autologous αβ T-cell adoptive therapy in solid-organ transplant recipients showed promising results [220]. As large-scale expansion of $V\delta1^+$ γδ T-cells using clinical-grade reagents has become feasible [221], a potential immunotherapy for kidney transplant recipients using unconventional T-cells is within reach (**Figure 4D**).

There is still much to be learned about unconventional T-cells and how to apply such knowledge in the clinic, especially with regard to glomerulonephritis, kidney fibrosis and acute kidney injury. In addition, with most research so far focusing on γδ T-cells, MAIT cells and iNKT cells, the role of other unconventional T-cell populations, in particular those restricted by CD1a, CD1b and CD1c, in the pathogenesis, treatment and diagnosis of nephrological conditions deserves more attention. Undoubtedly, the unique place of unconventional T-cells in the immune

system makes them highly suitable for the development of bespoke diagnostic and therapeutic solutions that will be of benefit for patients with acute and chronic kidney disease, and beyond.

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AUTHOR CONTRIBUTIONS

All authors contributed to researching data for the article, made a substantial contribution to discussion of content, wrote and reviewed/edited the manuscript before submission.

COMPETING INTERESTS

The authors declare no competing interests.

KEY POINTS

- Unconventional T-cells like γδ, MAIT and iNKT cells are distinct from classical $CD4^+$ and $CD8^+$ T-cells and contribute to sensing stress, infection and malignancy.
- Depending on the physiological context, unconventional T-cells may assume either protective or pathogenic roles in a range of inflammatory and autoimmune conditions related to acute and chronic kidney disease.
- Vγ9/Vδ2 T-cells and MAIT cells respond to metabolites shared by a wide range of microbial pathogens, which may have implications for early diagnosis, risk stratification and targeted treatment of peritoneal dialysis-related peritonitis.
- Non-Vγ9/Vδ2 γδ T-cells expand during CMV infection in kidney transplant recipients and contribute to viral clearance, suggesting that they can be harnessed for immune monitoring, and for adoptive immunotherapy in refractory CMV infections.
- IgA nephropathy is accompanied by oligoclonal expansion of γδ T-cells in blood and kidneys, which may contribute to immunopathology and correlates with disease progression.
- In murine models of glomerulonephritis, kidney γδ T-cells are an important source of IL-17A necessary for the recruitment of macrophages, neutrophils and T-cells, and for the development of kidney fibrosis.
- Murine type I and type II NKT cells have opposite roles during ischaemia-reperfusion injury and may be relevant for allograft tolerance and kidney protection during lupus or crescentic glomerulonephritis.

GLOSSARY

Adaptive immunity. Antigen-specific clonal expansion of individual T and B-cells carrying the right specificity and mounting targeted cellular and/or antibody responses against non-self (*e.g.* microbes, viruses, allergens) or self antigens (autoimmunity, tumours), with a hallmark being the establishment of immunological memory that makes future responses to the same antigen quicker and more efficient.

Antibody-dependent cellular cytotoxicity (ADCC). Immune mechanism through which effector cells carrying receptors for the fragment crystallisable (Fc) region of antibodies can recognise and lyse antibody-coated ('opsonised') target cells, typically exerted by NK cells via CD16 (IgG receptor FcγRIII) but also by macrophages, neutrophils or eosinophils via specific Fc receptors for IgG, IgA or IgE.

Anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis. Severe autoimmune disease that mainly affects small vessels in various organs (incl. the kidney in up to 80% of patients), accompanied by ANCA antibodies in serum and marked by excessive neutrophil activation and release of pro-inflammatory cytokines, reactive oxygen species and lytic enzymes.

Antibody-mediated rejection. Allograft rejection as a result of the recognition of mismatched donor MHC molecules by recipient B-cells, with no effective treatment available to halt donor-specific antibody (DSA)-mediated rejection, and hence poor prognosis.

Antigen presentation. Cellular process by which antigenic epitopes are displayed on the cell surface to neighbouring T-cells, typically as short peptides in the context of MHC class I and class II molecules in the case of classical $CD8^+$ and $CD4^+$ T-cells, respectively, or as non-peptide antigens in association with MHC-related molecules such as CD1 or MR1 in the case of unconventional T-cells.

Cytomegalovirus (CMV) infection. Almost asymptomatic in immunocompetent individuals but responsible for significant morbidity and mortality in immunocompromised patients; despite prevention strategies based on antiviral treatment, CMV seronegative recipients receiving an organ from seropositive donors have the highest risk of developing CMV disease (20%).

Immunoglobulin A (IgA) nephropathy. Most prevalent form of glomerulonephritis in the world and a common cause of end-stage kidney disease; appears to be a systemic disease where the kidneys are the targets of galactose-deficient IgA1, which stimulates mesangial cells to proliferate; secrete proinflammatory and profibrotic cytokines, components of the extracellular matrix and growth factors; activate the complement pathways; and release reactive oxygen species.

Innate immunity. Non-specific defence mechanism within hours of encountering non-self structures (*e.g.* pathogen, foreign object) or a danger signals (*e.g.* tissue injury, stress), mediated by innate immune cells such as natural killer cells, mast cells, granulocytes (eosinophils, basophils, neutrophils), monocytes, macrophages and DCs.

Ischaemia–reperfusion injury (IRI). Tissue damage after a period of oxygen deprivation (ischaemia) due to sepsis, thrombosis, organ transplantation and trauma, resulting in inflammation, oxidative stress and necrosis upon restoration of the normal blood supply.

Lupus nephritis. Result of immune complex formation and inflammation of the kidney glomeruli in up to 30% of patients with systemic lupus erythematosus, an autoimmune disease characterised by the presence of anti-nuclear autoantibodies.

Memory T-cells. Long-lived antigen-specific T-cells that remain in the body after the initial response has resolved, for instance upon clearing an infection, and that confer protection against the same stimulus, with effector memory T-cells and tissue-resident memory T-cells mounting

rapid recall responses at local sites, and central memory T-cells patrolling secondary lymphoid tissues.

T cell-mediated rejection. Recognition of mismatched donor antigenic determinants, which are mainly represented by the highly polymorphic molecules of the MHC complex, resulting in the priming of effector T-cells against these alloantigens, and ultimately in allograft rejection.

T cell receptor (TCR) repertoire. Summary of unique genetic rearrangements of the TCR in each T-cell within an anatomical or functional compartment, which for classical $CD4^+$ and $CD8^+$ T-cells are typically polyclonal and 'private', while unconventional T-cells are often oligoclonal and may carry invariant or semi-invariant, 'public' TCR sequences shared between people.

Table 1. Overview of unconventional human T-cell subsets. Further populations of αβ and γδ T-cells restricted by MR1, CD1a, CD1b, CD1c or CD1d have been identified using antigen-loaded or empty tetramers and/or in functional experiments [3,9,10,32,33,34,225,226,227,228].

Population	Surface markers and TCR usage	Restricting element	Description	Ref.
Phosphoantigen-reactive γδ T-cells	Vγ9^{+} Vδ2^{+} (TRGV9–TRGJP^{+} TRDV2^{+})	BTN2A1, BTN3A1	Respond to IPP and microbial HMB-PP; predominant γδ T-cell population in human blood (~1-5 % of all T-cells)	41,42
Cytomegalovirus-reactive γδ T-cells	Vγ9^{-} Vδ2^{+} (TRDV2^{+})	?	Expand in the blood of patients during acute CMV disease and respond to CMV-infected cells *in vitro*	175
	Vδ2^{neg} (largely TRDV1^{+} but also TRDV3^{+} or TRDV5^{+})	?	Expand in the blood of patients during acute CMV disease and respond to CMV-infected cells *in vitro*	58, 60, 92
Intestinal γδ T-cells	Vγ4^{+} Vδ1^{+} (TRGV4^{+} TRGD1^{+})	BTNL3, BTNL8	Recognise the butyrophilin-like molecules BTNL3/BTNL8, specifically found in the human intestine	65, 66
Mucosal-associated invariant T (MAIT) cells	Vα7.2^{+} CD161^{+} (TRAV1-2–TRAJ33^{+}, TRAJ12^{+} or TRAJ20^{+})	MR1	Recognise microbial vitamin B2 derivatives (~1-10 % of all T-cells in blood; enriched in gut mucosa and liver)	36
MAIT-like cells	Vα7.2^{-} CD161^{+} (TRAV36–TRAJ34^{+} TRBV28–TRBJ2-5^{+})	MR1	5-OP-RU specific T-cell population carrying a public TCR	46
Invariant natural killer T (iNKT) cells	Vα24–Jα18^{+} CD56^{+} (TRAV10–TRAJ18^{+} TRBV25-1^{+})	CD1d	Recognise exogenous α-GalCer and endogenous α-glycosylceramides	222, 223
Type II NKT cells	With heterogeneous TCRs	CD1d	Recognise self and non-self glycolipids, sulfolipids and phospholipids but not α-GalCer	57
Germline-encoded mycolyl lipid-reactive (GEM) T-cells	Vα7.2^{+} (TRAV1-2–TRAJ9^{+} TRBV6-2^{+} or TRBV30^{+})	CD1b	Recognise microbial glycolipids like glucose monomycolate and free mycolic acid	224

Table 2. Experimental models. Overview of studies studying unconventional T-cells in animal models of human kidney disease. All models listed are established in laboratory mice, with the exception of Heymann nephritis, a rat model.

Human disease mirrored by the model	Experimental model	Description	Main findings	Ref.
Crescentic glomerulonephritis	Accelerated nephrotoxic nephritis	Induced by *i.v.* injection of rabbit anti-mouse glomerular basement membrane antibodies	γδ T-cells recruit other T-cells and macrophages to the kidney interstitium	113
	Nephrotoxic nephritis	Induced by *i.p.* injection of nephrotoxic sheep serum	Resident Vγ4$^+$ γδ T-cells are major source of IL-17A and recruit neutrophils to the kidneys	15
			iNKT cells protect tissues via IL-4 and IL-10 production	116
ANCA vasculitis	Autoimmune MPO-ANCA glomerulonephritis	Immunisation with murine MPO in Freund's complete adjuvant (*i.p.*), followed by sheep anti-mouse glomerular basement membrane globulin	IL-17A produced by γδ T-cells promotes development of MPO-specific CD4$^+$ T-cells	115
Lupus nephritis	MLR/lpr mice	Mouse strain that carryies a null allele for Fas that develops lupus-like autoimmunity	γδ T-cell deficient MLR/lpr mice exhibit exacerbated glomerulonephritis	121
	Pristane-induced lupus	Development of lupus-like disease after single *i.p.* injection of pristane	γδ T-cells have APC-like properties and induce Tfh cell differentiation	123
			Kidney γδ T-cells promote glomerulonephritis via IL-17F expression and neutrophil recruitment	124
			NKT cells improve proteinuria via IL-4 production	126
Primary focal segmental glomerulosclerosis	Adriamycin-induced progressive glomerulosclerosis	Induced by *i.v.* injection of adriamycin	γδ T-cell kidney infiltration correlates with serum creatinine and glomerular sclerosis	127
Membranous nephritis	Heymann nephritis (rat)	Nephritis achieved by *s.c.* injection of isolated proximal tubule brush border components	Increase of interstitial γδ T-cells expressing invariant Vγ6/Vδ1 TCRs	130
Lesion after ischaemia-reperfusion	Ischaemia-reperfusion injury	Clamping of kidney pedicles for 30 minutes	Adenosine receptor-mediated inhibition of pro-inflammatory iNKT cells; type II NKT cells associated with decrease in inflammatory cytokines	100, 102

Table 3. Clinical applications. Overview of studies highlighting correlations of unconventional T-cell responses with clinical scenarios or outcomes, and implications for diagnosis, prognosis and therapy of different conditions.

Clinical context	Cell type	Observation	Potential clinical application	Ref.
Acute peritonitis in individuals receiving PD	Vγ9/Vδ2	Local increase/activation in infections by HMB-PP positive bacteria	Diagnosis of infection, prediction of the type of causative organism, prognosis of clinical outcomes	150, 157, 158
	MAIT	Local increase/activation in infections by riboflavin producing bacteria	Diagnosis of infection, prediction of the type of causative organism, prognosis of clinical outcomes	150
CMV infection after kidney transplantation	$V\delta2^{neg}$	Systemic increase during CMV infection	Monitoring for preventive and curative therapy; Immunotherapy	92, 176
	$V\gamma9^{-}/V\delta2^{+}$	Systemic increase during CMV infection	Monitoring for preventive and curative therapy; Immunotherapy	175
IgA nephropathy	$V\gamma9^{+}$ and/or $V\delta1^{+}$	Oligoclonal expansion in blood and kidneys; kidney-infiltrating γδ T-cells associated with progressive disease	Potential for diagnosis and/or monitoring of disease progression but more research is needed	107, 22, 108
Acute tubular necrosis	Type II NKT	Number of NKT cells correlates negatively with acute tubular necrosis severity	Potential for diagnosis and/or monitoring of disease progression but more research is needed	102
Kidney fibrosis	MAIT	MAIT cell numbers in kidney biopsies correlate with the degree of fibrosis and with GFR reduction	Potential for diagnosis and/or monitoring of disease progression but more research is needed	134

FIGURES LEGENDS

Figure 1. Recognition of unconventional ligands by unconventional human T-cells. Overview of self and non-self ligands recognised by human γδ T-cells, mucosal-associated invariant T (MAIT) cells, natural killer (NKT) cells and other CD1-restricted T-cells, compared to conventional $CD4^+$ T helper cells (Th) and $CD8^+$ cytotoxic T-cells (CTL) that recognise short antigenic peptides presented in the context of major histocompatibility complex (MHC) class II (HLA-DP, HLA-DQ, HLA-DR in humans) and MHC class I molecules (HLA-A, HLA-B, HLA-C in humans), respectively. The CD1 family of MHC class I-related proteins comprises CD1a, CD1b, CD1c and CD1d in humans, and is specialised in presenting lipid-based antigens; the role of a fifth member, CD1e, is unclear at present. The MHC-related molecule 1 (MR1) presents riboflavin (vitamin B2) metabolites and other non-peptide molecules to human (and murine) MAIT cells. Butyrophilin (BTN) and butyrophilin-like (BTNL) proteins regulate specific γδ T-cell subsets, indirectly or by direct binding to the γδ TCR.

Unconventional T-cell populations marked by restricted TCR usage are highlighted in orange colour; TCR chains that are invariant or semi-invariant are shown in blue. The β2 microglobulin (β_2m) subunit of MHC I, MR1 and CD1 molecules is highlighted in grey.

Further abbreviations: CMV, cytomegalovirus; EPCR, endothelial protein C receptor; EphA2, ephrin receptor A2; α-GalCer, α-galactosylceramide; GEM, germline-encoded mycolyl lipid-reactive; GMM, glucose-6-*O*-monomycolate; HMB-PP, (*E*)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate; IPP, isopentenyl pyrophosphate; 5-OP-RU, 5-(2-oxopropylideneamino)-6-D-ribitylaminouracil; PAg, phosphoantigen; sulfatide, 3-*O*-sulfogalactosylceramide.

Figure 2. Involvement of unconventional T-cells during glomerulonephritis. ***A.*** IgA nephropathy. ***Left:*** Peripheral blood $V\gamma9^+$ γδ T-cells express CD40L and produce TGF-β. Upon oligoclonal expansion in response to specific ligands, they enhance IgA class switching in B-cells and thereby drive IgA production in patients [107]. ***Right:*** The presence of kidney-infiltrating $V\delta1^+$ γδ T-cells is associated with progressive IgA nephropathy in patients. These cells display an oligoclonal TCR repertoire, suggesting an antigen-driven expansion [22].

B. ANCA/crescentic glomerulonephritis. In mice, kidney-infiltrating γδ T-cells producing IL-17A play an early non-redundant role in the recruitment of macrophages, neutrophils and αβ T-cells. Their involvement may be deleterious and contribute to the formation of crescents [15]. Activation of γδ T-cells in this model is dependent on IL-23 secreted by kidney DCs. In contrast, infiltration by NKT cells is associated with a downregulation of IFN-γ production and suppression of mesangial cell proliferation induced by LPS *in vitro*.

C. Lupus nephritis. ***From left to right***: $CD45RA^-$ $CD27^+$ $V\delta1^+$ γδ T-cells expressing Foxp3 are decreased in the blood of patients with active systemic lupus erythematosus, and have a potent anti-proliferative effect on autologous $CD4^+$ T-cells *in vitro*, via cell-to-cell contact and TGF-β-mediated inhibition [120]. In mice, $CXCR5^+$ γδ T-cells present antigens to naïve $CD4^+$ T-cells and initiate their differentiation into Tfh cells; newly generated Tfh cells activate cognate B-cells via CD40L and IL-21, resulting in the generation of high-affinity autoantibody-secreting plasma cells [123]. In pristane-induced models, γδ T-cell derived IL-17F induces the recruitment of neutrophils via CXCL1 and CXCL5, leading to tissue injury and the development of experimental glomerulonephritis [124], while α-GalCer activated NKT cells are able to improve proteinuria in an IL-4 dependent manner.

Figure 3. Unconventional T-cells in peritoneal dialysis patients. Schematic overview of γδ and MAIT cell responses to organisms producing HMB-PP and vitamin B2 metabolites during

acute peritonitis, and how such responses correlate with the severity of the peritoneal inflammation and short and long-term technique survival. γδ and MAIT cell derived cytokines and chemokines help recruit further immune cells to the site of infection and activate polymorphonuclear neutrophils (PMN), macrophages and the surrounding tissue [49,150, 154,155]. Mesothelial cells secrete inflammatory mediators amplifying the local response and at the same time undergo epithelial–mesenchymal transition (EMT), as first step in the development of peritoneal fibrosis.

Figure 4. Unconventional T-cells during CMV infection in kidney transplant recipients. ***A.*** ***Left:*** In mice, expansion of γδ T-cells occurs rapidly in liver and spleen after a CMV challenge (10-15 days), suggesting they act as early first-line defence and contribute to lymphoid stress tissue surveillance [181]. ***Right:*** In human blood, CMV-induced expansion of γδ T-cells occurs at an average of 50 days after CMV infection, following a kinetic similar to CMV-specific $CD8^+$ T-cells, suggesting they respond more in an adaptive manner [59,171].

B. Left: Anti-CMV functions of γδ T-cells. Non-Vγ9/Vδ2 γδ T-cells inhibit viral spread *in vitro* via IFN-γ, and kill CMV-infected cells through granzyme B and antibody-mediated cellular cytotoxicity [179,180]. ***Middle:*** αβ T-cell deficient mouse models show a protective role of γδ T-cells against murine CMV infection [181]. ***Right:*** In human kidney transplant recipients, early expansion of non-Vγ9/Vδ2 γδ T-cells correlates with rapid viral clearance and absence of CMV recurrence [176].

C. CMV sensing by γδ T-cells. Only two non-Vγ9/Vδ2 γδ TCRs ligands so far have been implicated in the recognition of CMV-infected cells: EPCR via a multimolecular stress signal involving ICAM-1/LFA-1, and annexin A2 which is considered a stress antigen upregulated upon

CMV infection [61,62]. Finally, CMV-induced non-Vγ9/Vδ2 γδ T-cells express CD16 (FcRγIIIa), which binds IgG-opsonised CMV virions.

D. Potential clinical application for diagnosis and immunotherapy. ***Left***: Non-Vγ9/Vδ2 γδ T-cells monitoring during the course of CMV infection in kidney transplant recipients may help personalise the duration of CMV treatment. ***Right***: Adoptive transfer of CMV-reactive expanded non-Vγ9/Vδ2 γδ T-cells represents an attractive approach for treating refractory or resistant CMV infections in kidney transplant recipients.

Figure 5. Unconventional T-cells and transplant rejection.

A. The role of γδ T-cells during T-cell mediated rejection (TCMR) has been approached in different mouse models. Skin-resident γδ T-cells could be important for the cross-priming of $CD8^+$ T-cells and enhancing skin graft rejection [196]. In mouse models of heart, lung, and skin transplantation, IL-17A production by γδ T-cells could be crucial for accelerating rejection, by inhibiting regulatory T-cell expansion and activating DCs [194].

B. The role of γδ T-cells during antibody mediated rejection (ABMR) has been identified at the efferent phase of the humoral adaptive response. CMV infection reshapes the $CD16^+$ lymphocyte compartment composition in CMV seropositive kidney transplant recipients who exhibit an equal number of $CD16^+$ NK cells and $CD16^+$ γδ T-cells. CMV-induced $CD16^+$ γδ T-cells are able to perform antibody-dependent cellular cytotoxicity (ADCC) against endothelial cells coated with donor specific antibodies (DSA) [198].

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