γδ T Cells in ARDs

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Autoimmune rheumatic diseases (ARDs), affecting ~1–1.5% of all humans, are associated with considerable life long morbidity and early mortality. Early studies in the 1990s showed numerical changes of the recently discovered γδ T cells in the peripheral blood and in affected tissues of patients with a variety of ARDs, kindling interest in their role in the immuno-pathogenesis of these chronic inflammatory conditions. Indeed, later studies applied rapid developments in the understanding of γδ T cell biology, including antigens recognized by γδ T cells, their developmental programs, states of activation, and cytokine production profiles, to analyze their contribution to the pathological immune response in these disorders.

Keywords: gammadelta T cells ; rheumatoid arthritis ; systemic lupus erythematosus ; systemic sclerosis ; ankylosing spondylitis ; juvenile idiopathic arthritis

1. Introduction

In the mid 1980s, the previously elusive nature of the T cell receptor (TCR) expressed by $CD4^+$ and $CD8^+$ major histocompatibility complex (MHC) restricted T cells had just been established to be encoded by rearranging α and β TCR gene [1][2]. However, the serendipitous discovery of a third rearranging gene, termed γ, in a murine clone of cytotoxic αβ T cells, confounded by absent expression of a protein encoded by this gene, raised questions relating to the role of this newcomer [3]. These were resolved in 1986, when two papers revealed human thymocyte derived $CD4^-CD8^-$ T cell clones and peripheral blood T cell clones expressing a second TCR composed of two polypeptide chains associated with the CD3 molecule, one of which was encoded by the “mysterious” γ gene, and the second later shown to be encoded by a fourth TCR gene, δ [4][5][6].

Since those early years, γδ T cells have been shown to be prototypes of “unconventional” T cells. Their unconventionality, is exemplified by the opportunity they present for broadening the “universe” of antigens that can be recognized by T cells. Thus, as opposed to MHC restricted $CD4^+$ and $CD8^+$ αβ T cells, γδ TCR do not recognize peptide antigens within classical MHC molecules. Rather, their T cell receptors mediate direct recognition of non peptidic molecules currently known to include cell surface expressed butyrophilins (whose recognition and stimulatory properties are enhanced by intracellular low molecular weight phospho-antigens), phycoerythrine, glycosides, t-RNA synthetase, and other intracellular enzymes, heat shock proteins, the non-classical MHC like molecules CD1, MR1, and endothelial protein C receptor (EPCR) [7]. Furthermore, different subsets of γδ T cells distinguished by the V genes used in their TCR may have evolved to recognize different antigens and presenting molecules. For example, human γδ TCR that use the Vγ9 and Vδ2 genes ($Vγ9Vδ2^+$ γδ T cells) recognize butyrophilin 3A1 to which a phosphoantigen has bound intracellularly on target cells [8]. By contrast, other butyrophilins, as well as CD1d, may serve as antigenic targets of the second major subset of human γδ T cells, namely those using the Vδ1 gene [9][10]. This unusual antigenic repertoire however, is only now beginning to be unraveled, and is likely to be greatly expanded and detailed in the future. In addition, γδ T cells follow unique intra- and extra-thymic pathways of functional maturation [11][12]. Thus, for example, imprinting of subsets of γδ T cells resulting in an innate ability to produce the potent proinflammatory interleukin (IL)-17, in the absence of TCR activation, takes place during thymic maturation [13]. This contrasts with the requirement for antigenic encounters in peripheral lymph nodes, in order for conventional naïve αβ T cells to acquire effector functions. An additional distinguishing feature is the affinity of certain subsets of γδ T cells, to establish residence, directly after exit from the thymus, in specific peripheral tissues, most prominently along mucosal and dermal epithelial surfaces [12]. Furthermore, the specific tissue is dictated by V genes of the γδ TCR [12]. These features, together with other broad functional properties overlapping those of innate and adaptive immune cells i.e., secretion of a wide spectrum of cytokines potential including tumor necrosis factor (TNF)α type I and II cytokines, to mediate potent cytotoxicity, help for B cells, immune regulatory potential, and even regulation of tissue metabolism, positions these cells to serve a unique and non redundant role within the immune system and has been the subject of recent excellent reviews, highly recommended to the reader [11][12][14]. Furthermore, γδ T cells were shown to undergone major perturbations in the context of infectious, autoimmune, and malignant diseases [15].

2. Rheumatoid Arthritis

2.1. Numerical Alterations of γδ T Cells in RA

In an early study, a decrease of $CD4^-CD8^-$ (mostly γδ T cells) in peripheral blood (PB) of RA patients relative to healthy controls (HC) was noted (1.38 ± 1.08% vs. 3.23 ± 2.12%, $p < 0.05$], whereas these cells were increased in synovial fluid (SF) of patients [16]. Similarly, a decrease in PB in both RA and psoriatic arthritis (PsA) patients relative to HC was found in a different cohort [17]. However, in another study, although RA in young (40.9 ± 7.5 years) was associated with higher levels of PB γδ T cells than in old (76.1 ± 4.9 years) patients, their percentage was not different from age matched controls [18]. Likewise, while increased γδ T cells were noted in the lamina propria in the intestinal mucosa (mean 5.5%, range 2–12%) in rheumatoid factor (RF) positive patients ($n = 8$) compared with RF negative RA patients and a disease control group ($n = 15$, mean 2%, range 0.5–5%; $p < 0.01$) similar changes were not detectable in PB [19]. In yet another study, the percentages (mean ± SEM = 6.3 ± 0.8%, $n = 22$) and absolute numbers (70 ± 11/microliters, $n = 22$) of γδ T cells in PB from RA patients were not different from those of 22 age-matched HC (7.5 ± 0.9%, 81 ± 17/microliters, respectively) [20]. Interestingly however, among a cohort of 24 RA patients, γδ T-cell levels were likewise not significantly different between controls, 4.46 ± 1.36%, gold salt treated (GST, 6.88 ± 1.73%), and total RA patients (2.73 ± 0.55%), but 42% of the GST treated group had γδ T-cell levels higher than the entire untreated RA group [18]. Finally, as opposed to these studies predominantly showing either unaltered or decreased levels of γδ T cells in the PB of RA patients, a single study reported 10 patients with RA in whom γδ T cells were 5.5% ± 4.38 (mean ± s.d.), which was significantly increased as compared with 22 healthy subjects (2.09 ± 1.01, $p < 0.001$) [21].

With respect to subsets of γδ T cells, one study reported that in early RA (> 6 months (m) < 8 m disease duration) the percentage of $Vγ9Vδ2^+$ T cells in the PB was the same as controls. Their percentage in synovium, however was higher than in PB of patients and controls. These cells also expressed high levels of human leukocyte antigen (HLA)-DR and CD86 [22]. Concurring with this, the total percentage of Vγ9Vδ2 T cells was the same as controls among another group of early RA patients, most of whom were anti citrulline peptide antibody (ACPA) positive. However, among these, there was an increase of Vγ9Vδ2 T cells bearing a terminal effector memory $CD27^-CD45RA^+$ phenotype (TEMRA) and a decrease of naïve $CD27^+CD45RA^+$ cells [23]. Contrasting with these results, among 19 adults with early active RA, 80% of whom were RF^+ or anti-cyclic citrullinated peptide (CCP) $^+$ and on no current steroid treatment, Vγ9Vδ2 T cells and regulatory T cells (Tregs) were lower, whereas the total percent of γδ T cells was same as in HC [24]. Likewise, among 68 patients with RA (not necessarily designated as early RA), 21 with osteoarthritis (OA) and 21 HC, the percent of γδ T cells in PB was found to be significantly lower in the RA patients, and the percent of $Vδ2^+$ T cells in PB was also decreased in RA relative to OA and HC. By contrast, in SF and synovial tissue $Vδ2^+$ T cells were increased (~5.9% vs. 1.2%). Interestingly, anti tumor necrosis factor (TNF)α treatment was associated with increased levels of $Vδ2^+$ cells in the periphery [25]. Similarly, Lamour found that the total γδ T cell percentage decreased relative to HC, and that the $Vδ2^+$ subset was decreased relative to the $Vδ1^+$ subset. Furthermore, human leukocyte antigen (HLA)-DR increased during active disease on γδ T cells of RA patients [26]. Thus, in RA, the PB γδ T cell subset expressing the common Vγ9 and Vδ2 combination in the TCR (Vγ9Vδ2 T cells), appears to be unchanged or decreased—in particular in advanced phases of the disease—and bears stigmata of having been activated during the disease process. Furthermore, since PB may be relatively depleted of Vγ9Vδ2 T cells, whereas synovial Vγ9Vδ2 T cells are relatively expanded in synovium relative to PB, transmigration of this subset to the site of inflammation appears to be one mechanism of accumulation of γδ T cell in the rheumatoid synovium.

In contrast to the findings in most of these studies, showing normal or decreased percentages of γδ T cells in the PB of RA patients, large expansions of these cells can be found in patients with RA and large granular lymphocyte (LGL) proliferation of γδ T cells. Thus, in one study, 3.6% of patients with RA had >10% LGL ($CD3^+CD56^+$) in the PB. These patients were not clinically distinct, other than developing cytopenias, but significantly more were under anti TNFα therapy and ~60% of the LGL expansions were γδ T cell clones [27]. Furthermore, among 14 patients with γδ T cell-LGL leukemia, (11 men and three women), six had a history of RA. Eight of 12 patients had a $CD4^-CD8^-$ phenotype, and 4 had a $CD4^-CD8^+$ phenotype. In this study, patients with γδ T-LGL leukemia were more likely to have RA than those with other forms of LGL leukemia ($p = 0.04$) and median overall survival for the six patients with RA was 209 months, compared to 62 months for eight patients without RA ($p = 0.7$) [28]. In another study, however, while 20% of patients with γδ LGL had RA (4/20), a similar proportion of 169 patients with αβ LGL also developed RA [29].

2.2. γδ T Cells in Rheumatoid Synovium

Whereas synovia from patients with OA, SLE and joint trauma did not show an increased presence of γδ T cells, these cells were increased in a subset of RA patients. RA patients with γδ T cell infiltrates in the synovium had an increased

tissue inflammation score compared to RA synovia with few γδ T cells [18.6 ± 5.8 versus 11.6 ± 4.2, $p < 0.05$] [30]. In another study, among 23 rheumatoid synovial membranes, using immunohistology and monoclonal antibodies (mAb), the majority showed only limited staining for δ-chain antibodies, with 20 of the 23 tissues appearing to have less than 1% of T lymphocytes expressing δ chains. Nevertheless, three tissues stained extensively for both δ (all γδ T cells) and δ TCS1 ($Vδ1^+$) in particular areas of the section. In these areas, small perivascular lymphocytic aggregates appeared to be composed mainly of γδ T cells [31]. In addition, the expression of CD16 was reduced, and HLA-DR increased in synovial γδ T cells in RA patients [32]. These findings indicate that γδ T cells participate in the inflammatory process occurring in the synovium in RA and express an activated phenotype.

2.3. TCR Gene Expression

A study of synovial membrane lymphocytes from the RA patients, which confirmed a selective expansion of γδ T cells (8.8% in synovial membrane versus 4% in PB) also found, by immunohistochemical studies, that the TCR of the γδ T cells was unusual inasmuch as most γδ T cells did not express Vδ or Vδ genes, that predominate in PB [33]. Further analysis of synovial T cells, using a mAb (B18) specific for Vγ8 revealed, indeed, that in PB of healthy persons, only 6 ± 5% and only 1 of 35 γδ T cell clones were $Vγ8^+$, whereas the $B18^+$ subset was a dominant γδ T cell population among intraepithelial lymphocytes (IEL) derived from the human intestine (74 ± 29%, $p < 0.002$), and in the SF of patients with RA (21 ± 18%, $p < 0.05$ compared with normal PB). Furthermore, the $B18^+$ subset was more frequent among IL-2-expanded γδ T cells (42 ± 20%) derived from synovial tissue than among IL-2-expanded cells derived from HC PB ($p < 0.002$) and PB from RA patients ($p < 0.02$). All $B18^+$ clones ($n = 7$) expressed mRNA for Vγ8 together with mRNA for Vδ1 ($n = 5$) or mRNA for Vδ3 ($n = 2$). Thus, γδ T cells expressing Vγ8, together with mainly Vδ1, form a major γδ T cell subset among the IEL of the gut and a highly frequent subset in the synovial tissue of patients with RA [34]. In another study, reverse transcriptase-polymerase chain reaction (RT-PCR), in conjunction with nucleotide sequencing, revealed a frequent usage of the Vγ3 gene segment in RA synovial fluid mononuclear cells (SFMC) which was rare in PBMC of healthy individuals, where the Vγ9 gene predominated. The Vγ3 gene in RA SFMC showed no conserved junctional sequence and Vγ3 expressing clones were non-reactive to mycobacterium tuberculosis, as opposed to the $Vγ9^+$ clones [35]. Others, using PCR to amplify TcR γ- and δ-chain transcripts, found SFMC expressing TCR γ-chain transcripts which used the same set of Vγ genes as peripheral blood mononuclear cells (PBMC). The majority of patients expressed a restricted SMC Vδ-chain repertoire biased towards Vδ1. Vδ2 mRNA transcripts were also detected, albeit at low levels, in some patients [36]. Interestingly, the level of expression of the 4 Vγ gene family members was determined by PCR, and 509 cDNA clones were derived from 8 SF and one PB sample from 2 patients with RA and one patient with JIA, subcloned and sequenced. Disproportionate expression of a subpopulation of TCR γ mRNA transcripts were found in each patient and some of these transcripts were expressed by T cells found in both joints, consistent with a common antigen driven response in the joints [37]. In addition, in contrast to control PBMC, Vδ1 chain cDNA derived from PBMC of three patients showed a strong bias towards usage of the same V-joining (J) combination and junctional region sequences, although the specific sequences were unique in each patient, whereas oligoclonality of the Vδ1 chain was less marked in SFMC of two of these patients and absent in SFMC of the other patients. For Vδ2, oligoclonality was detected in PBMC of two patients. In SFMC of a single patient, a dominant Vδ2 transcript was detected that utilized the Jδ2 segment, which was rarely expressed in the normal TCR repertoire. These results indicate in vivo clonal expansion of Vδ1- and Vδ2-expressing γδ T cells in the PB of RA patients contrasting with a synovial T cell infiltrate which consists largely of polyclonally expanded γδ T cells, but showing clonal dominance in some patients [38]. Moreover, it appears that γδ T cells may expand in RA synovium to consist a unique population characteristically enriched in $Vδ1^+$ T cells and often co-expressing Vγ8 and Vγ3 genes, which suggests they recognize MR1 [39]. In summary, the synovium in RA contains γδ T cells with a polyclonal repertoire, although sometimes containing oligoclonal expansions common to different joints. Synovial $Vγ9Vδ2^+$ T cells, which consist of the predominant phenotype in healthy PB, may be expanded in synovium relative to the patient's PB, but usually form a less prominent component of the synovial γδ T cell infiltrate. The infiltrate may include less common types of γδ T cells, but is usually enriched for $Vδ1^+$ T cells that use unusual Vγ genes, some of which have been associated with reactivity with non classical MHC like molecules. Together, these findings suggest that synovial γδ T cells may be selected by specific antigens found in the synovium.

2.4. Functions of γδ T Cells in RA

Vγ9Vδ2 T cells isolated from patients with early RA were found to be capable of presenting peptide antigens to $CD4^+$ T cells. In support of this, they expressed high levels of HLA-DR and CD86, molecules involved in antigen presentation, and characteristic of antigen presenting cells [22]. In addition, IFNγ (~50%), TNFα (~40%), and IL-17 (~3.7%) were demonstrated to be produced by the indicated percentages of RA synovial $Vγ9^+$ T cells. Furthermore, RA SF $Vδ2^+$ T cells expressed high levels of C-X-C motif chemokine receptor (CXCR) 3 and C-C motif chemokine receptor (CCR) 5 that were upregulated by TNFα in a nuclear factor (NF)-κb dependent pathway, and migrated to RA SF more efficiently than HC and

OA derived cells. Vδ γδ T cells, however, had lower levels of the chemokine receptors [25]. In another study, among 22 γδ T cell clones obtained from the SF and PB of one patient with inflammatory arthritis (and compared to 26 αβ TCR^+ T cell clones of the same and different patients), IFNγ was produced by 82% and IL-4 by 77% of the 22 γδ T cell clones whereas IL-10 was not. The mean levels of IL-4 were lower for clones derived from SF. Thus, the most common pattern was a γδ Th1-like pattern, primarily found in SF derived $Vδ1^+$ clones. A γδ Th0-like pattern (balanced production of both IFNγ and IL-4), a γδ Th1 pattern (IFNγ alone) and a γδ Th2 pattern (IL-4 alone) were also found. These three patterns were also seen in PB $Vδ2^+$ γδ T cells. However, γδ T cell clones produced lower levels of IFNγ ($p = 0.001$) and higher levels of IL-4 than αβ T cell clones ($p < 0.02$) [40]. In addition, in one patient with RA, LGL γδ cells, that expressed a $Vγ9^-$ $Vδ2^+$ phenotype, and constituted 60% of the PB T cells, did not proliferate, but did secrete TNFα when triggered with anti-CD3, and the addition of these cells to decreased their secretion of immunoglobulin (Ig) M from pokeweed mitogen-stimulated B cells from the patient, while augmenting IgG secretion [41]. In contrast to these potential pro-inflammatory and immunogenic functions, $CD4^+$ Th17 cells but not γδ T cells, were found in apposition to tartrate-resistant acid phosphatase positive osteoclasts in subchondral areas of inflamed joints in mice with collagen induced arthritis (CIA), and this pattern was reproduced in synovial biopsies of patients with RA [42]. Thus, γδ T cells of RA patients exhibit functional properties including antigen presentation, help for antibody production and predominantly TH1 like cytokine profiles, but may play a less significant role in bone resorption during the inflammatory process.

3. Rodent Models of Rheumatoid Arthritis

3.1. Rat Models

In Mycobacterium tuberculosis-induced rat adjuvant arthritis (AA), protocols to deplete of TCR γδ (bright) cells in PB and lymph nodes, did not influence clinical parameters. If rats were treated before the clinical peak of adjuvant arthritis, however, joint destruction was significantly more severe than in vehicle-treated rats. The critical time window of intervention seemed to be limited to the span between the onset and the clinical peak of synovitis, since only anti γδ TCR treatment given in this phase, and not protocols administered before induction or around the peak of the disease, aggravated the degree of joint destruction [43]. In another study of AA in rats mediated by T lymphocytes specific for Mycobacterium tuberculosis, T cells bearing the αβ TCR were depleted from circulation by treatment with a mAb against the rat αβ TCR which efficiently suppressed existing disease. By contrast, there was no evidence that γδ T cells contributed to AA induction [44]. Likewise, in oil-induced arthritis, a genetically restricted polyarthritis that develops in the DA rats after injection of the mineral oil Freund's incomplete adjuvant, disease was suppressed by $CD8^+$ T cells but not by depletion of γδ T cells with a mAb (mAb) [45]. Finally, in the model of intradermal injection of squalene, a role for genes within the major histocompatibility complex, was concluded from comparative studies of MHC congenic rat strains. Treatment with anti αβ TCR but not anti γδ TCR prevented disease [46]. In conclusion of these studies, it appeared that in these models of rat arthritis, γδ T cells may play a role if any, during the effector rather than induction phases of the disease.

3.2. Murine Model

In collagen induce arthritis (CIA)—induced by injections of collagen II in complete Freund adjuvant (CFA) with mycobacterium butyricum—in B10.Q male and DBA/1 female mice, CIA was no different in $TCRδ^{-/-}$ mice than in controls, but was, in contrast, abrogated in $TCRβ^{-/-}$ mice. The authors concluded that αβ T cells are necessary for CIA development and for an IgG response towards CII, whereas γδ T cells are neither necessary nor sufficient for development of CIA [47]. In another study, moreover, a mAb to TCR γδ had no effect, and actually slightly worsened arthritis, despite the fact that γδ T cells consisted up to 35% of the total T cells in the joints of mice with CIA. Some γδ T cells using Vγ1, -2, -4, and -6 and Vδ1, -2, -5, and -7 were found in the joints of normal mice, and this repertoire was similar to that found in arthritis joints [48]. These results therefore recapitulated those found in rat arthritis as detailed above.

However, when the individual responses of the two mains peripheral γδ T cell subsets, $Vγ1^+$ and $Vγ4^+$ cells, during CIA was examined, a more complex scenario unfolded. Thus, whereas both subsets increased in number, only the $Vγ4^+$ cells became activated during CIA. These $Vγ4^+$ cells appeared to be antigen (Ag)-selected, based on preferential Vγ4/Vδ4 pairing and very limited TCR junctions. Furthermore, in both the draining lymph node and the joints, the vast majority of the $Vγ4/Vδ4^+$ cells produced IL-17, a key cytokine in the development of CIA. In fact, the number of IL-17-producing $Vγ4^+$γδ T cells in the draining lymph nodes was found to be equivalent to the number of $CD4^+$αβ TCR Th-17 cells. When mice were depleted of $Vγ4^+$ cells, clinical disease scores were significantly reduced and the incidence of disease was lowered. A decrease in total IgG and IgG2a anti-collagen antibodies (Abs) was also seen. These results suggested that $Vγ4Vδ4^+$ γδ T cells exacerbate CIA through their production of IL-17 [49].

Further support for the role of γδ T cells in antigen induced arthritis, was obtained in a model wherein methylated Bovine Serum Albumin (mBSA, 8 mg/mL) was emulsified in an equal volume of CFA containing heat-killed M. tuberculosis. At day 7, mice were immunized intradermally with mBSA/CFA and a week later, mBSA was injected intra-articularly to induce mono-arthritis. Inflammation in the joint was associated with high levels of IL-17 producing γδ T cells, and the expression of retinoic acid receptor related orphan receptor gamma (RORγ)t was dependent upon IL-23 suggesting that IL-23 regulates IL-17A and RORγt expression in γδ T cells in arthritis [50]. Furthermore, in both CIA and as well as in samples from patients with RA, an inhibitor of RORγT suppressed IL-17 production in γδ T cells stimulated with IL1β and IL23 $^{+}$ IPP [51]. Further mechanistic research came from a study to understand the role of IFN-lambda1 (IL-29), the main cytokine of class II cytokines (including IL-10 and IFNα β) in humans. This cytokine is not expressed in mice, where IL-28A/B instead, plays the major role. In the setting of CIA in male DBA/1OlaHsd mice and IL28-/- mice, therapeutic administration of IL-28A decreased IL-1β, IL23, and Th17 and γδ T cells producing IL-17 in the draining lymph nodes but not in PB. The target of IL-28 was neutrophils, due to their expression of IL-28R, suggesting a neutrophil mediated mechanism for γδ T cell involvement in CIA [52]. Another model studied the role of ES-62, a phosphorylcholine (PC)-containing glycoprotein secreted by the filarial nematode Acanthocheilonema viteae that acts to modulate the host immune response in order to promote the establishment of chronic helminth infection. ES-62 selectively induced toll like receptor (TLR) 4^{+} γδ T cells with the capacity to produce IL-22 but not IL-17 during CIA [53]. In addition, ES-62 down-regulated IL-17 responses in mice with CIA by targeting a complex IL-17-producing network, involving signaling between dendritic cells and γδ or CD4^{+} T cells. Thus, although it did not inhibit IL-17 produced by direct activation with IL-1/IL-23, ES-62 modulated the migration of γδ T cells by direct suppression of CD44 up-regulation and, as evidenced by in situ analysis, dramatically reduced levels of IL-17-producing cells, including lymphocytes, infiltrating the joint [54]. In yet another model, IL-10 receptor dominant-negative transgenic (Tg) and control mice were immunized with bovine type II collagen to induce arthritis. Blocking IL-10 signaling in T cells rendered mice highly susceptible to CIA. The suppressive function of CD4^{+} Foxp3^{+} regulatory T cells was significantly impaired in Tg mice because of the reduced ability of Tregs from Tg mice to maintain their levels of Foxp3. The higher level of IL-17 mRNA detected in inflammatory joints of Tg mice, was attributed to the recruitment of IL-17^{+} γδ T cells into the arthritic joints since IL-10 deficiency did not affect the percent of CD4^{+} IL-17- producing cells in the joint [55].

γδ T cells were found to be the predominant population among IL-17-producing cells in the swollen joints of mice with CIA, and the absolute numbers of these cells increased in parallel with disease activity. However, IL-17-producing γδ T cells expressed chemokine receptor 6 were maintained by IL-23 but not by type II collagen in vitro, and were induced antigen independently in vivo. Furthermore, IL-17 production by γδ T cells was induced by IL-1β plus IL-23 independently of TCR triggering. However, in autoimmune arthritis in SKG mice which is induced using zymosan as an adjuvant, in contrast to what was observed in mice with CIA, IL-17-producing γδ T cells were nearly absent in the affected joints. In this study, it was noted in addition, that in joints of patients with RA, IL-17-producing γδ T cells were rarely observed, whereas Th1 cells were predominant [56]. Likewise, as previously noted, it has been found that in CIA, CD4^{+} Th17, and IL-17 producing γδ T cells in the joints of arthritic mice similarly induced osteoclastogenesis in vitro. However, individual depletion and adoptive transfer studies revealed that in vivo, Th17 cells dominated with regard to bone destruction. Thus, unlike γδ T cells, Th17 cells were found in apposition to tartrate-resistant acid phosphatase positive osteoclasts in subchondral areas of inflamed joints, a pattern reproduced in patient biopsies [42].

Taken together, while clearly demonstrating involvement of γδ T cells in experimental arthritis, these data highlight the need to dissect subsets of γδ T cells when analyzing their role in pathogenesis of antigen induced arthritis in mice, while supporting the idea that their role is not directly associated with a direct response to the instigating antigen, but rather is related to effector mechanisms such as IL-23 induced production of IL-17 at the site of inflammation.

Indeed, several models support the idea that in classical antigen induced arthritis, γδ T cells play an effector role downstream of and independent of direct antigen recognition. For example, it was demonstrated that, in the induction phase of CIA, CD4^{+}Th17 cells in the lamina propria are activated. In CD4^{+}Cre RORγ floxed mice arthritis was mitigated, despite continued production of IL-17 by γδ T cells [57]. By contrast, in arthritis that does not require any antigen to induce disease, but rather is induced by injected gene transfer of IL-23 in B10.RIII mice, γδ T cell depletion with mAb decreased neutrophils in joints and spleen while increasing IL-27 production by neutrophils and activated macrophages, resulting in abrogation of the arthritis. Blocking with anti TCR γδ mAb also resulted in reduced IL-17 but not TNFα, interferon (IFN)γ or interleukin (IL)-6. Thus, in this non antigen requiring form of arthritis, γδ T cells played a major role. It was further shown that IL-27 itself inhibited γδ T cells and reduced IL-23 induced arthritis [58]. In addition, IL-1 receptor(R) antagonist (a)-deficient (Il1rn$^{-/-}$) mice spontaneously develop arthritis in an IL-17- and T-cell dependent manner suggesting that excess IL-1 signaling caused by IL-1Ra deficiency induces IL-17 production from T cells and the development of arthritis. IL-1R and IL-23R expressing Vγ6^{+} γδ IL 17 cells expressing high levels of C-C chemokine receptor (CCR2) type 2 are the main producers of IL-17 in joints of Il1rn $^{-/-}$ mice. Importantly, without CD4 cells, no arthritis occurred, and the CD4^{+} T cells were

responsible for inducing C-C motif chemokine ligand (CCL) 2 in the joints, that attracted the pathogenic γδ T cells [59]. Interestingly, in yet another model it was shown that pathogenic γδ T cells may be under the control of other subsets of T cells. Thus, mice were given Salmonella enterica serovar Enteritidis #5694 by gavage. BALB/c Jα18−/− mice KO mice and anti CD1d treated mice developed more severe intestinal inflammation and worse arthritis. Infected mice had a higher percentage of IL-17 producing γδ T cells and depletion with anti γδ TCR partially abrogated joint inflammation. Mice treated with α galcer to activate induced natural killer (iNKT) T cells had less IL-17 γδ T cells and less arthritis but an increase of Th17 cells suggesting the pivotal role of IL-17 producing γδ T cells in this model [60]. Finally, a single intraperitoneal injection of mannan from the yeast *S. cerevisiae* into B10Q. Ncf1m1j/m1j (reactive oxygen species (ROS) deficient) mice resulted in a worse arthritis and psoriasis than that developing in wildtype B10Q mice. Arthritis was mediated by IL-17, and in this model the source of the cytokine was γδ and not αβ T cells. The secretion of IL-17 was dependent on TNFα produced by macrophages. It was thought that TLR2 expression by macrophages and γδ T cells might be responsible for the effect of mannan, revealing a mechanism for activation of pathogenic γδ T cells independent of a nominal antigen [61].

The main findings of these experimental models are summarized in Table 1. The cumulative data suggest that specific subsets of γδ T cells play an important role in the inflammatory response in the joint space in models of arthritis, primarily by secreting IL-17. Furthermore, this response appears to be independent of the inciting protein auto-antigen (e.g., collagen) used to induce disease. Thus, it appears that γδ T cell responses in arthritis are dependent, upon non TCR driven mechanisms, including cytokines (IL-1, IL-23, and IL-28) and chemokines affecting homing to the synovium, although a specific contribution of certain antigen selected γδ T cells (e.g., Vγ4Vδ4$^+$ T cells) may also play a role.

Table 1. γδ T cells in animal models of autoimmune rheumatic diseases.

Disease Model	Role of γδ T Cells	References
Rat adjuvant arthritis	**No role in disease induction. Possible role in effector phase of disease.**	[43][44][45][46]
Murine Collagen induced arthritis	**Vγ4/Vδ4$^+$ cells producing IL-17 are pathogenic. IL-17 production can be suppressed by inhibitor of RORγt and by IL-28A. ES-62, a phosphorylcholine containing glycoprotein and IL-10 reduce migration of IL-17 producing γδ T cells to the inflamed joint, which are maintained by IL-23, and are not associated with bone destruction.**	[49]
Murine BSA induced arthritis	**(RORγ)t$^+$ IL-17 producing γδ T cells dependent upon IL-23 accumulated in arthritic joints.**	[50]
Murine non antigen dependent arthritis	**IL-1R and IL-23R expressing Vγ6$^+$ γδ IL 17 cells are the main producers of IL-17 in joints of Il1rn $^{-/-}$ mice spontaneously developing arthritis. γδ T cells are responsible for arthritis in B10.RIII mice induced by gene transfer of IL-23. Arthritis induced by intraperitoneal injection of mannan is dependent upon IL-17 secreting γδ T cells.**	[58][59][61]
Murine IFNγ$^-$ knockout (KO)	**IL-17 secreting γδ T cells were shown to participate in arthritis and the systemic response to complete Freund adjuvant injection developing in these mice.**	[62]
Murine IL-23 gene introduction	**increased number of γδ T cells are found in Achilles tendon enthesis, aortic root, and adjacent to the ciliary body and secreted IL-17.**	[63]
Murine MRL/lpr model of SLE	**γδ T cells are protective from development of glomerulonephritis in the presence of αβ T cells, but mediate a less severe form of disease in their absence, mediated by cytokines and help for B cells. With age, some γδ T cells acquire a CD4$^+$B220$^+$ phenotype, and produce IL-17. In BLK$^{+/-}$.lpr mice expressing low levels of Bruton lymphocyte kinase gene IL-17 and IFNγ producing γδ T cells are increased enhanced and mediate glomerular damage. γδ T cells induce phosphopeptide P140 mediated apoptosis of lymphocytes, which is associated with amelioration of disease in MRL/lpr mice.**	[64][65][66]
lupus-prone NZB/NZW mice	**CD1d restricted γδ T cells may be protective in young, and pathogenic in old mice.**	[67]
Pristane induced model of SLE	**γδ T cells in the kidney expressed IL-17F and A and attracted neutrophils to the kidney. TCRδ$^{-/-}$ mice developed milder glomerulonephritis, due to decreased T follicular helper cell differentiation dependent upon γδ T cell secretion of Wnt ligands.**	[68]

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