L20. Memory T-cells in vasculitis

**Introduction**

Memory T-cells comprise the antigenic experience of an individual. Phenotype and function of memory T-cells are indicative of their imprinting conditions. Thus, deciphering T-cell memory is instrumental to understand how vasculitides develop and evolve. Analysis of T-cell memory is complicated by the fact that T-cells display considerable heterogeneity in terms of phenotype, function, and anatomical distribution. Whereas central memory T-cells (T<sub>CM</sub>) home to secondary lymphoid organs to mount antigen-driven proliferative responses, effector memory T-cells (T<sub>EM</sub>) migrate into peripheral tissues and display immediate effector functions such as cytokine production and/or cytotoxicity [1]. Persistent expansion of circulating effector memory T-cells (T<sub>EM</sub>) and abundance of T<sub>EM</sub> in inflammatory lesions suggests a fundamental alteration of the T-cell response in different vasculitides such as granulomatosis with polyangiitis (GPA, Wegener’s) and giant cell arteritis (GCA) [2–6].

**Genetic risk factors predisposing to altered T-cell function in vasculitides**

Various genetic risk factors predispose to vasculitis. However, most associations are descriptive and their functional impact is unknown [7,8]. Polymorphisms of the cytotoxic T-lymphocyte-associated protein (CTLA-4) gene and the leptin receptor have been suggested to modulate the activation threshold of T-cells in GPA [9,10]. The R<sub>620W</sub> gain-of-function polymorphism of the protein tyrosine phosphatase non-receptor 22 (PTPN22) is associated with GPA and other rheumatic diseases. PTPN22 is involved in T- and B-cell receptor signaling [11]. The polymorphism results in an up-regulated basal PTPN22 phosphtase activity and altered gene expression profile in GPA-patients. Anti-inflammatory interleukin (IL)-10 production is reduced in these patients. The R<sub>620W</sub> PTPN22 allele is associated with faster progress to end-stage kidney disease and relapse. Interestingly, the geographic distribution of the disease-related PTPN22 allele mirrors the north-south gradient of the GPA-incidence in Europe. The allele is virtually absent in African and Asian populations, in which GPA is less common [12].

Genes within the major histocompatibility complex (MHC) generally exert by far the strongest single genetic effect in autoimmune disorders. Particular MHC alleles may facilitate autoantigen presentation or affect intrathymic selection of autoreactive T-cells [8]. Recently, the first genome-wide association study in antineutrophil cytoplasmatic autoantibody (ANCA)-associated vasculitides (AAV) has confirmed differences in the genetic background and microscopic
Aberrant memory T-cell responses in vasculitides

Persistent expansion of TEM in peripheral blood suggests a fundamental alteration of the T-cell response in different vasculitides including AAV and GCA [4,5,17–19]. Percentages of circulating TEM decrease during active disease and increase with remission indicating migration of TEM towards inflamed sites during disease exacerbation in GPA [5]. In line with this finding, TEM are found in inflammatory lesions in GPA [4]. Moreover, TEM are detected in urine during renal activity [20]. Interestingly, memory T-cell precursors, so-called very early memory T-cells (TvEM), are also increased in peripheral blood [21]. TvEM represent a pool of cells from which TEM and TEM derive and, thus, are probably closely related to memory stem cells [22,23]. Conversely, the frequency of circulating naive T-cells (TN) is decreased [5,21,24]. On the transcriptional level, upregulation of the interleukin-7 receptor (IL-7R) pathway and T-cell receptor (TCR)-mediated signaling in CD8+ T-cells is associated with poor prognosis in AAV [25]. The expanded TEM population contains distinct memory cell subsets including CD45RA- “revertants” (TEMRA) and Th1-type CD4+ TEM lacking co-stimulatory CD28 expression, i.e. CD28- T-cells in GPA [4,26]. Aberrant T-cell costimulation is suggested by abnormal expression of the activating NKG2D receptor, the inhibitory PD-1 receptor, the co-stimulatory receptors CD134 and GITR (glucocorticoid-induced TNF-receptor-related protein) and CC-type chemokine receptors (CCR4, CCR5, CCR6) [21,27–31]. Chemokine receptors and CD134 are thought to be involved in T-cell migration to inflamed tissues [3,27,30]. As mentioned above, Th1-type CD28- TEM are found in inflammatory lesions in GPA [4]. Renal outcome correlates with tubulointerstitial infiltration with T-cells in AAV [32]. IL-15 is expressed in granulomatous lesions, where it could sustain local T-cell differentiation and survival in GPA. IL-15 is also involved in the upregulation of NKG2D expression on T-cells and NKG2D-ligand MIC on antigen-presenting cells potentially favoring antigen-independent T-cell activation [28]. CD4+NKG2D+ TEM display NK-cell-like cytotoxicity towards microvascular endothelial cells in vitro. This finding suggests that T-cell-mediated vascular injury could add to PR3-ANCA-induced vascular damage in the pathogenesis of AAV [29]. Expansion of circulating CD28- T-cells has been shown in various chronic inflammatory and autoimmune disorders such as rheumatoid arthritis, spondyloarthritis, GPA and GCA [4,19,26–29,33]. CD28- T-cells display TEM and TEMRA phenotypes in GPA [26]. The frequency of CD4+CD28- TEM correlates with the cumulative disease extent thereby reflecting the chronic inflammatory burden of an individual [33]. The expansion of CD4+CD28- TEM has been suggested to be driven by latent cytomegalovirus (CMV) infection in rheumatoid arthritis and GPA [34,35]. CMV is known to sustain so-called memory CD8+ T-cell inflation in healthy individuals. Antigen-dependent and -independent mechanisms contribute to CMV-associated memory cell inflation [36]. However, differences in the phenotype of CMV-specific T-cells and mode of distribution of CD28- TEM frequencies between GPA-patients and healthy controls suggest a role of factors other than CMV in driving memory cell expansion in GPA [26,37,38].

Anomalous cytokine responses in vasculitides

Increased frequencies of circulating total Th1-type and Th17 cell populations have been reported in GPA and GCA [4,6,21,27,39–42]. Th1-type and Th17 cells are recruited to temporal arteries in GCA. Whereas Th17 cells were shown to be sensitive to glucocorticoid treatment, Th1-type cells were not affected in an animal model of GCA [42]. Regulatory T-cell function is impaired in AAV potentially favoring chronic inflammation [43]. The cytokine response of peripheral blood PR3-specific T-cells is skewed towards an increase of Th2-type, Th17, Th17/Th1, Th17/Th2 and Th22 cell fractions in GPA [44–47]. In contrast, PR3-specific T-cells display solely Th2-type cytokine responses in EGPA suggesting an influence of the underlying disease on the cytokine response of antigen-specific cells [47]. Th17 cells promote recruitment of neutrophils and sustain inflammation in experimental glomerulonephritis [48,49]. However, Th17 cells are scarce in nasal and kidney biopsies from patients with AAV. Instead, the majority of IL-17 expressing cells are neutrophils ([50]; A. Müller, personal communication).

Conclusion and outlook

T-cells display considerable alterations in phenotype and function favoring loss of tolerance and chronic inflammation in vasculitides. While ANCA-induced acute pulmonary and renal vascular damage has been demonstrated in animal models, granuloma formation was not observed in these models. It has been hypothesized that the pathogenesis of granulomatous inflammation predominantly found in the respiratory tract of GPA- and EGPA-patients is separate from acute systemic vasculitis and in particular T-cell-dependent [51]. Further studies are needed to define the cause of T-cell alterations and their role in the pathogenesis of vasculitides more precisely.

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References


Kidneys in ANCA-associated vasculitis: What to learn from biopsies?

Introduction
In 2010 a histopathologic classification of antineutrophil cytoplasmic autoantibody (ANCA)-associated glomerulonephritis (AAGN) was devised by an international group of renal pathologists and nephrologists, comprising four classes: focal, crescentic, mixed and sclerotic class biopsies. A first validation study, incorporated in the initial publication, demonstrated that this phenotypical order of classes corresponded to the order of severity of renal impairment during follow-up. Moreover, sclerotic class biopsy patients were also at higher risk for death within the first year after diagnosis [1]. We here review follow-papers on our classification study.

Two validation studies were published after the initial publication, one from China [2] and one from Japan [3]. The Chinese study incorporated 121 patients: 49 with granulomatosis with polyangiitis (GPA), 68 with microscopic polyangiitis (MPA) and 4 with renal-limited vasculitis (RLV), however, there was a predominance of myeloperoxidase (MPO)-ANCA positivity (108/121 patients). Thirty-three patients had a focal class, 24 a crescentic, 53 a mixed, and 11 a sclerotic class biopsy. The classes correlated with serum creatinine at the time of biopsy and renal response to treatment. Probability of progressing to end-stage renal disease (ESRD) increased with ascending categories of focal, mixed, crescentic and sclerotic class. The Japanese study incorporated 87 patients with a diagnosis of MPA only (all MPO-ANCA). Renal survival was worst for the sclerotic class. Similar to the Chinese study, the probability of progressing to ESRD increased with ascending categories of focal, mixed, crescentic and sclerotic class. The Japanese study incorporated 87 patients with a diagnosis of MPA only (all MPO-ANCA). Renal survival was worst for the sclerotic class.

In all but the original study, patients with crescentic class biopsies. Renal survival at 1 year for the focal, mixed, crescentic and sclerotic class was 100%, 96%, 86%, and 29% respectively. These figures show that outcome was relatively good and fairly similar for the focal, mixed and crescentic classes, whereas outcome was unfavorable for patients with sclerotic class biopsies, 10/14 reaching ESRD within 5 years.

At the American Society of Nephrology-meeting in 2012, there were numerous reports on validation studies of the histopathological classification for AAGN. Casian et al. [4] performed a validation study on 92 renal biopsies with a mean number of 18 glomeruli from patients with AAGN. Mean follow-up was 62 months. Mortality was higher for patients with sclerotic class biopsies. Renal survival at 1 year for the focal, mixed, crescentic and sclerotic class was 100%, 86%, 72% and 61% respectively. These data show a significant difference between the classes, however, the phenotypical order of the classes is different compared to the original validation study, but similar to the results demonstrated by the Japanese [3] and Chinese [2] investigators. In all but the original study, patients with crescentic class biopsies show better outcome than those with mixed class biopsies. Whereas the relatively large number of MPO-ANCA positive patients was taken by the Muso et al. and Chang et al. as a probably reason to account for the difference, this hypothesis is now contradicted by the new data by Casian et al. [4], which come from European patients. That a crescentic pattern of disease would correspond to better outcome than a mixed pattern would seem plausible, because of a larger...