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_{CM}) home to secondary lymphoid organs to mount antigen-driven proliferative responses, effector memory T-cells (T_{EM}) 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_{EM}) and abundance of T_{EM} 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 R620W 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 phosphatase activity and altered gene expression profile in GPA-patients. Anti-inflammatory interleukin (IL)-10 production is reduced in these patients. The R620W 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 cytoplasmic autoantibody (ANCA)-associated vasculitides (AAV) has confirmed differences in the genetic background between GPA and microscopic polyangiitis (MPA) [13]. Proteinase-3-specific (PR3)-ANCA-positive GPA is strongly associated with the human leukocyte antigen allele HLA-DRB1*0401, whereas myeloperoxidase-specific (MPO)-ANCA-positive MPA is associated with a HLA-DQ background [13,14]. GPA shares its HLA-DR association with chronic beryllium disease, another chronic granulomatous disorder. MPA and eosinophilic granulomatosis with polyangiitis (EGPA, Churg-Strauss) are not HLA-DR associated [14]. Thus, AAV appear to constitute 3 separate diseases with shared clinical and pathological features rather than 3 phenotypes of a single disease entity [13–16].

Aberrant memory T-cell responses in vasculitides

Persistent expansion of T_{EM} 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 T_{EM} decrease during active disease and increase with remission indicating migration of T_{EM} towards inflamed sites during disease exacerbation in GPA [5]. In line with this finding, T_{EM} are found in inflammatory lesions in GPA [4]. Moreover, T_{EM} are detected in urine during renal activity [20]. Interestingly, memory T-cell precursors, so-called very early memory T-cells (T_{VEM}), are also increased in peripheral blood [21]. T_{VEM} represent a pool of cells from which T_{CM} and T_{EM} derive and, thus, are probably closely related to memory stem cells [22,23]. Conversely, the frequency of circulating naïve T-cells (T_{N}) 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 T_{EM} population contains distinct memory cell subsets including CD45RA “revertants” (T_{EMRA}) and Th1-type CD4+ T-cells lacking co-stimulatory CD28 expression, i.e. CD28- T-cells in GPA [4,26]. Aberrant T-cell co-stimulation is suggested by anomalous 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- T<sub>EM</sub> are found in inflammatory lesions in GPA [4]. Renal outcome correlates with tubulointerstitial inflammation 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<sup>+</sup> T<sub>EM</sub> 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<sup>-</sup> T-cells has been shown in various chronic inflammatory and autoimmune disorders such as rheumatoid arthritis, spondylarthritis, GPA and GCA [4,19,26–29,33]. CD28<sup>-</sup> T-cells display T<sub>EM</sub> and T<sub>EMRA</sub> phenotypes in GPA [26]. The frequency of CD4<sup>+</sup>CD28<sup>-</sup> T<sub>EM</sub> correlates with the cumulative disease extent thereby reflecting the chronic inflammatory burden of an individual [33]. The expansion of CD4<sup>+</sup>CD28<sup>-</sup> T<sub>EM</sub> 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<sup>+</sup> 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<sup>-</sup> T<sub>EM</sub> 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.

**Disclosure of interest** The author declares that he has no conflicts of interest concerning this article.

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Lecture


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