T-cell mediated immunity in Wegener's granulomatosis
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CHAPTER 1

Introduction to this thesis

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Introduction

Wegener’s granulomatosis (WG) is a systemic autoimmune vasculitis affecting small and medium-sized vessels. It is characterized by extravascular necrotizing granulomatous inflammation in the upper and/or lower respiratory tract combined with systemic small vessel vasculitis manifested in the kidney as pauci-immune necrotizing crescentic glomerulonephritis. WG has two different clinical stages termed localized and generalized disease. In localized disease WG is, in most cases, restricted to the upper and/or lower respiratory tract, and in generalized disease systemic vasculitis affecting various organs including the kidneys is present. In many cases the disease starts as localized disease and progresses to the generalized phase, whereas in few patients (10-15%) the disease remains in the localized phase for as yet unknown reason. WG has an estimated prevalence of 26/million in the United States and 40-60/million in Europe. The disease can affect individuals at any age, with a peak incidence between the 4th and 5th decade, and is slightly more common in men. Ninety seven percent of all patients are Caucasian, 2% are Black and 1% are of another race.

This disease was initially reported in two patients by Heinz Klinger, a German Medical student, in 1931. Five years later, Friedrich Wegener, a German pathologist, described a distinct syndrome in 3 additional cases and recognized a collection of cells in inflamed tissues that he termed granuloma. Hence the disease became known as Wegener’s granulomatosis. He suggested that the disease was induced by an allergic reaction to an infection. In many cases of vasculitis, particularly allergic vasculitis, lesions result from deposition of immune-complexes. However, immunohistologic evaluation of lesions in WG, particularly in the kidneys, demonstrated an absence or paucity of immunoglobulins. The first hint for a pathogenic autoantibody in WG arose in 1982, when Davies and coworkers reported the presence of serum anti-neutrophil antibodies in eight patients with pauci-immune necrotizing glomerulonephritis. This observation was confirmed by Hall et al. in 1984. In 1985, van der Woude et al. established the close association between active WG and anti-neutrophil cytoplasmic autoantibodies (ANCA) suggesting an autoimmune pathogenesis of WG. These autoantibodies were detected by indirect
immunofluorescence on ethanol-fixed neutrophils. This assay revealed two
different patterns of ANCA: a cytoplasmic pattern (c-ANCA) and a
perinuclear pattern (p-ANCA), which suggests different antigenic
specificities of ANCA\textsubscript{s}\textsuperscript{14,15}. Subsequent studies identified the two major
antigenic specificities of ANCA, that are proteinase 3 (PR3-ANCA producing
a c-ANCA pattern) and myeloperoxidase (MPO-ANCA producing a p-ANCA
pattern)\textsuperscript{15-18}. The majority of patients with WG are positive for PR3-ANCA
(80-90\%). The presence and level of PR3-ANCA correlates with disease
activity in WG, which suggests a pathophysiological role of these
autoantibodies.

Pathogenetic role of PR3-ANCA in vasculitis

Although the etiology of WG remains unclear, several studies have
shed light on the immune mechanisms that may play a role in the
pathophysiology of this disease. Based on \textit{in vitro} and animal studies\textsuperscript{19-24},
postulated mechanisms for ANCA-mediated vasculitis can be summarized
as follows: cytokines released during an inflammatory reaction, such as
tumor necrosis factor-\(\alpha\) (TNF\(\alpha\)) or interleukin-1 (IL-1), are capable to pre-
activate (prime) resting neutrophils which results in surface expression of
PR3, so becoming accessible for interaction with ANCA. These pro-
inflammatory cytokines also induce upregulation of adhesion molecules on
the vascular endothelium as well as on neutrophils during priming. As a
consequence, primed neutrophils adhere to the endothelium and these
adherent cells expressing PR3 can be fully activated by ANCA. It is
assumed that ANCA bind with their F(ab\textsuperscript{'})\textsubscript{2} -fragments to surface expressed
PR3 on neutrophils and also interact via Fc-fragments with Fc-receptors,
particularly the Fc\(\gamma\) RIIa-receptor, on the same cell, which enhances
neutrophil activation resulting in degranulation, release of lytic enzymes and
superoxide production. These toxic products cause endothelial cell injury
ending up in vasculitis.

ANCA antibodies belong primarily to the IgG isotype with a
predominance of IgG1- and IgG4 subclasses, suggesting that production of
these autoantibodies is antigen-driven and T-cell-dependent and providing
hints for the involvement of T-cells in disease pathogenesis\textsuperscript{25}.
Chapter 1

T-cell involvement in WG

Several observations support the involvement of T-cells in the pathogenesis of WG. Important evidence regarding their role in disease manifestation came from the clinical observation that remission could be induced in WG-patients by antibodies directed at T-cells\textsuperscript{26,27}. This finding raises the question whether tissue injury and vasculitis may also be mediated by an aberrant T-cell mediated immune response. Indeed, abnormal phenotype and function of T-cells was observed in patients with WG. Percentages of activated T-cells in the peripheral blood increased in patients with active disease as compared to healthy controls, and this increase persisted during remission\textsuperscript{28}. Also, elevated levels of soluble interleukine-2 receptor (sIL2R), a T-cell activation marker, were found in serum from patients during major relapses of the disease\textsuperscript{29}. The majority of expanded circulating T-cells in WG-patients lack expression of the co-stimulatory molecule CD28 and show upregulation of the differentiation markers CD57 and CD45RO which are features of effector memory T-cells\textsuperscript{30-33}. Analysis of patients’ sera for soluble markers associated with Th1-cells (interferon [IFN]-\(\gamma\), sCD26) and Th2-cells (interleukin [IL]-4, IL-5, IL-10, IL-13, sCD23, sCD30) disclosed a shift towards a Th2-type response in patients with active generalized disease\textsuperscript{34}. Consistently, a relative increase of cells expressing Th1-associated markers (IFN\(\gamma\), CD26, and CCR5) was detected in nasal granulomatous lesions from WG-patients with localized disease, whereas Th2-associated markers (IL-4, and CCR3) were dominated in generalized disease, which also suggests a shift towards a Th2-response during systemic involvement\textsuperscript{35,36}. In the peripheral blood, upregulated expression of CCR3 as well as CCR5 was observed on memory CD28T-cells, both in localized and generalized disease, suggesting migratory capacity of these cells\textsuperscript{37}. Importantly, the ligand (RANTES) for CCR3 and CCR5 is expressed in granulomatous lesions of the respiratory tracts which favor migration of these cells into inflammatory sites\textsuperscript{38,39}. Indeed, lymphocytes accumulating in lung lesions of WG-patients with active disease appear to consist mainly of CD4\(^+\)CD28 memory T-cells with less CD8\(^+\)T-cells\textsuperscript{38}. These cells, thus, could contribute to the formation of granuloma and tissue damage and could constitute a novel target for therapy.
Aim and outline of this thesis

The capacity of the immune system to trigger immune responses via effector T-cells plays an important role in determining disease outcome. In T-cell mediated immune responses, naïve T-cells are induced to differentiate into T-cells with effector function (Th1, Th2, and Th17) or T-cells with regulatory function (TReg cells). Abnormal skewing of the immune response towards effector T-cells away from TReg cells as well as imbalance between effector- and TReg cells, more specifically, impairment of TReg cell function, may contribute to the development and/or progression of WG and may participate in vascular damage in this disease. The aim of the present study was to investigate the phenotype and function of pathogenic T-cells in WG and to elucidate the role of TReg cells in this disease.

In chapter 2, we review the literature regarding the role of T-cells in ANCA-associated vasculitis. In particular, attention is given to the involvement of effector memory CD4⁺T-cells in the pathogenesis of this autoimmune inflammatory disease. In order to analyze the effector limb of the immune system in WG, we investigate in chapter 3 the distribution and state of activation of peripheral naïve and memory CD4⁺ and CD8⁺T lymphocytes in this disease as well as the functional role of memory T-cells based on the expression of type1- and type2-associated surface markers, in patients in remission and patients with active disease. This study includes cross-sectional and follow-up data on lymphocyte subsets. Since several studies have described effector T-cells in urine from patients with renal inflammation, we analyzed the presence of effector T-cells in the urinary sediment as a measure of renal disease activity in patients with WG. The results of this analysis are described in chapter 4. The homeostasis of peripheral naïve and memory T-cells is controlled by regulatory T-cells (TReg). A decrease in frequencies and/or defective function of TReg cells have been documented in several systemic autoimmune diseases as reviewed in chapter 5. Therefore, we investigate in chapter 6 whether abnormalities in TReg cells occur in patients with WG. Besides TReg cells, IL17-producing Th cells (Th17) are thought to be key initiators and regulators of inflammation. In chapter 7, we assess the distribution of Th1/Th2/Th17 cells and investigate the presence of Th17-cells specific for the autoantigen PR3 in
WG-patients. Finally, summary and general discussion as well as future perspectives are presented in chapter 8.

REFERENCES


