

# Cellular and Molecular Aspects of Goodpasture Syndrome

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Goodpasture syndrome, a rare human autoimmune disorder, is characterized by the presence of pathogenic autoantibodies that react with the components of the glomerular basement membrane. The clinical condition of the Goodpasture syndrome is characterized by an acute necrotizing glomerulonephritis, often with accompanying pulmonary hemorrhage. Notably, the Goodpasture antigen has been localized to the noncollagenous domain of the  $\alpha 3$  chain of type IV collagen. Additionally, human leukocyte antigen-DR2, and to a lesser extent human leukocyte antigen-DR4, have been identified as important restriction elements. The role of T cells in Goodpasture syndrome is indicated by the highly restricted specificity of the antibody response and the strong major histocompatibility complex class II association. In this review article, we briefly describe the latest views on the molecular and cellular themes of Goodpasture syndrome.

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## INTRODUCTION

In 1919, Ernest Goodpasture first described the occurrence of rapidly progressive glomerulonephritis (GN) associated with lung hemorrhage in an 18-year-old man with influenza infection. The term, Goodpasture syndrome (GS), was first used by Stanton and Tange in 1958 to describe the combination of pulmonary hemorrhage and GN.<sup>1</sup> However, in about one-third of patients with GS, direct immunofluorescence of kidney biopsy demonstrates linear binding of autoantibodies to the glomerular basement membrane (GBM). The anti-GBM antibodies are the noncollagenous-1 (NC1) domain of the  $\alpha 3$  chain in type IV basement membrane collagen ( $\alpha 3$ [IV] NC1).<sup>2</sup> Over the years, as the etiology of the disease has become clearer, and GS is now known to be associated with the presence of anti-GBM autoantibodies, both circulating and depositing in the kidneys.<sup>3</sup> The clinical spectrum of this disease is variable. In some cases, GN with anti-GBM antibodies may be found without pulmonary hemorrhage.<sup>4-6</sup>

Despite being thought of as a prototypic antibody-

mediated autoimmune disease, it is becoming apparent that both humoral and cellular immune mechanisms act in concert to initiate and perpetuate disease.<sup>7</sup> Accumulating data have shed light on the molecular pathogenesis of anti-GBM disease and provided a more complete framework, on which we can build our understanding of autoimmune kidney disease.<sup>7</sup>

## EPIDEMIOLOGY

Goodpasture syndrome is an uncommon disease, having an incidence of 0.5 to 1 cases per million of the population with a slight preponderance of males to females. The age at which the onset of the disease starts ranges from 10 to 90 years with bimodal peak distributions around 30 to 60 years.<sup>8</sup> The preponderance of individuals showing the disease around 30 years are men who often present with pulmonary hemorrhage. Those around 60 years are mostly women who commonly have GN alone.<sup>9</sup> The disease is more common in Caucasians than Blacks, and is common in the Maori people of New Zealand.<sup>10</sup> The incidence of the disease

can present all-year round, but it is thought to increase in the spring and early summer. Some localized outbreaks have been associated with infection. Reports of temporal and geographic clustering of the disease suggest that a pathogen or environmental factor may be involved.

### CLINICAL ASPECTS AND DIAGNOSIS

Goodpasture syndrome may be associated with either GN, lung haemorrhage, or both. It is sometimes defined as a doubling of plasma creatinine with partial creatinine clearance within 3 months; however, kidney function may be lost rapidly within days. Lung hemorrhage has been reported in up to two-thirds of patients, which appears dependent on the exposure to pulmonary irritants. For instance, tobacco smoking is associated with a high prevalence of lung hemorrhage in patients with GS.<sup>11-13</sup> The clinical spectrum of the disease extends from mild lung or kidney disease alone to life-threatening combinations of both.

Diagnosis of GS is made by detection of circulating anti-GBM antibodies, and more specifically, the anti- $\alpha 3(\text{IV})$  NC1 antibodies on solid-phase immunoassays.<sup>14</sup> Kidney biopsy provides definitive diagnosis. On light microscopy, the early changes are of a focal proliferative GN. This proliferative response usually progresses to necrosis and extensive crescent formation with interstitial inflammation. The pathognomonic finding on direct immunofluorescence is the linear deposition of immunoglobulin G (IgG) along the GBM and sometimes along the distal tubular basement. Previous studies have shown that two-thirds of the studied cases show linear binding of complement component 3 whilst the other one-third also show IgA and/or IgM binding.<sup>15,16</sup> Measurement of circulating antibodies levels can be used to monitor disease progress and the outcome of treatment. The GBM is directly accessible to circulating antibodies through the fenestration in the glomerular capillary endothelium cells. The main immunoglobulin subclass involved in GS is IgG1, which contributes to the complement fixation. Antibody-mediated damage occurs by complement activation and recruitment of neutrophils and macrophages.<sup>17</sup>

### ETIOLOGY

Like other autoimmune diseases, the etiology

of GS is multifactorial. There is evidence that the interplay of immunologic, humoral, and environmental factors in genetically susceptible individuals results in GS.

### Environmental Factors

The current understanding of autoimmune disorders suggests that an environmental factor initiates a disease in a genetically susceptible individual. In GS however, as in most autoimmune disorders, the precise initiating events are not known. Hydrocarbons are known to cause damage to pulmonary endothelial cells and so could expose components of the alveolar basement membrane to cells of the immune system, initiating an immune response. There is some evidence suggesting a role for disparities in occupational exposure and smoking as one of the environmental factors predisposing to lung hemorrhage in GS.<sup>18</sup> The peak of incidence in the spring and early summer suggests a role for viral infections and reaction to airborne pollen. However, no specific viral or bacterial infection has been identified preceding the onset of the disease.<sup>19</sup>

### Genetic Factors

The importance of genetic factors, especially the genes of major histocompatibility complex has been increasingly recognized in determining susceptibility to autoimmune diseases. Because of the low incidence of GS, it is not possible to examine the inheritance within affected families of genes that may predispose to this disease. There are however several reports of GS occurring in siblings and in identical twins although there are also cases of identical twins discordant for the disease.<sup>20-22</sup> Population studies have shown that GS is strongly associated with specific major histocompatibility complex class I and class II genes.<sup>23,24</sup> Another genetic factor that has been associated with GS is the Gm allotype of the IgG (IgG heavy chain constant region).<sup>25</sup> The Goodpasture antibody epitope, as yet undefined, is currently the focus of molecular mapping studies by various groups worldwide.

### PATHOGENESIS OF GOODPASTURE DISEASE Availability of Goodpasture Antigen

The target of anti-GBM antibodies, the  $\alpha 3(\text{IV})$  NC1, is distributed on selected basement membranes

throughout the body, especially those in the lung, the kidneys, the choroid plexus, the uveal tract, the thymus, and the cochlea. Although all patients with GS develop GN, only 40% develop pulmonary hemorrhage and very few develop ocular lesions and none become deaf. This pattern of pathogenesis reinforces the point made earlier that the autoimmune disease only develop upon recognition of the autoantigen ( $\alpha 3$ [IV] NC1) by the immune system. The recognition of the antigen, however, depends on its availability to the immune cells in different tissues as discussed below.

In the case of the kidney, the GBM supports the endothelial cells of the glomerular capillaries on one side and the epithelial cells of the urinary space on the other side. The endothelial cell, the GBM, and the foot processes of the epithelial cell form the filtering unit of the glomeruli. Water, small solutes, and ions are allowed to pass into the urinary space, while plasma proteins and macromolecules are retained in the capillaries. As such, the endothelial cells are fenestrated, so that the GBM is exposed to circulating leukocytes, particularly, B cells. This pattern facilitates the recognition of the antigen in the GBM by B cells and the production of the anti-GBM antibodies. The major components of the GBM are type IV collagen, laminin, and heparin sulphate proteoglycans.

In the lung, the basement membrane of the alveoli separates alveolar epithelial cells from capillary endothelial cells, which are joined by tight junctions. Injury to the endothelial lining is necessary for antibodies to gain access to alveolar basement membrane. It is presumed that the permeability of alveolar capillary endothelial cells is increased by direct toxic effects (ie, cigarette smoke) acting within the lungs, and thus, exposing the previously concealed alveolar basement membrane to circulating antibodies. In the ear, however, the cochlea basement may remain inaccessible to autoantibodies at all times.

#### **Fitness of Target Antigen to anti-Glomerular Basement Membrane Antibodies**

In the past 2 decades, many investigators have focused on the molecular nature of the antigen of renal GBM that binds to Goodpasture autoantibodies. Knowledge of the exact antigen is of fundamental importance in delineating the molecular basis of the disease and in designing

diagnostic tests and specific therapies. It is expected that the epitope for both B and T cells may be on the same protein as a result of the requirement of T cell help for B cells to produce the specific antibody. Production of the autoantigen as a recombinant molecule for the in vitro study of the pathogenesis of GS is necessary, since it is only possible to purify small quantities of the human autoantigen. The recombinant antigen produced in *Escherichia coli* is insoluble and is poorly recognized by patients' autoantibodies. Goodpasture syndrome autoantibody binding depends on the antigen conformation. Thus, it is essential that the tertiary structure of the autoantigen is preserved.

The monomeric building block of type IV collagen is a triple helical molecule which is made up of 6 different  $\alpha$  chains,  $\alpha 1$  to  $\alpha 6$ . Each chain is characterized by an NC1 of about 230 amino acids at the carboxyl terminus, along collagenous domain of about 1400 amino acids and 7S domain at the amino terminal.<sup>26</sup> The triple helical monomers are assembled into a suprastructure through end-to-end interactions of NC-1=NC-1 dimers and 7S-7S tetramers. The NC1 hexamer can be excised from the suprastructure by collagenase digestion yielding different kinds of hexamers, dimers, and monomers that differ in the  $\alpha$  chain of the original of NC1 subunits and with molecular weights of 160 kD to 180 kD, 43 kD to 56 kD, and 24 kD to 30 kD, respectively. The  $\alpha 1$  and  $\alpha 2$  are found in all vascular basement membranes, but  $\alpha 3$  and  $\alpha 4$  are tissue specific. The complete amino sequence of these six chains of human type IV collagen has been reported.<sup>27,28</sup> The pI of the  $\alpha$  chain varies over a wide range as follows:  $\alpha 1$ , pI = 8.5;  $\alpha 2$ , pI = 4.6;  $\alpha 3$ , pI > 9.3.<sup>29</sup>

Glomerular basement membrane is similar in structure to basement membranes elsewhere; however, GBM is similar in structure to basement membranes elsewhere, otherwise, it contains  $\alpha 1$  to  $\alpha 5$  chains, but does not contain  $\alpha 6$ .<sup>30</sup> The Goodpasture antigen towards which anti-GBM autoantibodies form has been found to reside in the  $\alpha$  chain of type IV collagen.<sup>31</sup> The corresponding epitope has also been characterized and located within the globular NC1 domain of the  $\alpha 3$  chain.<sup>32</sup> Two-dimensional western blotting studies have shown that the autoantibody response is largely restricted to this cationic  $\alpha 3$  NC1 domain in all patients.<sup>33</sup> The genes for all the six  $\alpha$  chains of

type IV collagen have been cloned,<sup>13</sup> and the recombinant proteins are expressed in prokaryotic and eukaryotic systems.<sup>34</sup> It has been shown with using these proteins that sera from 85% of patients with GP react exclusively with the  $\alpha 3(\text{IV})$  NC1. In a few patients, there is limited reactivity with  $\alpha 5$ ,  $\alpha 4$ , and  $\alpha 1(\text{IV})$  NC1 domains.<sup>35</sup> Previous studies have also shown that a component of  $\alpha 3(\text{IV})$  NC1 serves as a T cell autoantigen, since T cell proliferation has been observed in response to purified affinity components of GBM, and to  $\alpha 3(\text{IV})$  NC1 monomers purified by gel filtration and reverse-phase high-performance liquid chromatography.<sup>33</sup>

### Association of Goodpasture With Human Leukocyte Antigen Genes

Similar to other autoimmune diseases, GS is strongly associated with the inheritance of human leukocyte antigen (HLA) class II genes with 80% of patients carrying the HLA-DRB1\*15 haplotype. The HLA-DR and HLA-DQ class II molecules, whose primary function is to bind and present peptides derived from extracellular proteins to CD4+ cells, play a central role in the regulation of immune responses. It is likely, therefore, that the HLA-DRB1\*1501 or DQB\*0602 alleles contained in the DRB1\*15 haplotype are the of primary susceptibility genes in the GS. In order to study T-cell recognition of the GS antigen-HLA complex, it was necessary first to define which HLA-DR or HLA-DQ alleles conferred susceptibility to the disease and to characterize these HLA molecules, as they would most likely be involved in the binding and presentation of the autoantigen.

Serological typing studies in patients with anti-GBM disease have shown an increased incidence of HLA-DR2 compared with normal controls in several studies worldwide.<sup>22</sup> An association between the severity of the disease and the major histocompatibility complex class I gene has been described.<sup>23</sup> For instance, an association between HLA-DR2 and HLA-B7 and disease severity has also been reported,<sup>24</sup> where patients with both DR2 and B7 have significantly higher creatinine levels and crescent scores than those with HLA-DR2 alone. The association of the HLA-DR2 specifically with susceptibility to GS was originally described in a serological typing study of 17 Caucasian patients,<sup>23</sup> and it was confirmed in a follow-up study of 38 patients.<sup>24</sup> The DR2 specificity, however,

is encoded by at least 5 HLA-DRB1\*15 and 6 HLA-DRB1\*16 alleles, which are closely linked to HLA-DRB5, HLA-DQA, and HLA-DBQ genes. Analysis of HLA of a second group of 53 British patients showed that this association was with the HLA-DRw15 and HLA-DRw6 haplotypes,<sup>36</sup> and 21 of 23 American patients, studied using a polymerase chain reaction-based method, inherited the HLA-DRB1\*1501 and HLA-DQB\*0602 haplotypes.<sup>37</sup> These results are similar to those reported on Australian patients.<sup>38</sup> An association with specific Gm allotypes of the IgG heavy chain constant region has also been reported; Gm1, 2, 21 (axa) was present in 54% of patients compared with 16% of controls.<sup>25</sup>

### IMMUNOPATHOGENESIS

In patients with GN, the linear binding of IgG to GBM has been demonstrated by direct immunofluorescence of kidney biopsies.<sup>2</sup> Circulating anti-GBM antibodies have been detected in patients' sera using a collagenase-solubilized preparation of human or sheep GBM, further purified to the monomeric components by high-performance liquid chromatography, as a ligand for enzyme-linked immunosorbent assay.<sup>14</sup> The anti-GBM antibodies are predominantly made up of IgG1 and IgG4 subclasses, although IgM and IgA autoantibodies may be present in up to one-third of the cases. Total immunoglobulin and serum complement levels are usually normal.<sup>13</sup> Clinical improvement is directly related to a fall in circulating anti-GBM antibodies.<sup>9</sup>

Autoantibodies in GS have been shown to be pathogenic in passive transfer experiments in the 1960s, where antibodies, purified from the serum of patients with GS, were injected into squirrel monkeys, who developed proteinuria within 24 hours, with linear binding of the antibodies to the GBM and a proliferative but not crescentic nephritis. The close relationship between the antibody levels and the severity of disease and the effectiveness of plasma exchange, which removes circulating antibodies when treating GS, provides further evidence for a profound role of antibodies in the pathogenesis of this disease.<sup>39</sup> The antibody epitope has not yet been clearly defined. The epitope is conformational since the reduction of the internal disulphide bonds of  $\alpha 3(\text{IV})$  NC1 leads to loss of recognition by autoantibodies. There is



evidence that amino terminal end of  $\alpha 3(\text{IV})$  NC1, including the junctional region with the triple helix, is essential for antibody recognition.<sup>40</sup>

Although the pathogenesis of GS is mediated by the anti-GBM antibodies, it has been established that autoantibodies alone are not sufficient to induce the classical disease. Furthermore, T cells from patients with GS have also been shown to proliferate in vitro to affinity purified Goodpasture antigen.<sup>33</sup> With this regard, there is increasing evidence for the importance of cell-mediated immunity in the initiation and maintenance of GS. The highly restricted antibody response and strong associations suggest that the autoimmune response is likely to be a T-cell-dependent type. In line with this notion, in the only reported case of GS occurring in pregnancy,<sup>41</sup> an unaffected baby with circulating anti-GBM antibodies was born shortly before the mother died from severe GN. This report suggests that the pathogenesis of GS involves cell-mediated immune damage in addition to humoral mechanisms. Furthermore, the strong association between HLA-DR22 and GS suggests the involvement of the trimolecular (TCR-peptide major histocompatibility complex class II) complex in the pathogenesis of GS. T cell appears to be involved not only in B-cell activation, but also in tissue injury. Assessment of kidney biopsy specimens from patients showed marked T cell and macrophage infiltration in the inflamed glomerulus. Maximal cell numbers were present in the early stages of GN with T-cell influx preceding macrophage accumulation. Direct evidence of the importance of cell-mediated immunity in the disease has been accumulated through experiments in animal models,<sup>42</sup> where T cells and macrophages infiltration have also been demonstrated in experimental autoimmune glomerulonephritis, a rat model for GS that is induced by the injection of an autoantigen.

T helper cells are an important element of the host's immune response to eliminate invading pathogens. Several subsets of T helper cells exist, including the T helper 17 subset that produces interleukin (IL)-17A. Interleukin-17A induces pro-inflammatory cytokines and chemokines and mediates neutrophil recruitment to the site of infection.<sup>43,44</sup> T helper 17 cells have themselves been recently shown to induce antigen-specific cell-mediated proliferative glomerulonephritis,

and there is increasing evidence to implicate T helper 17 cells in anti-GBM disease.<sup>43,44</sup>

Based on the type of the antigen presenting cells, the nature of antigens, and the cytokine milieu, CD4+ T cells exhibit high plasticity to differentiate into different subsets with stimulatory or regulatory functions.<sup>45</sup> For instance, T helper cells can differentiate into T helper 1 and T helper 2 type cells, which produce inflammatory (IL-2, interferon- $\gamma$ , tumor necrosis factor- $\alpha$ , and IL-12) and anti-inflammatory (IL-4, IL-10, and transforming growth factor- $\beta$ ) cytokines, respectively.<sup>45,46</sup> T helper cells can also differentiate into a third type of T helper cells designated as T helper 17 type cell that produces IL-17 and mimics the effects of T helper 1 cells. With this regard, it has been found previously in a preclinical model that crescentic glomerulonephritis and lung hemorrhage associate with the emergence of an IL-12/T helper 1-like T-cell profile, which was found to be attenuated in disease-susceptible mice tolerized orally to  $\alpha 3(\text{IV})$  collagen before immunization.<sup>47,48</sup> Interestingly, a recent study showed that mice deficient in IL-23 can be protected from GS, coinciding with lower autoantibody titers, less glomerular IgG deposition, and decreased production of inflammatory cytokines including the typical T helper 1 cytokine interferon- $\gamma$  and tumor necrosis factor- $\alpha$  as well as IL-17A and monocyte chemoattractant protein 1.<sup>49</sup> These data suggest a protective role for interferon- $\gamma$  and immunopathogenic roles for IL-23 and IL-17A. As such, therapeutic regimes aiming at targeting these molecules can open a new avenue for successful treatment of this disease.

Under certain conditions, T helper type cells can differentiate into regulatory T cell, which produces immunosuppressive cytokines such as transforming growth factor- $\beta$  and IL-10. These regulatory T cells, which represent about 5% to 10% of CD4+ T cells in the steady state, play a central role in immune homeostasis and in preventing autoimmune diseases.<sup>50,51</sup> Regulatory T cells exist naturally and are called natural regulatory T cells expressing CD25 and Foxp3. T cells can also convert into regulatory T cells upon certain antigen recognition and are called antigen-specific regulatory T cells that secrete IL-10 and/or transforming growth factor- $\beta$ . Indeed, regulatory T cells are required to control the infection-induced immunopathology

in a host, including autoimmunity.<sup>52</sup> In a recent study using a preclinical model, it has been shown that the reduced severity of GS induced in IL-12 deficient mice by anticollagen was not due to increased regulatory T cells since these mice did not show increased proportions of CD4+ CD25+ FoxP3+ cells or IL-10 levels early in the immune response.<sup>49</sup> In a clinical study, in contrast, the peripheral tolerance, involving regulation by antigen-specific CD25+ regulatory cells, has been found to play a significant role. This study demonstrated no evidence of accumulation of T cell population with regulatory phenotype at the time of acute presentation. However, at the time of chronic presentation (ie, from 3 months onward), a T cell population with a regulatory phenotype (CD25+) capable of suppressing the response to the Goodpasture autoantigen was observed. Following depletion of these regulatory T cells, the frequencies of autoreactive-, GBM-, and collagen  $\alpha 3(\text{IV})\text{NC1}$ -specific T cells were significantly increased, with 71% convalescent patients.<sup>53,54</sup> These data demonstrate that in GS, regulatory CD25+ T cells might play a significant role in suppressing the autoimmune response. The emergence of these cells at the time of chronic presentation may explain the reduced disease severity at this late stage of the disease. Therefore, unraveling the mechanisms required for the development and elaboration of these cells would allow development of novel therapeutic approaches for inducing hyporesponsiveness in Goodpasture disease.

## TREATMENT

Goodpasture syndrome is fatal if untreated, since it results in a progressive impairment of kidney function in affected individuals. Early series showed a mortality rate of almost 100% at 6 months, either due to end-stage renal failure or pulmonary hemorrhage. The advent of dialysis prolonged survival, but patients remained dialysis dependent. As the autoimmune nature of this disease became clearer, immunosuppressive therapy was introduced. Intensive plasma exchange to remove circulating autoantibodies with concurrent administration of corticosteroids (prednisolone) and cytotoxic drugs (cyclophosphamide) to prevent their resynthesis has been reported to be successful unless the patient is already anuric or the plasma creatinine is greater than 600  $\mu\text{mol/L}$ .<sup>55</sup> Plasma exchange may

have other immunoregulatory effects and could potentiate the effects of immunosuppressive drugs in controlling autoimmunity.<sup>55</sup> These treatment modalities have made kidney transplantation a viable alternative in these patients.

Levy and colleagues examined 71 treated patients with anti-GBM antibody disease who received plasma exchange, prednisolone, and cyclophosphamide. They found that patients with a creatinine concentration less than 500  $\mu\text{mol/L}$  (5.7 mg/dL) had 100% patient survival and 95% kidney survival at 1 year and 84% patient survival and 74% kidney survival at the last follow-up. Additionally, in patients with a creatinine concentration of 500  $\mu\text{mol/L}$  or more ( $\geq 5.7$  mg/dL) who did not require immediate dialysis, kidney survival rates were 83% and 82% at 1 year and 62% and 69% at the last follow-up. In patients with dialysis-dependent kidney failure, survival rates were 65% and 8% at 1 year and 36% and 5% at the last follow-up, respectively.<sup>56</sup>

The potential side effects of nonspecific immunosuppression and the severity and life-threatening nature of the disease, if left untreated, continue to propel research towards a better understanding of the mechanisms of the disease and the development of more specific treatment regimens. In patients with end-stage renal disease due to anti-GBM-antibody disease, the recurrence rate after transplantation is as high as 50% and delaying kidney transplantation until circulating anti-GBM antibody levels have been undetectable for at least 12 months reduces the recurrence rate to 5% to 15%.<sup>57</sup>

## CONCLUSIONS

Although, GS is a rare human autoimmune disorder, it can result in progressive impairment of kidney function in affected individuals and is fatal if untreated. Understanding the molecular and cellular themes of this disorder will lead to better treatment.

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## CONFLICT OF INTEREST

None declared.

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