Goodpasture's autoimmune disease — A collagen IV disorder

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Abstract

Goodpasture's (GP) disease is an autoimmune disorder characterized by the deposition of pathogenic autoantibodies in basement membranes of kidney and lung eliciting rapidly progressive glomerulonephritis and pulmonary hemorrhage. The principal autoantigen is the α345 network of collagen IV, which expression is restricted to target tissues. Recent discoveries include a key role of chloride and bromide for network assembly, a novel posttranslational modification of the antigen, a sulfilimine bond that crosslinks the antigen, and the mechanistic role of HLA in genetic susceptibility and resistance to GP disease. These advances provide further insights into molecular mechanisms of initiation and progression of GP disease and serve as a basis for developing of novel diagnostic tools and therapies for treatment of Goodpasture's disease.

Introduction

Over the last half a century of studies, Goodpasture's (GP) disease has emerged as a model disorder for exploring mechanisms that underlie autoimmunity. GP disease is an organ-specific autoimmune disorder characterized by linear deposits of autoantibodies along the glomerular basement membrane (GBM) (Fig. 1), rapidly progressive glomerulonephritis, and often pulmonary hemorrhage. Pathogenic autoantibodies target specific type of collagen IV network classifying GP disease as an autoimmune collagen IV disorder. In the absence of pulmonary lesions, which occurred in about half of the patients, it is often defined as anti-GBM disease. GP is a rare disorder with the incidence of 1–2 cases per 1 million population per year [1,2]. Without emergent treatment, it rapidly progresses to the end-stage renal failure with a permanent loss of kidney function and fatal outcome in about half of the patients [3,4]. Early detection and combination treatment by the plasma exchange and immunosuppression to remove pathogenic autoantibodies significantly improve renal outcome and survival during last several decades [5–7]. GP disease affected both man and women with about equal frequency. The age distribution is bimodal with the first peak of occurrence during the third decade with a higher prevalence among men, and frequently observed pulmonary involvement. The second peak occurs around the age of 60 years, less frequently associated with pulmonary symptoms. Goodpasture's disease is a monophasic disorder with low recurrent rate [2,8].

In a landmark study Lerner et al. showed that passive transfer of circulating or kidney-bound autoantibodies from GP patients to recipient monkeys produced severe glomerulonephritis, which provides the first

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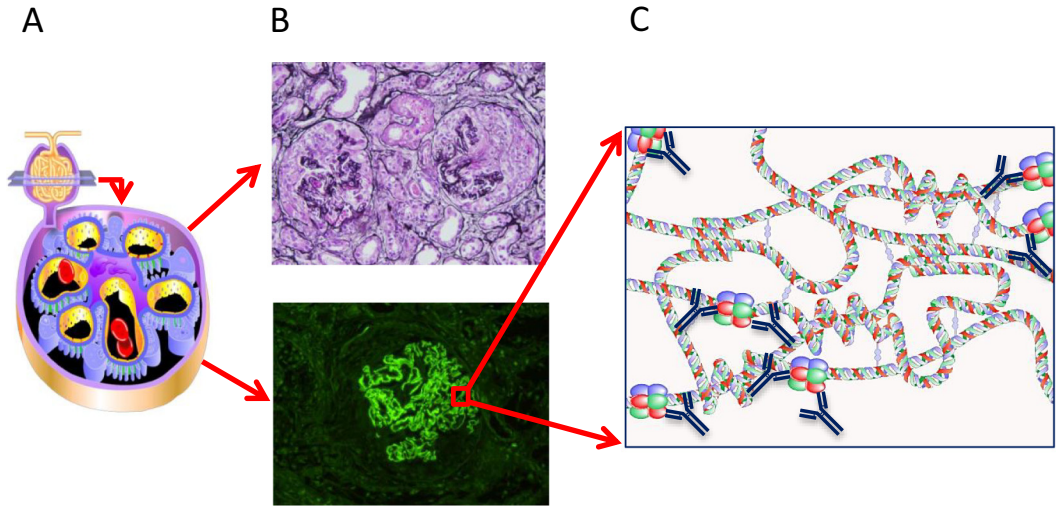

Fig. 1. A, Schematic diagram of the kidney glomerulus showing glomerular basement membrane (GBM), a key component of filtration barrier, as thin layer (blue ribbon) between endothelial cells (yellow) and podocytes (blue). B, Light and fluorescent microscopy of renal biopsy from Goodpasture's disease patient. Crescentic glomerulonephritis, a marker of severe glomerular injury, is made up of proliferating epithelial cells that line the Bowman's capsule, and infiltrating macrophages (top, Jone's silver stain). Immunofluorescent staining shows characteristic linear deposition of IgG autoantibody along the GBM (bottom). C, NC1 hexamer of α345 collagen IV network in GBM is a target autoantigen for pathogenic Goodpasture autoantibody.

evidence that antibody per se can cause the autoimmune disease [9]. Subsequent search for the antigen identified the non-collagenous (NC1) domain of a novel α3 chain of collagen IV as a target for the pathogenic autoantibody in the glomerular and alveolar basement membranes [10,11]. Moreover, immunization with the recombinant α3 NC1 protein induced severe proteinuria and glomerulonephritis in animal models that closely resembled human GP disease [12,13]. Collectively, these findings fulfill criteria for Koch's postulates as applied to an autoimmune disorder, demonstrating a direct cause-effect relationship between a self-antigen and a pathogenic autoantibody in GP disease.

Following studies led to the discovery of the α4, α5 and α6 chains and the emergence of collagen IV as a family of six α-chains (α1–α6), which assembled in three distinct networks [14–16]. Collagen IV is a main constituent of all basement membranes, specialized form of extracellular matrix, which support tissue integrity and perform numerous key functions including cell signaling, morphogenesis, and tissue regeneration [17]. While Goodpasture's disease has been long recognized as an autoimmune collagen IV disorder, other basement membrane components are also targeted by antibodies in several autoimmune diseases [18].

Later studies identified distinct autoantibody targeting α5 NC1 domain in majority of GP patients and demonstrated their pathological relevance [19,20]. This defined the α345 network of collagen IV as GP autoantigen (Fig. 1), which expression is restricted to the basement membranes of kidney and lung underlying the pathogenesis of GP disease. Consequently, four pathogenic epitopes for GP autoantibodies were mapped within α3 and α5 NC1 domains [19,21,22].

Etiology of the GP disease remains largely unknown, but recent studies emphasized the role for conformational changes within α345 collagen IV network in eliciting an autoimmune response [19]. These conformational changes might result from aberrant posttranslational modifications of the autoantigen. In this respect, two enzymes were discovered recently, which might interact with Goodpasture autoantigen and potentially form a ternary complex in the GBM. Peroxidasin, an extracellular heme peroxidase, catalyzes the formation of sulfilimine crosslinks in collagen IV, which confer structural reinforcement to collagen networks and immune privilege to Goodpasture autoantigen [23]. Consequently, dysregulation of peroxidasin may perturb networks structure leading to the autoimmune disease. Second enzyme, Goodpasture binding protein (GPBP) is unusual serine protein kinase which phosphorylates human α3 NC1 domain [24]. GPBP is strongly expressed in human GBM, and its overexpression has been associated with an expanded and disorganized GBM in mice [25], suggesting that aberrant expression or activation of GPBP might result in increased phosphorylation of the autoantigen and initiate the autoimmune response in GP disease [24].

In the current review, we focus on recent advances in the characterization of pathogenic autoantibodies, architecture of the Goodpasture autoantigen and structure of the GP epitopes. We also summarized recent findings on the role of T cell tolerance in the

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