Review

Basement membranes and autoimmune diseases

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Abstract

Basement membrane components are targets of autoimmune attack in diverse diseases that destroy kidneys, lungs, skin, mucous membranes, joints, and other organs in man. Epitopes on collagen and laminin, in particular, are targeted by autoantibodies and T cells in anti-glomerular basement membrane glomerulonephritis, Goodpasture's disease, rheumatoid arthritis, post-lung transplant bronchiolitis obliterans syndrome, and multiple autoimmune dermatoses. This review examines major diseases linked to basement membrane autoreactivity, with a focus on investigations in patients and animal models that advance our understanding of disease pathogenesis. Autoimmunity to glomerular basement membrane type IV is discussed in depth as a prototypic organ-specific autoimmune disease yielding novel insights into the complexity of anti-basement membrane immunity and the roles of genetic and environmental susceptibility.

Introduction

Autoimmunity affects up to 20% of the US population, a prevalence similar to that of heart disease and cancer. Many autoimmune diseases strike young adults and destroy vital organs and tissues, causing extensive morbidity and disability over a lifetime. Annual treatment costs are estimated in the range of $100 billion [1]. Medications commonly used to treat autoimmune disorders have devastating long-term effects, adding to the toll on patients. The root cause remains unknown, and therapies are nonspecific and fraught with serious complications. Novel less toxic treatments are urgently needed, but rational design will require better understanding of disease pathogenesis.

It is thus notable that for multiple autoimmune diseases the target antigen (Ag) is a basement membrane (BM) component. Epitopes on collagens and laminins, in particular, in kidney, lung, joints, skin, mucous membranes, and other tissues are targeted by autoantibodies and T cells. Humoral autoimmunity is prominent, and identification of autoantibodies in the circulation or tissue is key to diagnosis; elimination or suppression of autoreactive lymphocytes is a major goal of therapy. This review will examine major diseases linked to BM reactivity (Table 1), with reference to the historical context and a focus on investigations in man and animals that advance our understanding of disease pathogenesis. Special attention is paid to autoimmunity to type IV collagen in renal glomerular and pulmonary alveolar BMs, because meticulous dissection of antigenic epitopes and pathogenic mechanisms in these diseases has provided novel paradigms for induction of autoimmunity targeting BM and a blueprint for approaching less well defined diseases.

Autoimmune anti-GBM glomerulonephritis and Goodpasture's disease

Clinical manifestations and epidemiology

Autoimmune anti-glomerular basement membrane (GBM) glomerulonephritis (GN) and its systemic counterpart Goodpasture's (GP) disease, the

Table 1. Major diseases linked to autoimmunity to basement membrane components.

Human diseases	Major organ system	Key clinical features	BM target
Anti-GBM GN & GP disease	Kidney & Lung	GN with renal failure & lung hemorrhage	α3(IV)NC1 collagen α5(IV)NC1 collagen
Bronchiolitis obliterans (post lung transplant)	Lung	Fibro-obliterative pulmonary failure	Collagen V
Rheumatoid arthritis	Synovial joints	Destructive arthritis	Collagen II (native & citrullinated)
Autoimmune dermatoses			
Bullous pemphigoid	Skin	Epidermal-dermal blisters	Collagen XVII/BP180
Epidermolysis bullosa acquisita	Skin	Epidermal-dermal blisters	Collagen VII
Anti-laminin γ1 pemphigoid	Skin	Epidermal-dermal blisters	Laminin γ1 chain
Anti-laminin-332 mucous membrane pemphigoid	Mucous membranes	Epidermal-dermal blisters	Laminin-332 (laminin-5)

Abbreviations: BM, basement membrane; GBM, glomerular basement membrane; GN, glomerulonephritis; GP, Goodpasture's; NC1, noncollagenous domain1.

term used when clinical lung involvement is evident, are considered a prototype for organ-specific autoimmunity. Although rare, anti-GBM GN was the first human nephritis for which an intrinsic glomerular Ag target was well characterized and clinical and pathologic manifestations duplicated in animal models by transfer of patients' IgG and by Ag immunization. Thus, anti-GBM nephritis has been considered a key disease with which to dissect mechanisms and interventions relevant to human nephritis, with anticipation that insights will be far reaching.

Anti-GBM GN and GP disease affect both sexes, with a bimodal age distribution showing peaks around age 20 and 60–70 years of age [2]. Disease occurs in children but is rare [3]. Clinical manifestations can be severe, and include rapidly progressive glomerulonephritis with irreversible renal failure and catastrophic lung hemorrhage due to involvement of the alveolar capillaries. This clinical phenotype reflects the highly restricted, tissue-specific distribution of the dominant target Ag, the non-collagenous 1 (NC1) domain of the α3 chain of type IV collagen, or α3NC1. Expression of α3(IV) collagen is limited to BM of renal glomerular capillaries and tubules, alveolar capillaries, cochlea, anterior lens capsule, Descemet's membrane, ovary, and testis [4]. Sites other than kidney and lung appear to be protected from autoantibody attack.

Patients often present with nonspecific symptoms, including malaise, weakness, and fatigue due to anemia or renal failure, or complain of dark or blood-tinged urine, coughing up blood (hemoptysis), or difficulty breathing. Anemia is common and may be due to occult blood loss from renal or lung involvement, identified as infiltrates on chest radiograph. Signs of inflammation in the glomerulus, the filtering unit of the kidney, are typically present, including blood and protein in the urine (hematuria and proteinuria). Some patients present with rapidly progressive GN (RPGN), a clinical syndrome with rapid loss of glomerular filtration rate, often defined as 50% loss within 3 months or a rise in serum creatinine of greater than 1 mg/dL/week. Among patients presenting with RPGN, uremia, oliguria, and hypertension are common.

Evidence of renal insufficiency usually prompts kidney biopsy, which typically reveals focal and segmental necrotizing crescentic GN (Fig. 1). Direct immunofluorescence findings are pathognomonic, with intense linear deposition of IgG and often C3 along the glomerular capillary walls. IgG1 and IgG4 subclasses predominate, though all subclasses can be seen [5–8]. Linear tubular BM IgG staining may also be detected. Electron microscopy is negative for dense deposits. Diagnosis of anti-GBM antibody-mediated GN or GP disease requires identification of anti-GBM autoantibodies, either in the circulation or deposited in a linear fashion along the glomerular or alveolar BM. Lung biopsy is uncommon, but when performed typically reveals diffuse intraalveolar hemorrhage and intraseptal hemosiderin-laden macrophages. Tissue biopsy may be critical to determine the correct diagnosis, because cases of anti-GBM GN and alveolar hemorrhage due to anti-GBM IgG but with undetectable circulating anti-GBM autoantibodies are reported [9].

Approximately 25% of anti-GBM GN or GP disease patients co-express antineutrophil cytoplasmic autoantibodies (ANCA). In some cases, renal biopsy shows histopathologic features of both anti-GBM GN (linear GBM IgG deposits) and ANCA vasculitis (extraglomerular vasculitic lesions) [10–12]. Both perinuclear (P, anti-myeloperoxidase) and cytoplasmic (C, anti-proteinase 3) ANCA have been detected, though anti-MPO ANCA may dominate among dual positive patients with crescentic GN [12]. The origins and pathogenic significance of this dual autoantibody positive disease remain unclear, as does the impact on clinical manifestations and patient prognosis.

Anti-GBM GN is usually an aggressive disease with rapid progression to renal failure, with a low likelihood of renal functional recovery once a patient becomes dialysis dependent. Urgent autoantibody removal and immunosuppressive therapy is