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Review Article

Nonimmunologic targets of immunosuppressive agents in podocytes

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Abstract

Proteinuria is a characteristic finding in glomerular diseases and is closely associated with renal outcomes. In addition, therapeutic interventions that reduce proteinuria improve renal prognosis. Accumulating evidence has demonstrated that podocytes act as key modulators of glomerular injury and proteinuria. The podocyte, or glomerular visceral epithelial cell, is a highly specialized and differentiated cell that forms interdigitated foot processes with neighboring podocytes, which are bridged together by an extracellular structure known as the "slit diaphragm" (SD). The SD acts as a size- and charge-selective barrier to plasma protein. Derangement of SD structure or loss of SD-associated protein results in podocyte injury and proteinuria. During the past decades, several immune-modulating agents have been used for the treatment of glomerular diseases and for the reduction of proteinuria. Interestingly, recent studies have demonstrated that immunosuppressive agents can have a direct effect on the SD-associated proteins and stabilize actin cytoskeleton in podocyte and have therefore introduced the concept of nonimmunologic mechanism of renoprotection by immunomodulators. This review focuses on the evidence that immuno-modulating agents directly target podocytes.

Introduction

Minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) are one of the most common and important causes of nephrotic syndrome (NS), accounting for >75% of NS cases in children [1]. In adults, MCD and membranous nephropathy (MN) are most frequent causes of idiopathic NS [2]. Heavy proteinuria, hypoalbuminemia, edema, and related complications such as thromboembolism, infection, and malnutrition are typical symptoms and signs of NS; in particular, a large amount of protein in the urine often leads to progression to end-stage renal disease. In addition, proteinuria is an indicator of treatment response and important long-term prognostic marker in renal disease progression. Increasing evidence suggests that podocyte injury plays an important role in the development of proteinuria and pathogenesis of various glomerular diseases, including MCD, FSGS, and MN. Podocytes are terminally differentiated and cover the urinary surface of glomerular basement membrane. Foot process from one podocyte forms interdigitation with the foot processes of adjacent podocytes to form the slit diaphragm (SD), which functions as the ultimate filter with 4- × 14-nm-sized pores. Since the discovery of mutation of *NPHS1* gene, which codes for nephrin (an SD-associated protein), in patients with Finnish-type congenital NS, mutations of several podocyte-associated genes including *CD2AP*, TRPC6 [17], *NPHS2*, and *NEPH1* were found to be associated with NS [3,4]. Podocytes and

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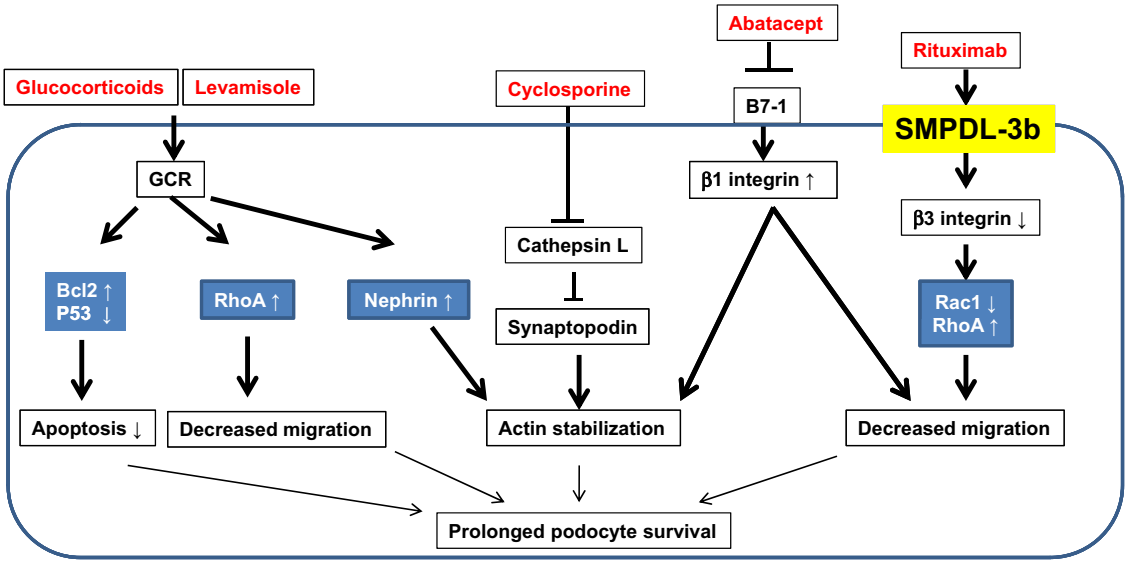

Figure 1. Schematic diagram showing nonimmunologic targets of immunosuppressive agents in podocytes. Glucocorticoids and levamisole attenuate podocyte apoptosis and increase in RhoA activity and decrease in degradation of synaptopodin protein. Soluble urokinase receptor and lipopolysaccharide activate B7-1 signaling and cathepsin L activity, whereas cyclosporine and abatacept inhibit synaptopodin degradation. Rituximab enhances sphingomyelinase-like phosphodiesterase 3b expression and stabilizes synaptopodin.
GCR, glucocorticoids receptor; LPS, lipopolysaccharide; SMPDL-3b; sphingomyelinase-like phosphodiesterase 3b; suPAR, soluble urokinase receptor.

SD-associated molecules have therefore become an important target for therapeutic interventions in proteinuric kidney diseases. Synaptopodin is an SD-associated protein, which maintains podocyte integrity. Dephosphorylation or ubiquitination (or in some cases both) of synaptopodin induces derangement of actin cytoskeleton, which results in foot process effacement [5]. Immunologic and metabolic stimuli including activation of cytokine- and calcineurin-dependent mechanisms lead to degradation of synaptopodin and podocyte injury [6].

Various immunosuppressive agents have been widely used to treat glomerular diseases and the effects of these drugs were thought to be solely immune mediated [7,8]. However, during the past decade, advances in podocyte biology and pathogenesis of proteinuric disease unveiled new molecular players responsible for the development of proteinuria; in addition, unexpected mechanisms of action of widely used immunosuppressive agents that are independent of their traditional immunomodulatory function have been discovered [9].

In this mini review, we describe the main targets of immunosuppressive agents in podocytes and review their mechanisms of action independent of immunological function. Furthermore, we also suggest potential new targets for drug development in podocytes. Because side effects develop in a high proportion of patients with prolonged and high-dose immunosuppressive treatment, it is important to understand the optimal doses and target of immunosuppressive agents, as low doses or specific targeted therapy may be more beneficial in patients with proteinuric kidney diseases. Fig. 1 shows a schematic diagram for nonimmunologic targets of immunosuppressive agents in podocytes. Potential targets of immunosuppressive agents in podocytes are given in Table 1.

Evidence of immunologic mechanisms in idiopathic NS

Shalhoub [10] hypothesized that MCD is associated with lymphocyte-derived permeability factor and increasing evidence suggests that cell-mediated immune systems are activated in MCD. Development of MCD is coincidental in Hodgkin's lymphoma, which is a T-cell disorder [11]. Incidence of atopy, which is also associated with cell-mediated hypersensitivity, is higher in patients with MCD [12]. Idiopathic NS responds to immunosuppressive agents such as corticosteroid and cyclosporine to suppress cell-mediated immunity. In addition, immunologic mechanisms are supported based on several clinical observations that relapse of MCD is experienced after viral or bacterial infections, inhaling allergens, and vaccination. Some studies reported that T cells are clonally expanded and cytokines derived from activated T and B cells are elevated in patients with idiopathic NS [13,14]. van den Berg and Weening [15] also demonstrated that interleukin (IL)-10 and IL-13 as cytokines produced by T lymphocytes are elevated in patients with MCD. IL-10 and IL-13 were normalized after remission of NS, whereas the protein concentrations and messenger RNA (mRNA) levels were upregulated again following NS relapse [15]. In addition, autoantibodies to PLA2R1 bind to epitopes on specific domains of PLA2R1 expressed on the podocyte surface and this phenomenon is demonstrated as a key pathogenetic mechanism in idiopathic MN [16,67]. However, cyclosporine therapy reduced proteinuria in human and experimental Alport's syndrome models and in patients with *NPHS2* mutation and nonimmunological and genetic glomerular diseases. Although cyclosporine decreased proteinuria in patients with MN, repeat kidney biopsy results showed many large electron-dense immune deposits [18–21]. Recent studies also demonstrated that circulating permeability factors are related to the development of NS [22]. These observations suggest that the action of these agents might be beyond immune mechanisms.

Nonimmunologic targets of immunosuppressive agents in podocytes

Glucocorticoids

Glucocorticoids has been widely used for many years and is the standard first-line drug for patients with MCD and FSGS;