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Review

New insight into the pathogenesis of minimal change nephrotic syndrome: Role of the persistence of respiratory tract virus in immune disorders

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ABSTRACT

The pathogenesis of minimal change nephrotic syndrome (MCNS) is a complex clinical problem which, unfortunately, has been in need of significant breakthroughs for decades. Improved understanding of the mechanisms is important to develop effective treatment strategies. To our knowledge, the pathogenesis of MCNS is multifactorial, involving both intrinsic and extrinsic factors, reasonable to be regarded as a "long chain" cascade reaction. Current studies implicating that the disease could probably be caused by immune disorders, however, have focused merely on the middle or terminal of this "long chain". It remains unclear what really triggers the immune disorders. It is noteworthy that the close association of respiratory tract infection with the occurrence, relapse and aggravation of nephrotic syndrome has been confirmed for over two decades. Derived from what we demonstrated in earlier studies, that the persistence of respiratory tract virus may contribute to the onset and development of MCNS, this review summarizes current evidence investigating the possible mechanisms of viral persistence, and discusses the role of viral persistence in the pathogenesis of MCNS. The key point is: whether the persistence of respiratory tract virus results in immune disorders. The available evidence under review also highlight the fact that the background of genetic susceptibility to the disease was found in many patients, which could be triggered by extrinsic factors, e.g. by the infection of respiratory tract virus.

Contents

Abbreviations: MCNS, minimal change nephrotic syndrome; IL, interleukin; GBM, glomerular basement membrane; CD, cluster of differentiation; INS, idiopathic nephrotic syndrome; RSV, respiratory syncytial virus; Flu, influenza virus; PIV, parainfluenza virus; PBMC, peripheral blood mononuclear cell; HSV, herpes simplex virus; HBV, hepatitis B virus; CTL, cytolytic T lymphocyte; FKN, fractalkine; TNF-R, tumor necrosis factor receptor; DC, dendritic cell; CLRs, C-type lectin receptors; TLRs, toll-like receptors; DC-SIGN, dendritic cell-specific intercellular adhesion molecule-3 grabbing non-integrin; NS, nephrotic syndrome; Treg, regulatory T cell; AR, autosomal recessive; AD, autosomal dominant; CNS, congenital nephrotic syndrome; FSGS, focal segmental glomerulosclerosis; DMS, diffuse mesangial sclerosis.

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1. Introduction

Minimal change nephrotic syndrome (MCNS) is the most common glomerular disease in children. Despite its favorable prognosis, relapse is very common, leading to increased morbidity, complications and decreased quality of life [1]. This challenge in the management of MCNS has compelled pediatric nephrologists to pay high attention to the exploration of the pathogenesis of the disease.

Although MCNS could be due to a number of causes, the immune disorder is the most characteristic. For many years, the majority of researches in the pathogenesis of the disease have primarily focused on the role of the immune system. Two important progresses have been made in the immunologic pathogenesis: (1) MCNS is related to abnormalities of T cell subsets and/or function, as well as an imbalance of the cytokine network. (2) Interleukin-8 (IL-8), interleukin-13 (IL-13) act on heparin sulfate of glomerular basement membrane (GBM) and podocin, nephrin of podocytes, sequentially resulting in the direct injury to the glomeruli [1–3]. Indeed, the pathogenesis of MCNS is a complex clinical problem, and could reasonablybe regarded as a "long chain" cascade reaction. Current studies focused merely on the middle or terminal of this "long chain"; however, it remains unclear what really triggers the immune disorders; it also needs researches located on the "top of long chain".

It is noteworthy that the close association of respiratory tract infection with the occurrence, relapse and aggravation of idiopathic nephrotic syndrome (INS) has been confirmed for over two decades. However, the role of respiratory tract virus infection in the pathogenesis of MCNS has not attracted enough attention up to now. Early in the 1970s, a retrospective study by Habib *et al.* revealed the close relationship between respiratory tract infection and MCNS. Further study also showed that the onset or relapse of the disease usually occurred in winter or spring, with the prevalence of the respiratory tract virus [4,5]. Another prospective study of 32 children with INS was done by MacDonald *et al.* found that the most common virus isolated from respiratory secretions of patients was respiratory syncytial virus (RSV), followed by influenza virus (flu) and parainfluenza virus (PIV), and 71% of relapse cases had symptoms of upper respiratory tract infection [6].

Based on above reports, our work group carried out a series of studies laying the groundwork for the hypothesis that identified the infection of respiratory tract virus as an important contributor to MCNS, with certain achievements: (1) The evidence that the presence of respiratory tract viruses in epithelial cells of the respiratory tract, serum, peripheral blood mononuclear cells (PBMC), urine and renal tissue of patients with MCNS were provided. (2) The respiratory tract virus could probably result in MCNS by multiple mechanisms, including the immunologic injury and/or direct inflammatory reaction. (3) Successful construction of RSV nephropathy animal model provided the available evidence on the role of respiratory tract virus in the pathogenesis of MCNS [4,7–11]. Interestingly, the study of RSV nephropathy animal model found that the disease occurred in two stages. In the first stage (within 30 days post-infection), the damage to the respiratory tract and kidney was mainly caused by direct inflammatory reaction of RSV. In the second stage (more than 30 days post-infection), the respiratory manifestation of RSV infection disappeared; however, proteinuria excretion, edema and foot process effacement were more obvious, clinically similar to a patient with MCNS. These observations indicated that there might be some other underlying mechanisms beyond the direct inflammatory reaction, such as immune disorders after viral infection. Derived from what we demonstrated in earlier studies that the above immune disorders may be related to the persistence of respiratory tract virus, which develops as a result of immune evasion [12]. Clearly, there is a need to investigate whether these concepts of viral persistence, immune disorders and MCNS can be unified. For this reason, the exploration in the relationship between the persistence of respiratory tract virus and MCNS during the past decades has provided new evidence: (1) Respiratory tract virus including RSV, flu and PIV can be detected in multiple tissues of patients with MCNS. (2) During the later stage of the disease, although the respiratory manifestation of RSV infection had disappeared in the animal model, the positive signal of immunofluorescence for RSV G and F protein in glomeruli lasted until 120 days post-infection. (3) RSV G and F protein in renal tissue of the animal model can be detected by Western blotting until the later stage of the disease [7–11]. As described above, it therefore stands to reason that the pathogenesis of MCNS may be relevant to viral persistence, which requires that the respiratory tract virus can escape from immune surveillance of the host. In this way, the host is unable to eliminate the virus completely. The continuous replication of the virus at a low level can disturb the homeostasis of the host, leading to immune disorders. On the basis of these studies, it has been proposed that the persistence of respiratory tract virus may contribute to the onset of MCNS and should be located at the "top of long chain" regarding the pathogenesis.

2. Possible mechanisms of viral persistence

The typical viral infection is acute, and induces the host defensive response to clear the foreign agents and leave the host with virus-specific immunity. However, a number of viruses are capable of persistence, such as herpes simplex virus (HSV), measles and hepatitis B virus (HBV). Aiming to persist, a delicate balance must be achieved so that, on the one hand, the host is not killed by the virus; on the other hand, the virus is able to evade the immune defense. The mechanisms of viral persistence range along a spectrum. At one extreme is virus that continues to replicate at high titers for a long time, while at the other extreme is virus that becomes latent, replicating for short periods of time at intervals. Between both ends is the example of smoldering infection that shares characteristics of both replication and latency [13]. So far, only a few studies have found that respiratory tract virus could become persistent. Taking RSV for instance, there is lack of research about the mechanisms of RSV persistence, owing to the high frequency of viral antigenic variation and complex immune response of the host. To our knowledge, a brief overview of possible mechanisms is described below.

2.1. Immunologically privileged sites

There are a few organs and tissues that appear to favor viral persistence, particularly the brain and kidney. It's realized that at least two factors account for viral persistence in the brain. First, the blood–brain barrier limits the trafficking of lymphocytes through the brain and, second, neurons express little if any MHC class I molecules rendering them relatively poor targets for virus-specific cytolytic T lymphocyte (CTL). The kidney is the other major organ that frequently harbors persistent viruses. However, there is no clear explanation why virus in the kidney could be able to evade the immune system. It has been speculated that lymphocytes may not readily cross the subendothelial basement membrane to access infected glomerular epithelial cells [13].

2.2. Antigenic drift

As a paramyxovirus of the genus *pneumovirus*, RSV has two subtypes, and G protein is the main antigenic protein distinguishing between the two subtypes [14]. RSV infection commonly occurs every 2 to 3 years throughout life, since RSV cannot induce long-lasting virus-specific immunity [15]. The reason for recurrent infection is unknown, partly owing to antigenic variations that make it easy to escape from the immune surveillance of the host. Immune evasion occurs via changing the antigenic epitope in the C-terminal variable region of G protein. Moreover, the variations of G protein are likely to have different genetic bases, such as nucleotide substitution, gene deletion and insertion, as well as the change of glycosylation pattern and the length of amino acid chain [16–21].