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Mechanism of Proteinuria in MCD Including Role of CD80

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Mechanisms of Proteinuria in MCD Including Role of CD80
Minimal change disease (MCD) represents the most common form of idiopathic nephrotic syndrome (INS) in children and is also common in adults. The term MCD refers to a histological pattern characterized by the presence of podocyte foot process effacement and minor o absent abnormalities on light microscopy and immunofluorescence in the context of idiopathic nephrotic syndrome. These observations have led to the concept of MCD as podocytopathy, but its pathogenesis is not fully understood. Traditionally, MCD has been considered a T cell disease in that T-cell derived factors directly target podocytes leading to podocyte rearrangement and proteinuria. However, the observation that Rituximab, a B cell depleting therapy, is effective in preventing relapses in MCD has switched interest to B cells. Likewise, our group have identified two unexpected players in the disease pathogenesis: the lungs and the endothelium. In this presentation, we will review the latest postulated mechanisms of disease from different perspectives:

1. **Role of T cells**. While many circulating T-cell derived cytokines have been postulated as candidate circulating factor in MCD, none have been validated in humans. Recently, it has been found that patients with INS have an increased amount of hyposialylated Ig M on the T cell surface, and this associated with greater disease severity. Additionally, experimental studies support that the presence of hyposialylated IgM predisposes T cell to release factors that injure cultured podocytes.

   Role of podocytes and CD80. Several proteins expressed by human podocytes have been linked to the pathogenesis of MCD including CD80, c-mip, angiopoietin like 4, etc. Due to time constrains, in this review we will focus on the role of CD80 in MCD. Mechanistically, CD80 is thought to prevent talin binding to β1 integrin and its downstream signaling and to prevent Neph1 binding to nephrin, thereby altering actin polymerization and organization. More recently, a study used different genetic animal models to test the role of podocyte CD80. Authors found that podocyte CD80 mediates proteinuria and disease progression through β-catenin signaling.

   Role of B cells and autoantibodies. Anti-UCHL1 antibodies were the first to be identified in patients with INS, and experimental data support a pathogenic role of these autoantibodies in the disease, though the mechanisms remain unknown. Subsequently, other circulating autoantibodies against podocyte proteins have been described. Particularly interesting is the observation of anti-nephrin auto-antibodies in INS/MCD as these are known to mediate podocyte injury in experimental models. More recently, auto-antibodies against the vascular endothelium have been reported in nearly all patients with INS, yet their role in the pathogenesis of proteinuria is unknown. One could postulate that these may cause endothelial injury which could potentially be the initial insult to the glomerular filtration barrier in MCD.

   Role of pulmonary surfactants. Our group found that patients with INS/MCD have high