Extrafollicular B cells and anti-slit diaphragm autoantibodies underly a shared autoimmune pathogenesis in childhood and adult idiopathic podocytopathies

ISN INTERNATIONAL SOCIETY OF NEPHROLOGY

Introduction

Idiopathic podocytopathies likely stem from anti–slit diaphragm autoimmunity.

This study examines how these autoantibodies relate to B-cell dysregulation across children and adults.

Methods

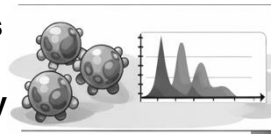
-Anti-CRB2
-Anti-Nephrin

Multicenter cohort

N = 82 - Idiopathic podocytopathies
N = 22 - Other glomerulopathies
N = 28 - Healthy controls

-Kidney biopsy - stained for IgG deposits
-Imaged with Confocal microscopy & High-resolution structured illumination microscopy

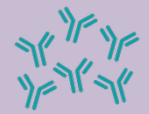
Peripheral blood B cell phenotype was assessed by Flow cytometry



Single-cell RNA-sequencing used to evaluate B cell transcriptional signatures & clonality

Results

Anti-CRB2 ⟶ all active idiopathic podocytopathies
↑↑↑ in adults (27/31 [87%] vs. 23/51 [45%], P< 0.01)
↓ in remission (51 vs. 115 µg/mL, P < 0.01)



Double seropositivity in 14/82 (17%)

IgG deposits + CRB2 identified in glomeruli of anti-CRB2 seropositive patients

Expansion of extrafollicular T-bet^{+} CD21^{low} atypical B cells = associated with autoimmunity (both children and adults)

In children, both autoantibodies correlated with atypical B cell expansion

Adults with ↑ frequencies of classical memory B cells = ↑↑ degree of B cell dysregulation than children

Single-cell RNA-seq in children ⟶ highly dysregulated, activation-prone B-cell pool enriched for VH4-39^{+} clonotypes

Conclusions: 1. Anti-CRB2 autoantibodies are prevalent in all idiopathic podocytopathies, especially in adults
2. Anti-CRB2 autoantibodies can co-occur with anti-Nephrin autoantibodies.
3. In children and adults, different B cell subtypes correlate with autoantibody production in each age group, potentially explaining the variation in treatment response.

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