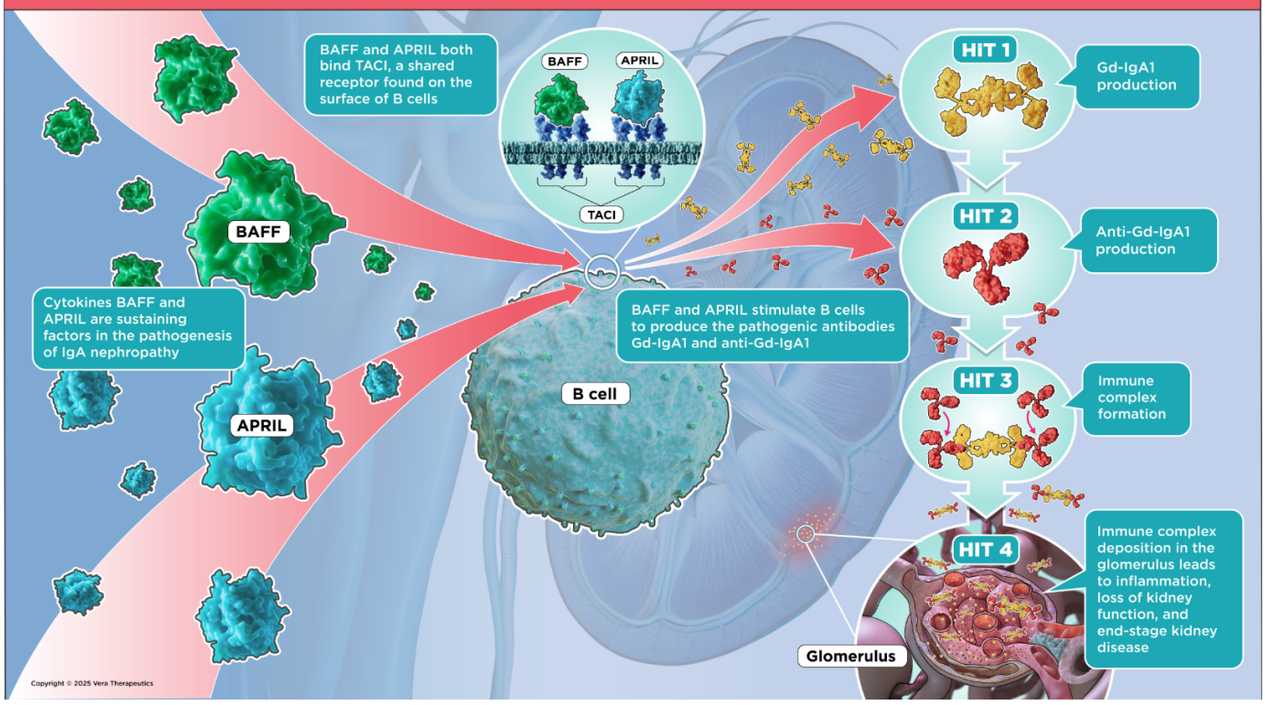
The Role of BAFF and APRIL in IgA Nephropathy

Figure: BAFF and APRIL Drive B Cells to Produce Pathogenic Antibodies in IgA Nephropathy



Introduction

IgA nephropathy (IgAN) is a chronic, autoimmune kidney disease characterized by progressive, irreversible kidney damage and is the most common primary glomerulonephritis worldwide.[1,2] It is typically diagnosed before the age of 40 and carries a high risk of kidney failure, with at least 50% of patients progressing to end-stage kidney disease (ESKD) within 10 to 20 years.[3] A large, long-term outcomes study of UK patients with IgAN revealed that even patients with low proteinuria levels faced significant risks of kidney failure.[3] This underscores the limitations of supportive care regimens, which primarily seek to manage proteinuria and other symptoms of chronic kidney disease (CKD) but fail to address the specific underlying mechanism of IgAN, leaving a high lifetime risk of ESKD.[1,3] Here, we describe the pathogenic role of B cells and their cytokine drivers, BAFF and APRIL — potential therapeutic targets specific to IgAN and other autoimmune kidney diseases.[4]

Understanding the role of B cells in IgAN: the 4-hit hypothesis

Key characteristics of IgAN are the formation and glomerular deposition of immune complexes containing galactose-deficient-IgA1 (Gd-IgA1) and autoantibodies against Gd-IgA1, which is succinctly illustrated by the 4-hit hypothesis (Figure).[4] The central role of immune complexes in IgAN pathology reflects what is now understood to be a B-cell–driven autoimmune disorder.[4]

Antibody-secreting B cells are responsible for producing the Gd-IgA1 of "Hit 1" (Figure).[4] IgA antibodies are normally found in mucosal tissues, but in IgAN, dysregulated B cells migrate away from mucosal sites and lead to increased Gd-IgA1 levels in circulation, where it appears foreign to the immune system.[4] As part of an immune response against Gd-IgA1, anti-Gd-IgA1 autoantibodies emerge as "Hit 2" (Figure).[4] Binding of autoantibodies to Gd-IgA1 forms the immune complexes (Hit 3) that eventually deposit in glomeruli and lead to kidney injury and damage (Hit 4) (Figure).[4] Specifically, the accumulation of immune complexes within the kidney trigger inflammation that can lead to fibrosis, irreversible damage to nephrons, and high risk of kidney failure.[4]

What is driving B-cell activity in IgAN?

BAFF and APRIL are cytokines belonging to the tumor necrosis factor (TNF) superfamily and are key regulators of B-cell homeostasis and function.[4] They signal through a shared receptor called TACI, which is expressed on B cells (Figure). Due in part to the shared receptor, BAFF and APRIL are known to have overlapping and redundant functions.[4,5]

BAFF and APRIL are implicated in a variety of processes that are associated with IgAN pathogenesis including survival, trafficking, and activation of antibody-producing B cells.[4] They are thought to be sustaining factors for B cells producing Gd-IgA1 (Hit 1) and their related autoantibodies (Hit 2), highlighting their potential value as therapeutic targets.[4]

Conclusion

Understanding the roles of B cells, BAFF, and APRIL in IgAN, especially in relation to the 4-hit hypothesis, may provide insights into how emerging therapeutic approaches could target the upstream pathogenesis of IgAN and potentially modify the course of disease.

References

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