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Short Communication

GWAS-Follow-up Studies Identified a Connection Between Abnormal LIF/JAK2/STAT1 Signaling and Overproduction of Galactose-Deficient IgA1 in the Tonsillar IgA1-Secreting Cells from Patients with IgA Nephropathy

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DESCRIPTION

IgA nephropathy (IgAN) is a common primary glomerulonephritis with its characteristic IgA1-containing glomerular immunodeposits. Patients with IgAN have a high rate of progression to kidney failure; up to 40% of patients reach that stage within 20-30 years since the diagnosis, despite receiving optimized standard care.

A suspected connection between IgAN and the mucosal immune system is highlighted by the fact that the main production sites of IgA1 reside in the mucosal tissues, and that a common clinical feature at the onset of IgAN is macroscopic hematuria with a concurrent upper respiratory-tract infection, i.e., synpharyngitic hematuria [1,2].

The "multi-hit hypothesis" has been proposed to explain the pathobiology of IgAN [3], wherein Galactose-deficient IgA1 (Gd-IgA1) glycoforms are recognized by Gd-IgA1-specific IgG autoantibodies to form immune complexes. These complexes bind other proteins, such as complement C3, and some of the resultant complexes may deposit in the glomeruli and induce kidney injury. Notably, serum levels of Gd-IgA1 and IgG autoantibodies are predictive of disease progression [4-7]. Although the precise location of the cells producing Gd-IgA1 *in vivo* is still under investigation, tonsillar B cells have been proposed to be significant producers of Gd-IgA1, potentially explaining why tonsillectomy improves clinical symptoms of some IgAN patients [8,9].

We previously demonstrated that Interleukin-6 (IL-6), a pro-inflammatory cytokine with multiple roles in immune responses, selectively increases the production of Gd-IgA1 in IgA1-producing cell lines from IgAN patients; this process is mediated by an abnormal activation of STAT3 [10]. Although serum Gd-IgA1 levels are genetically co-determined, this IL-6-mediated process can further elevate serum Gd-IgA1 levels in patients with IgAN [11-13].

Genome-Wide Association Studies (GWAS) of multi-ethnic cohorts uncovered multiple candidate genes involved in mucosal immunity that are associated with the development of IgAN [14-16]. Some of these genes, such as *ITGAM* and *TNFSF13*, encode proteins regulating mucosal lymphoid tissues involved in IgA production. A subset of patients with IgAN have elevated serum levels of A Proliferation-Inducing Ligand (APRIL), a cytokine from Tumor-Necrosis Factor (TNF) ligand superfamily member 13 encoded by the *TNFSF13* gene. Furthermore, Toll-like Receptor 9 (TLR9) may be involved in the pathogenesis of IgAN *via* APRIL pathway that affect maturation of plasma cells [17]. Recent clinical trials have reported that administration of an inhibitor of APRIL, TACI-IgG Fc fusion protein (Atacicept), to IgAN patients decreased serum levels of Gd-IgA1 and improved proteinuria [18]. Similarly, a humanized IgG2 monoclonal antibody (Sibeprenlimab), a neutralizing antibody for APRIL, has been also reported to decrease serum levels of Gd-IgA1 and improve proteinuria [19].

Another IgAN-associated locus is the *HORMAD2* locus that contains several genes, including *LIF* and *OSM* that encode cytokines called Leukemia Inhibitory Factor (LIF) and Oncostatin M (OSM), respectively. Furthermore, this GWAS locus is associated with IgAN as well as serum IgA levels and tonsillectomy [20-22]. A recent study postulated that this locus is likely involved in the development of IgAN in association with TLR9 pathways [23]. LIF is an IL-6-related cytokine that uses gp130 for signal transduction and has been previously implicated in mucosal immunity and was identified as a potential drug target [20,24]. Prior studies of LIF/OSM cytokines revealed that LIF stimulation of immortalized IgA1-producing cell lines derived from peripheral blood of IgAN patients increased Gd-IgA1 production [25]. Follow-up analyses of the signaling mechanisms

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implicated STAT1-mediated abnormal activation of Src-family kinases, including Lyn [26]. Lyn, identified in LIF-mediated signaling abnormalities in peripheral blood-derived IgA1-secreting cell lines from IgAN patients, is a non-receptor kinase with a key signaling role in inflammation. The corresponding gene, *LYN*, was recently identified as one of the 16 new IgAN-associated GWAS loci [20].

In summary, we identified that the signaling via the LIF/JAK2/STAT1 pathway is involved in LIF-mediated Gd-IgA1 overproduction by immortalized IgA1-producing cell lines derived from tonsils of patients with IgAN [27]. Notably, studies of peripheral-blood mononuclear cells and kidney tissues indicated that enhanced activation of STAT1 in IgAN patients may affect the kidney function [28].

JAK/STAT is a major pathway that responds to and transduces inflammatory signals from extracellular ligands, such as cytokines and chemokines [29]. GWAS revealed a strong association of the genomic locus that contains LIF with the risk of IgAN [15,30]. Furthermore, other GWAS publications revealed that the same locus was associated with acute tonsilitis and chronic inflammation of tonsils leading to tonsillectomy as well as with IgA serum levels [21,22].

CONCLUSION

The abnormal LIF/JAK2/STAT1 signaling and the elevated production of Gd-IgA1 in tonsillar cells in IgAN patients may play a significant role in disease development and progression. Understanding the mechanisms involved in production of Gd-IgA1 in IgAN will be useful in development of future disease-specific therapies.

DISCLOSURES

JN and YS are co-inventors on US patent application 14/318,082 (assigned to UAB Research Foundation). JN is a co-founder and co-owner of and consultant for Reliant Glycosciences, LLC.

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