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Nasopharyngeal immune niches in IgA nephropathy; from tonsillar Gd-IgA1 production to the NALT–kidney axis

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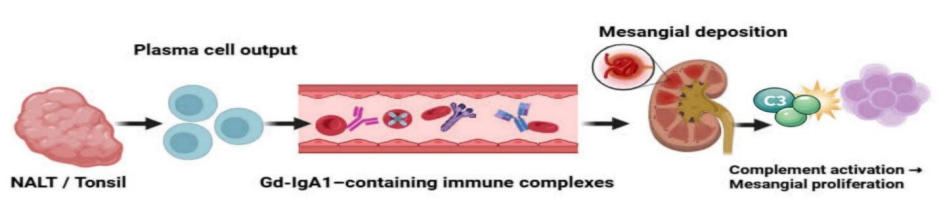
ABSTRACT



The NALT–kidney axis describes how mucosal immune outputs reach the systemic circulation and finally the glomerular mesangium. Plasma cells originating in nasopharynx-associated lymphoid tissue (NALT) or tonsillar germinal centers can home to systemic sites, including the bone marrow, sustaining elevated serum galactose-deficient IgA1 (Gd-IgA1). Then, circulating Gd IgA1 forms immune complexes with anti Gd IgA1 IgG/IgA, which deposit in the mesangium and then trigger complement activation, which is across with mesangial proliferation, and extracellular matrix expansion.

Implication for health policy/practice/research/medical education:
Nasopharyngeal immune niches centered in the palatine tonsils and adjacent epipharyngeal lymphoid tissue are now recognized as critical mucosa-associated lymphoid tissue sites that shape both systemic IgA responses and kidney-targeted immunopathology in IgA nephropathy. Within this framework, tonsillar production of galactose-deficient IgA1 (Gd-IgA1) and the propagation of inflammatory signals along a nasopharynx-associated lymphoid tissue (NALT)–kidney axis offer an integrated explanation for synpharyngitic hematuria, the dynamics of glomerular vasculitis, and the clinical benefit of tonsil-focused interventions in selected patients.

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Introduction

Immunoglobulin A nephropathy (IgAN), the most prevalent primary glomerulonephritis globally, remains a significant cause of end-stage kidney disease despite decades of research (1). Its pathogenesis is increasingly understood through the lens of mucosal immunity, with the nasopharyngeal region emerging as a critical, yet underappreciated factor (2). The traditional view centered on systemic immune dysregulation is evolving towards a model where localized immune activity within nasopharyngeal lymphoid tissues, particularly the tonsils and the broader nasopharynx-associated lymphoid tissue

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(NALT), initiates a cascade culminating in kidney damage. This complex relationship, conceptualized as the NALT–kidney axis, positions the nasopharynx not merely as a site of infection or inflammation, but also as a specialized immune niche where the pathogenic hallmark of IgAN as the galactose-deficient IgA1 (Gd-IgA1) is predominantly generated and also where aberrant immune responses are primed, which finally targeting the glomeruli (3). Previous authors detected that, the palatine tonsils are B cell–dominant lymphoid organs lacking afferent lymphatics, functioning as induction sites for oral and nasopharyngeal mucosal immunity. Their surface is composed of non-keratinizing squamous epithelium that invaginates deeply to form crypts, ending in lymphoepithelial symbiosis zones rich in M cells, dendritic cells, and memory B cells that orchestrate antigen sampling and activation of local immune circuits (4). In IgAN, the crypt architecture and surrounding parenchyma are morphologically altered (5); since, non-lymphoepithelial crypt areas expand with increasing glomerular damage, and the T cell–rich interfollicular regions are markedly enlarged and populated with activated T cells and mature dendritic cells, suggesting sustained antigen-driven T cell activation (5-7).

Search strategy

We conducted a literature search across valid databases, including PubMed, Directory of Open Access Journals (DOAJ), Web of Science, EBSCO, Scopus, Embase, and Google Scholar search engine, using relevant keywords such as 'Immunoglobulin A nephropathy', 'endothelial dysfunction', 'NALT–kidney axis', 'IgA nephropathy', 'end-stage kidney disease', 'inflammation', 'oxidative stress'.

A short look at the IgAN pathogenesis

The establishment of IgAN pathogenesis is the multi-hit hypothesis. The first hit involves the production of Gd-IgA1. This aberrant glycosylation arises from dysregulation of key glycosyltransferases within IgA1-producing plasma cells (8). The second hit is the generation of autoantibodies, predominantly of the IgG or IgA isotype residues on these Gd-IgA1 molecules (8). The third hit involves the formation of immune complexes between Gd-IgA1 and these autoantibodies. These circulating immune complexes are nephritogenic (9). The fourth hit entails the deposition of these immune complexes within the glomerular mesangium, triggering local inflammation, complement activation, particularly by the alternative and lectin pathways, mesangial cell proliferation, extracellular matrix expansion, and eventually, progressive scarring and loss of kidney function (10). Though the systemic circulation is the conduit, the origin of the pathogenic Gd-IgA1 is increasingly traced to mucosal sites, with the nasopharynx taking center stage (9).

Introducing nasopharynx-associated lymphoid tissue

The NALT–kidney axis refers to a functional immunological connection through which inflammatory and immune events initiated in the upper airway mucosa, especially the epipharynx, adenotonsillar structures, and broader NALT, propagate systemic signals that modulate glomerular and tubulointerstitial injury in the kidney (11). Hence, the concept of a NALT–kidney axis represents an emerging, though not yet definitively proven or universally accepted, framework in immunology and pathophysiology. It proposes a bidirectional communication pathway linking the immune surveillance and inflammatory responses initiated in the nasopharyngeal mucosa, particularly within the NALT, with the functional state and inflammatory milieu of the kidneys (11). While less established than the well-documented gut-kidney axis, growing evidence from infection models, autoimmune disorders, and chronic disease studies suggests that immune activation at this critical upper respiratory gateway can exert significant systemic effects, potentially influencing renal health and disease progression (11,12). Therefore, this potential axis requires dissecting the roles of NALT, the mechanisms of long-distance immune communication and the clinical contexts where nasopharyngeal and renal pathologies intersect (11). In fact, NALT is a key component of the mucosa-associated lymphoid tissue system, strategically positioned at the entrance of the respiratory and digestive tracts (13). It should remember that, the name of NALT is often conducted interchangeably with Waldeyer's ring, including the adenoids and palatine tonsils; however, it specifically refers to diffuse and organized lymphoid aggregates in the dorsal nasopharynx (14). Its primary function is immunosurveillance, through inhaled antigens, pathogens, and environmental particles. Upon encountering a threat, NALT initiates localized immune responses, including the activation of antigen-presenting cells like dendritic cells, proliferation of T and B lymphocytes, and the production of immunoglobulins, particularly secretory IgA, which provides mucosal defense (15). Then, activated immune cells within NALT do not remain confined; since, they can enter the systemic circulation by lymphatic drainage and the bloodstream (16). In the next step, these cells, along with soluble inflammatory mediators can disseminate throughout the body, potentially reaching distant organs like the kidneys (16). Importantly, the kidneys themselves are not immunologically inert; they contain resident immune cells as the dendritic cells, macrophages and T cells, across with expression of receptors for numerous inflammatory signals (17). Renal tubular and endothelial cells can also

produce cytokines and chemokines in response to systemic inflammation, contributing to local tissue responses that may range from protective repair to detrimental fibrosis and dysfunction (18).

Focus on nasopharynx

The human nasopharynx harbors a sophisticated network of organized lymphoid tissues, constituting NALT (15). Waldeyer's ring, comprising the palatine tonsils, pharyngeal tonsil, and lingual tonsil, represents the most prominent and well-studied components. These structures are strategically positioned at the aerodigestive tract entrance, functioning as inductive sites for mucosal immunity. They test the inhaled and ingested antigens, facilitating the generation of antigen-specific IgA responses essential for immune exclusion and homeostasis at mucosal surfaces (19). Within the tonsillar crypts, a unique microenvironment exists, rich in dendritic cells, T follicular helper cells, B cells at various stages of differentiation, and stromal cells. This niche is bathed in cytokines and factors derived from constant exposure to the external environment, including the diverse microbiome and airborne antigens (20). Critically, this microenvironment appears permissive, and perhaps even instructive, for the production of Gd-IgA1 in genetically susceptible individuals. Studies comparing tonsillar tissue from IgAN patients versus controls consistently reveal significant differences (21). Tonsillar B cells from IgAN patients demonstrate an intrinsic predisposition towards producing Gd-IgA1. This condition is linked to dysregulated expression of glycosylation enzymes, through reduced C1GALT1 and Cosmc mRNA and protein levels, alongside elevated ST6GALNAC2, specifically within the tonsillar lymphoid tissue. In this regard, the local cytokine milieu is a key driver (9); whereas, the elevated levels of B-cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL), produced by tonsillar dendritic cells, macrophages, and epithelial cells, particularly in response to microbial stimuli or chronic inflammation, have been repeatedly documented in IgAN tonsils (22). The BAFF and APRIL are potent survival and differentiation factors for B cells; since, they directly influence IgA class-switching and, importantly, promote the production of Gd-IgA1 by modulating the expression of glycosyltransferases (23). Accordingly, tonsillar T follicular helper cells, essential for providing help to B cells within germinal centers, also exhibit abnormalities in IgAN (23). Recent studies found that, an increased frequency of T follicular helper cells, particularly subsets expressing high levels of ICOS and PD-1 correlates with higher serum Gd-IgA1 levels and more severe disease (24). These T follicular helper cells likely provide excessive help to autoreactive or Gd-IgA1-producing B cell clones within the tonsillar germinal centers (25). Furthermore, the tonsillar microbiome itself may be a trigger. Dysbiosis, characterized by shifts in bacterial composition throughout increased *Haemophilus, Streptococcus* and *Prevotella* is observed in IgAN patients (26). Specific microbial components or chronic subclinical infections may perpetuate local inflammation, sustaining high BAFF/APRIL production and creating a self-reinforcing loop that favors the generation and survival of Gd-IgA1-producing plasma cell precursors (23).

Focus on the cellular constituents of the NALT

On the cellular level, NALT harbors diverse lymphocyte subsets, including B cells, CD4 and CD8 T cells, Th17 cells, group 3 innate lymphoid cells (ILC3), and antigen-presenting cells that collectively shape mucosal and systemic immunity (27,28). In human nasopharyngeal tissue, ILC3 and Th17 cells exhibit reciprocal patterns that are influenced by bacterial colonization (28); for example, Streptococcus pneumoniae carriage in children correlates with increased IL-22–producing ILC3 in adenotonsillar tissue, whereas Staphylococcus aureus stimulation skews towards stronger Th17 expansion (28). These ILC3–Th17 dynamics influence the balance between barrier-protective cytokines such as IL-22 and proinflammatory mediators such as IL-17, with downstream effects on systemic inflammation and vascular activation that may impinge on renal microcirculation and glomerular endothelial cells (29). In parallel, B cells in organized NALT structures undergo affinity maturation and class-switch recombination providing a source of mucosal and systemic antibodies including IgA that can participate in immune complex deposition in the kidney (30,31).

Mechanistic impact of NALT–kidney axis

The NALT–kidney axis is conducted by the activated lymphocytes, especially memory T cells and IgA-producing B cell precursors and also inflammatory mediators like IL-6, TNF-α, IL-1β, IL-17 and BAFF, which generated in NALT enter the bloodstream. These circulating factors can directly affect the kidney (11,32). Pro-inflammatory cytokines can bind to receptors on renal cells, triggering intracellular signaling cascades that promote inflammation, oxidative stress, endothelial dysfunction, and fibrosis (33). Meanwhile, TNF-α can induce apoptosis in tubular cells, while IL-6 can stimulate mesangial cell proliferation in the glomeruli (34). Activated immune cells homing to the kidney, potentially guided by chemokines produced in response to systemic inflammation or specific renal damage signals, can infiltrate the tissue (35). Once within the kidney, these cells may either help resolve infection

or, if dysregulated, contribute to bystander tissue damage through the release of more cytokines, reactive oxygen species, or direct cytotoxic effects. Another potential route involves neural pathways (36). The nasopharynx is densely innervated, and inflammatory signals can activate the vagus nerve or other autonomic pathways, leading to neurogenic inflammation or modulating renal blood flow and sympathetic tone, indirectly influencing kidney function and inflammation (37). Furthermore, the renin-angiotensin-aldosterone system (RAAS), a key regulator of blood pressure and fluid balance centered in the kidneys, is exquisitely sensitive to systemic inflammation (38). Moreover, cytokines like IL-6 can upregulate angiotensinogen production in the liver and angiotensin II type 1 receptors in various tissues, including the kidney, amplifying RAAS activation. Then, RAAS activation creates a vicious cycle where inflammation provokes RAAS, further promotes oxidative stress and inflammation within the kidney, exacerbating damage (38). Clinical evidence supporting this axis is most compelling in specific contexts. Several investigations detected that mucosal infections, particularly recurrent tonsillitis or upper respiratory tract infections, are well-recognized triggers for the onset or exacerbation of IgAN (39). Some studies showed that, tonsillectomy, removal of a major NALT component, can significantly reduce proteinuria and hematuria in some IgAN patients, particularly in Asian populations, and may slow disease progression. This condition suggests that eliminating the source of chronic antigenic stimulation or aberrant immune cell activation in the NALT directly benefits the kidneys (40). The mechanism likely involves reducing the systemic load of Gd-IgA1 and the immune complexes that deposit in the glomeruli (40, 41). Likewise, acute infections further illustrate the link. Severe upper respiratory infections, including influenza and notably SARS-CoV-2, are frequently associated with acute kidney injury (42). While direct viral invasion of renal cells occurs in some cases; nevertheless, systemic inflammation is a major driver (43). The intense immune activation in the nasopharynx and lungs during these infections floods the circulation with cytokines known as cytokine storm (42,44). This systemic inflammatory response can cause renal vasoconstriction, reduce glomerular filtration rate, promote endothelial damage leading to micro-thrombi, and directly injure tubular cells, culminating in acute kidney injury (42,43). The nasopharynx, as the initial site of viral replication and immune activation for many respiratory pathogens, is therefore a critical ignition point for this cascade affecting the kidneys (45). On the other hand, chronic conditions also hint at a connection. Patients with chronic rhinosinusitis or persistent adenoid hypertrophy often exhibit low-grade systemic inflammation (46,47). While direct causation is harder to prove, epidemiological studies suggest associations between chronic upper airway inflammation and an increased risk of developing chronic kidney disease or accelerating its progression, potentially mediated through sustained low-level inflammatory burden impacting renal vasculature and parenchyma (48).

Conclusion

The NALT–kidney axis is a compelling hypothesis that bridges mucosal immunology and nephrology. It posits that immune responses initiated in the nasopharyngeal lymphoid tissue can disseminate systemically via cellular trafficking and soluble mediators, significantly influencing renal inflammation, function, and susceptibility to injury. While strongest evidence exists for IgA nephropathy and acute infections like severe influenza or COVID-19, where nasopharyngeal inflammation correlates with renal complications, the axis likely represents a broader principle of mucosal-organ crosstalk.

Authors' contribution

Conceptualization: Ahmad Shajari and Azita Sadeghzade.
Data curation: Azita Sadeghzade and Elham Kebriyaei.
Investigation: Ahmad Shajari and Hossein Mardanparvar.
Supervision: All authors.
Validation: Hossein Mardanparvar and Ali Emadzadeh.
Visualization: Ali Emadzadeh.
Writing–original draft: All authors.
Writing–review and editing: All authors.

Conflicts of interest

The authors declare that they have no competing interests.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized Perplexity to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

Ethical issues

Ethical issues (including plagiarism, data fabrication, and double publication) have been completely observed by the authors.

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