# Secondary IgA nephropathy

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**IgA nephropathy is the most common primary glomerulonephritis worldwide. Its frequent coexistence with inflammatory, infectious, or malignant processes raises the possibility of a pathologic rather than coincidental association. Major strides have been made to elucidate the underlying pathophysiologic events that culminate in the development of primary IgA nephropathy. Whether secondary forms of the disease share common pathways triggered by underlying disorders or different mechanisms leading to similar pathologic findings remains to be determined. In this article we describe the most frequent etiologies for secondary IgA nephropathy and review the available literature for the pathophysiology.**

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Since the initial description of IgA nephropathy (IgAN) in 1968, significant progress has been made in understanding the pathogenesis of the most common primary glomerulonephritis in the world.[1] The diagnosis is established by examination of renal tissue showing IgA as the dominant or co-dominant Ig in glomeruli, usually accompanied by complement C3 and frequently with IgG and IgM.[1] The IgA is exclusively of the IgA1 subclass, with galactose content less than that of most circulatory IgA1.[2] The tissue origin of the galactose-deficient IgA1 (Gd-IgA1) is still debatable, with a mucosal origin suspected.[3,4] Alternatively, polymeric IgA1 may be produced in the bone marrow owing to altered homing of Gd-IgA1–producing cells (Figure 1).[5] Patients with IgA vasculitis with nephritis (formerly termed Henoch-Schönlein purpura nephritis) have histologic features indistinguishable from IgAN, suggestive of a systemic form of the disease that causes IgAN.[1] Confocal microscopy imaging shows co-localization of IgA with complement C3, consistent with an immune complex–driven process. The presence of C3 co-deposits without C1q in the mesangium indicates that complement activation is through the alternative pathway, lectin pathway, or both.[6]

We have proposed that the glomerular IgA represents deposits of circulating complexes composed of Gd-IgA1 bound by autoantibody (IgG or IgA) specific for Gd-IgA1 hinge-region *O*-linked glycans.[7,8] An alternative hypothesis postulates that latent mesangial deposits of Gd-IgA1 may be bound by autoantibodies from the circulation, forming immune complexes *in situ*.[9] Although mesangial cells can degrade immunodeposits,[7] it is possible that, when this system is "overwhelmed," alternative processes cause pathologic cellular activation and tissue injury.

IgAN may be discovered in patients with many nonrenal diseases. In these circumstances, IgA–immune complex-mediated renal injury may develop secondarily owing to pathogenic steps similar to those of IgAN or markedly different mechanisms of disease. Herein we review the more commonly encountered causes of secondary IgAN.

## Secondary IgAN

IgAN has been documented in patients with various comorbidities, ranging from chronic liver disease and inflammatory states to chronic infections and neoplasms (Table 1). Although IgAN in those cases is often referred to as being secondary to the underlying systemic disorder, there is no consistent definition of secondary IgAN in the literature. No

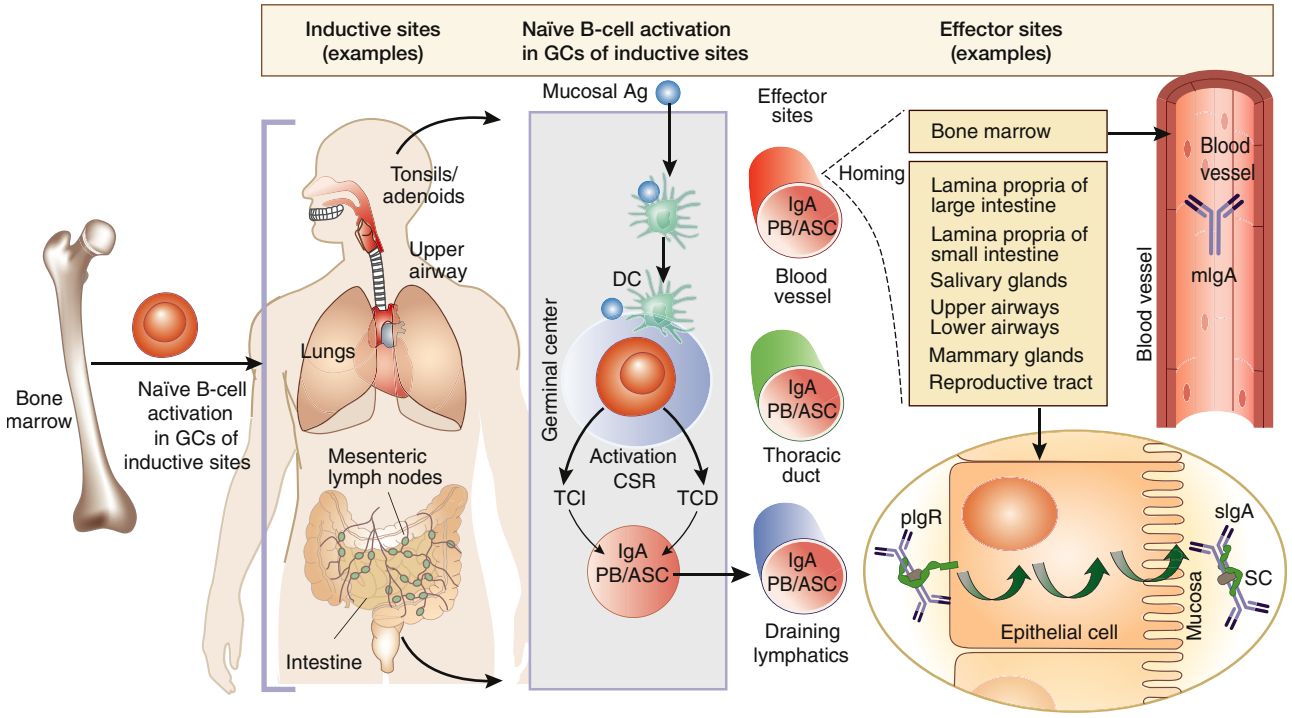


**Figure 1 | Mucosal immune system and circulatory and mucosal IgA.** The mucosal immune system consists of inductive and effector sites. Inductive sites are the tissues where naïve B cells are exposed to antigen. Inductive sites include Peyer's patches (small and large intestine), bronchus-associated lymphoid tissue, tonsils, and adenoids. The interaction of antigens (mucosa-derived) with B cells occurs in the germinal centers (GC) of the inductive sites. T-cell–dependent (TCD) and T-cell–independent (TCI) activation of B cells ($IgM^+$, $IgD^+$) can result in isotype class-switch to IgA; the $IgA^+$ plasmablasts (PB) and antibody-secreting cells (ASC) express tissue-specific homing receptors.[56,57] These activated B cells enter the thoracic duct via the draining lymphatics and then recirculate to the lamina propria of the intestine and other mucosal epithelium (effector sites).[57] In primary IgAN, the tissue origin of galactose-deficient IgA1 (Gd-IgA1) is still debated, but evidence indicates its mucosal origin: (i) Gd-IgA1 in mesangial deposits is polymeric, typical of IgA1 produced in mucosal tissues; (ii) macroscopic hematuria frequently manifests during an active respiratory tract and gastrointestinal tract infection; and (iii) polymeric IgA1 produced at mucosal sites has a higher capacity for binding to a lectin specific for *N*-acetylgalactosamine (the terminal sugar in galactose-deficient glycans of Gd-IgA1) than does serum IgA1 in healthy individuals.[58,59] In contrast, other studies support the concept that polymeric IgA1 is produced in the bone marrow in patients with IgAN.[58] Thus, it has been postulated that patients with IgAN have IgA1-producing cells with altered homing receptors when migrating from an inductive site to an effector site in gut mucosa and therefore mistakenly "home" to the bone marrow.[5] TCD mechanisms involve 2 pathways: (i) CD40L on activated effector T cells and its interaction with CD40 on B cells; and (ii) involvement of cytokines, transforming growth factor, and interleukins. TCI mechanisms involve dendritic cells (DC) expressing B-cell activating factor and a proliferation-inducing ligand.[56] IgA plasmablasts destined for the intestinal lamina propria express chemokine receptors CCR9 (small-intestine homing) and CCR10 (large-intestine homing), the cognate ligands of which are expressed by respective intestinal epithelial cells. The IgA plasmablasts mature into IgA-secreting plasma cells in the lamina propria, to secrete polymeric IgA, composed of 2 or more monomeric units (either IgA1 or IgA2) joined by disulfide bonds between C-terminal tail pieces of each monomer and a single J chain. The polymeric IgA secreted by IgA-producing cells in mucosa can bind to polymeric Ig receptors (pIgR) on the basolateral surface of the mucosal epithelial cells and are internalized and then transcytosed into vesicles to the mucosal apical surface. The extracellular portion of the receptor (the secretory component, SC) is cleaved and remains attached to the pIgA that is secreted as secretory IgA (sIgA). Most of the IgA in serum originates from bone marrow and is monomeric IgA1 (mIgA; IgA1 ~84%, IgA2 ~16%; monomers >90%, polymers <10%). In contrast, mucosal IgA consists mainly of sIgA (>95%) with distribution of the 2 subclasses differing, depending on the specific mucosal site. sIgA is present in circulation at low concentrations, possibly owing to mucosal retrograde transport.[60] CSR, class-switch recombination.

specific histologic features differentiate primary from the so-called secondary cases. Mesangial deposits of IgA, sometimes with proliferative glomerulonephritis, are present in as many as 4%–16% of the general population in some regions.[10] Therefore, an association between IgAN and any coexisting disease may be simply due to exacerbation or recognition of coincidental primary IgAN. Nonetheless, the increased frequency of concurrence with select conditions suggests a potential causative relationship. Those conditions represent the focus of this review.

## Liver disease

Liver disease is the leading cause of secondary IgAN. The prevalence varies, depending on the cohort size, etiology of liver disease, demographics, and criteria for kidney biopsy. IgAN has been found in 9%–25% of patients biopsied at the time of liver transplantation.[11–14] Conversely, in a French cohort of 356 patients with biopsy-proven IgAN, 9% had cirrhosis.[15] The frequencies of hematuria and proteinuria range from 10% to 90% in patients with IgAN and cirrhosis, depending on the size of study population and light