known that the level of 25(OH)D_3 in circulation is about ~1000-fold higher than that of calcitriol. Therefore, under normal conditions, it is conceivable that many renal and extrarenal cells are capable of generating calcitriol from circulating 25(OH)D_3 to maintain a high local concentration of calcitriol for VDR-mediated autocrine and/or paracrine functions (Figure 2). However, this hypothesis raises more questions. For example, how does one investigate the significance of these VDR-mediated autocrine/paracrine functions in the cardiovascular system? Are these functions impaired in CKD? If yes, at what glomerular filtration rate does this mechanism become impaired? Answers to these questions may help us further understand the benefits of VDR modulator therapy in reducing the CVD risk in CKD.

CONCLUSION

In summary, the paper by Chen *et al.*[9] provides interesting data showing that the regulation of NPR-A may be one of the mechanisms by which VDR activation is associated with cardiovascular benefit in CKD.

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IgA nephropathy: Immune mechanisms beyond IgA mesangial deposition

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IgA nephropathy is attributable to mesangial IgA immune complex deposition. The pathogenic potential of frequently colocalized IgG deposits may depend on polarized T-helper cytokines that modulate Fcγ receptors of infiltrating macrophages, leading to either activation or inhibition that determines glomerular injury.

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In the complex web of potential mechanisms implicated in the pathogenesis of IgA nephropathy, IgA glomerular deposits remain the *sine qua non* phenotype of the disease. Despite almost four decades of clinical and experimental investigations, the immunologic processes that induce and perpetuate glomerular IgA deposition remain a clinical challenge to identify. A decade after Jacque Berger's seminal report of "IgA glomerular deposits in renal disease," an experimental animal model was developed demonstrating that polymeric IgA immune complexes lead to IgA glomerular deposits. This was followed by a cascade of clinical investigations that reported IgA immune complexes in the circulation and renal tissues of patients with IgA nephropathy. Now it is well recognized, as described in a comprehensive clinical review,[1] that "primary IgA nephropathy is an immune-complex–mediated glomerulonephritis defined immunohistologically by the presence of glomerular IgA deposits accompanied by a variety of histopathologic lesions." From this characterization it is implicit that not all IgA immune deposits possess equivalent pathogenic potential, as the glomerular landscape usually represents a wide spectrum that varies from minimal or no lesion to severe sclerosis. Thus, the enigma of glomerular IgA deposition is wrapped in the mystery of absent correlation between the intensity of the IgA deposits and the extent of glomerular injury. The experimental findings of Suzuki *et al.*[2] (this issue) shed new investigative light to unwrap this mystery.

Over the years, several valuable experimental models of IgA nephropathy have been developed that have provided insightful clues to the pathogenesis of the disease. Collectively, the experimental immunologic and histopathologic

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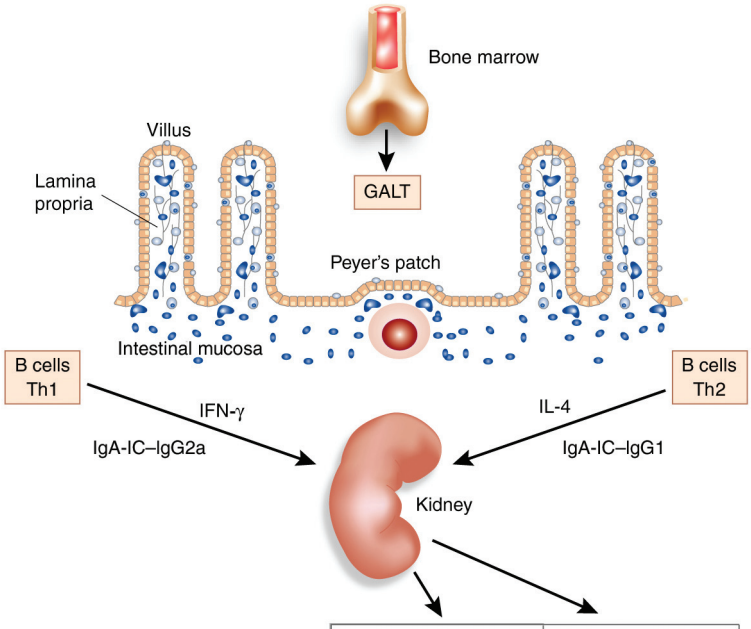

Functional motif	Receptor	Th 1 IgA-IC–IgG2a	Th 1 IFN-γ	Th2 IgA-IC–IgG1	Th2 IL-4
ITAM	FcγRI	+		–	
ITAM	FcγRIII	++		+	
ITAM	FcγRIV	+++	↑↑↑	–	
ITIM	FcγRIIB	–	↓	++	↑↑↑
Macrophage activation		High		Low	
Glomular injury		Severe		Minimal	

Figure 1 | Postulated immunopathogenic mechanisms associated with IgA nephropathy in the ddY model. The simplified scheme illustrates how the pathogenic potential of an IgA immune complex (IgA-IC) glomerular immune deposit is influenced by the colocalized subclass IgA interaction with Fcγ receptors (FcγRs) on infiltrating macrophages that affects the magnitude of their activation and consequently the extent of glomerular injury. In this model, stem cells in the bone serve as a reservoir of autoimmune B cells that home to the mucosa of the gut-associated lymphoreticular tissue (GALT) to generate polymeric IgA. T-helper 1 (Th1) polarization in the GALT will lead to B-cell immunoglobulin class switching favoring IgG2a that reacts with the antigenic component of the IgA-IC, generating a detrimental complex composite of IgA-IC-IgG2a. Conversely, a Th2 bias leads to production of IgG1 reactive with IgA-IC that generates complex composite of IgA-IC-IgG1 with low nephritogenic potential. Circulating interferon-γ (IFN-γ) and interleukin-4 (IL-4) produced, respectively, by Th1 and Th2 in the GALT modulate glomerular injury by affecting FcγR expression on macrophage infiltrates and consequently the magnitude of their activation by the IgA-IC–IgG deposit. ITAM, immunoreceptor tyrosine-based activation motif; ITIM, immunoreceptor tyrosine-based inhibition motif.

findings in these models recapitulate the clinical condition. Among these models, the ddY model with spontaneous glomerular IgA deposition, described initially by Imai *et al.*,[3] has been extensively investigated in Japan, in particular by the prolific laboratory of Yasuhiko Tomino. In this non-inbred strain of mice, IgA deposits occur at 16 weeks of age. Onset of glomerular injury, however, is variable; it is prominent at 20 weeks in some mice, is delayed to 40 weeks in some, and remains quiescent in others. On the basis of unparalleled large-scale performance and evaluation of open renal biopsy from 361 mice, Suzuki *et al.*[2] were able to sort the ddY mice into three groups: early onset, delayed onset, and quiescent. A central role of the bone marrow cells (BMCs) in development of IgA nephropathy was confirmed by transplantation among the groups. BMCs transplantation from quiescent (Q) donor to early-onset (EO) recipient markedly blunted the development of injury in the EO group. In contrast, BMCs transplantation from an EO donor induced glomerular injury in Q recipients and aggravated the glomerular lesion in EO recipients. Concurrent with the progression of glomerular lesion, there was a striking alteration in the glomerular deposits' composition, whereby IgG2a colocalized with an intensity equal to that of IgA. The significant correlation between the circulating level of serum IgA/IgG2a complexes and the glomerular injury score of the EO group is suggestive of causality. This prompted further investigation that compared intracellular content and *in vitro* production of interferon-γ (IFN-γ) and interleukin-4 by mitogen-stimulated spleen T lymphocytes. Enhanced IFN-γ production in the EO group suggested T-helper 1 (Th1)-polarized activity that contributed to the evolution of IgG2a immune deposits.

Knowledge about the role of T cell-mediated immunity in general, and Th1/Th2 polarization in particular, in initiation and progression of clinical IgA nephropathy is in short supply and is not well understood. Clinical reports of enhancement in both circulating Th1 and Th2 T-lymphocyte subsets, and of Th2 predominance at the single-cell level of analysis in patients with IgA nephropathy,[4] need to be reconciled with the postulate of Suzuki *et al.*[2] More recently, Chao *et al.*,[5] using a B cell-deficient model of experimental IgA nephropathy, demonstrated that the antigen and cognate IgA immune complexes activate T cells that indirectly, without infiltrating the glomerulus, contribute to injury. The requirement for T cells was evident by the failure of such immune deposits to induce glomerular injury in the same strain of mice with combined B- and T-cell deficiency. It is of note that the attempt by Suzuki *et al.*[2] to passively transfer T cells and serum from EO mice failed to induce IgA nephropathy in recipient nude mice. This suggests that the stem cell in bone marrow is a prerequisite for the development of the disease. Most relevant to the observation of Th1 polarization in the ddY model, the data of Suzuki *et al.*[2] are highly consistent with the previous report of Nogaki *et al.*,[6] which showed increased IFN-γ

and decreased interleukin-4 production by mitogen-stimulated $CD4^+$ cells from ddY mice producing high IgA. Of great interest also is that, in the first description of the ddY model, Imai *et al.*[3] reported a steep rise of IgG2a at 40 weeks that coincided with definitive mesangial proliferation. Nonetheless, the most significant aspect of the findings of Suzuki *et al.*[2] is the detection of circulating IgA immune complexes containing IgG2a, whose level correlated with the score of glomerular injury. Although the source and composition of such complexes are unknown, their nephritogenic potential is ascertained.

What are the source and antigen composition of IgA/IgG2a immune complexes in ddY mice, and how do they precipitate in glomerular injury? Suzuki *et al.*[2] extensively discuss their findings in terms of Th1 polarization; this need not be reiterated here. A different perspective on their results, however, compels me to postulate that glomerular injury emerges from the convergence of different effectors and mediators. It is well established that stem cells in the adult mouse bone marrow represent the cellular reservoir of B-1 cells that are selected by self-antigens; this B-1 repertoire tends to be autoreactive and plays an important role in mucosal immunity. The decrement in albuminuria, observed by Suzuki *et al.*[2] in the irradiated EO recipients between weeks 1 and 5 after transplantation of BMCs from similar EO donors, suggests this latency period might be required by the transplanted autoimmune B cells for repopulating the lymphoid organs before they differentiate into autoantibody-producing cells. Earlier insightful studies by Kawaguchi[7] examined and compared Peyer's patches and spleen cells of ddY mice at 40 weeks and concluded that gut-associated lymphoreticular tissue, not the spleen, plays an important role in the pathogenesis of the high IgA response and glomerular IgA deposition observed in this strain. Furthermore, Wakui *et al.*[8] reported that ddY mice develop mainly IgG-class and partly IgA-class anti-histone autoantibody after 40 weeks of age, and that histone–anti-histone complexes may contribute to the development of murine glomerulopathy. Like the B cells, autoimmune T cells in gut-associated lymphoreticular tissue may contribute to injury. In support of this conjecture is the elegant experimental model reported by Wang *et al.*,[9] who demonstrated that T cell-mediated mucosal immunity concurrent with the appearance of anti-DNA antibodies leads to severe I gA nephropathy.

IgA immune complexes (IgA-IC) containing IgG antibody glomerular deposits are a well-recognized feature of IgA nephropathy. Their pathogenic significance, however, has not been elucidated. This may be due to divergent activities of IgGs that can now be explained through selective engagement of their isotype-constant Fc region with specific cellular receptors (FcγRs). Structurally, four different classes of FcγRs have been identified with different affinities that vary from high (FcγRI) to low (FcγRII and FcγRIII), with the most recently discovered, FcγRIV, having selective and intermediate affinity for mouse IgG2a and IgG2b.[10] The majority of these receptors (FcγRI, FcγRIII, FcγRIV) are classified as activating, because they transmit intracellular signaling via immunoreceptor tyrosine-based activation motif (ITAM), whereas FcγRIIB is inhibitory, as it transmits signal via immunoreceptor tyrosine-based inhibition motif (ITIM). As illustrated in Figure 1, a simplified model postulates that glomerular injury is dependent on the activation status of infiltrating macrophages. The composite IgA-IC–IgG2a isotype interaction with the paired expression of activating and inhibitory receptors causes a high activation-to-inhibition ratio, triggering generation of mediators that produce injury. By comparison, the composite IgA-IC–IgG1 isotype, with higher affinity for the inhibitory FcγRIIB and a lack of interaction with the activating FcγRI and FcγRIV receptors, produces a low activation-to-inhibition ratio, keeping the macrophage quiescent with minimal or no injury. It is of note that the proinflammatory extrarenal IFN-γ potentiates IgA-IC–IgG2a deposits by upregulating activating FcγRs and blocking expression of the inhibitory FcγRIIB. Conversely, interleukin-4 upregulates the inhibitory FcγRIIB on macrophages, thereby dampening further the pathogenic potential of IgA-IC–IgG1 complexes. As is indicated above, this minimalist framework model is far from being comprehensive. It does not account for the important roles of the antigen, complement system, genetic background, and a host of unknown epistatic modifiers involved in disease susceptibility and severity.

The promising experimental findings of Suzuki *et al.*[2] usher in an exciting era in IgA nephropathy research: the era of correlating the nature of the immune deposits with glomerular progression to injury. The new investigations also encourage us to continue to build on the experimental models as a roadmap for which clinical studies to pursue. The intensive experimental work is bearing fruit and shows a solid potential to bridge the gaps in our knowledge of IgA nephropathy.

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