T-cell homing receptor expression in IgA nephropathy

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Abstract

Background. IgA nephropathy (IgAN) is characterized by mesangial deposition of polymeric IgA (pIgA). In IgAN, mucosal pIgA production is reduced while systemic production is increased, making the latter the likely source of mesangial pIgA, and suggesting a displacement of pIgA-producing cells from mucosal to systemic sites. Upon activation, lymphocytes migrate through the circulation up-regulating homing receptors (HR) which direct their return to appropriate effector locations. We investigated the HR expression of T-cell subsets in IgAN, healthy adults and membranous nephropathy (MN).

Methods. Peripheral blood cells were labelled for CD3, CD4 and CD8, and for L-selectin (naive cells), integrin α4β1 (systemically homing cells) and integrin α4β7 (mucosally homing cells) and analysed by flow immunocytometry.

Results. In IgAN, CD3 T cells displayed reduced L-selectin and increased α4β1hi expression, with no difference in α4β7. No abnormality of T-cell HR expression was found in MN. Both IgAN and healthy adults maintained their patterns of T-cell HR expression when studied again at a later time point, and the changes in IgAN were entirely accounted for by the CD4 T-cell subset with CD8 HR expression being normal.

Conclusions. The consistently reduced L-selectin expression by CD4 T cells indicates increased activation of this subset in IgAN. These activated cells express α4β1 rather than α4β7, and therefore home to systemic effector sites. CD4 T cells regulate antibody production, including IgA. As pIgA is overproduced in systemic sites in IgAN, we hypothesize that these activated systemic pIgA production observed in IgAN.

Keywords: IgA nephropathy; α4 integrins; lymphocyte homing; pathogenesis; T cell

Introduction

IgA nephropathy (IgAN) is one of the commonest patterns of glomerulonephritis (GN), and is characterized by deposition of polymeric IgA (pIgA) in the renal mesangium. A number of subtle disturbances of the IgA immune system have been reported in IgAN [1], which together lead to the presence in the blood of pIgA molecules with a propensity to mesangial deposition, although the mechanisms underlying this phenomenon have yet to be fully elucidated.

Human IgA production occurs in two distinct immunological compartments: mucosal and systemic. The vast majority of IgA is produced at mucosal surfaces. This is almost exclusively polymeric and is transported directly across the mucosal epithelium into external secretions, with very little entering the blood. Serum IgA, which is mostly monomeric (mIgA), arises from the systemic immune compartment and is mainly produced in the bone marrow. Therefore, pIgA can be considered to be the mucosal IgA phenotype. The factors controlling pIgA production rather than monomeric IgA (mIgA) in mucosal immune tissue are unknown, but it is clear that lymphocytes encountering antigen at mucosal sites are at some point subjected to influences which strongly favour pIgA production over that of mIgA and other immunoglobin isotypes.

There is good evidence for disturbances in lymphocyte populations in patients with IgAN. The numbers of pIgA-producing plasma cells are reduced in the duodenal mucosa of patients with IgAN [2], but increased in the bone marrow [3,4], arguing against overproduction of mucosal pIgA, but rather suggesting a systemic source for mesangial pIgA. Immunization studies show exaggerated systemic pIgA responses to both systemic and mucosal antigens [5,6], while some mucosal pIgA responses to mucosal antigen challenge are reduced in IgAN [7,8]. Furthermore, elevated circulating pIgA antibody levels have been described against mucosal antigens such as polio, Helicobacter pylori, and food and environmental components in IgAN [9,10]. Therefore, although the circulating pIgA in IgAN is likely to arise from a...
systemic source, it may well be driven by mucosally encountered antigens. Overall, this picture strongly suggests a shift of mucosal-type antibody production from mucosal to systemic sites, and indicates that abnormal control of the fine balance between the mucosal and systemic immune systems may underlie the pathogenesis of IgAN.

Restriction of cell- and antibody-mediated immune responses to appropriate sites in the body is achieved by the interactions of specialized adhesion molecules, or homing receptors (HRs), expressed on the surface of B and T lymphocytes with vascular endothelial ligands. The expression of lymphocyte HRs varies with the activation status of the cell, and naïve, effector and memory lymphocytes display different homing characteristics [11]. The main HR of naïve lymphocytes is L-selectin (CD62L). L-selectin can bind both the peripheral lymph node adhesion molecule (PNAd) and the mucosal addressin cell adhesion molecule (MAdCAM-1), and therefore, mediates the migration of naïve lymphocytes through both systemic and mucosal lymphatic tissues [12]. If antigen is encountered in these induction sites, lymphocytes differentiate into short-lived effector T cells and a minor fraction of long-lived memory T cells and migrate through the circulation before homing back to the site of antigen encounter to elicit immune responses appropriate to the location, for example to direct, the dominant production of pIgA antibodies at mucosal sites.

T cells are pivotal in the control of antigen-driven adaptive immune responses, and it is likely that mucosally activated T cells play an important role in driving mucosal antibody production towards a plgA bias. Effector T lymphocytes (CD4 and CD8) downregulate CD62L [13], whilst up-regulating expression of \( \alpha_4 \)-integrin HRs dependent upon the site of activation [14]. The best characterized integrin HRs are \( \alpha_4\beta_1 \) (also known as VLA-4) and \( \alpha_4\beta_7 \) [15]. The ligand for \( \alpha_4\beta_1 \) is vascular cell adhesion molecule 1 (VCAM-1) [16], the expression of which is up-regulated at non-mucosal sites of inflammation [17]. Therefore, T cells expressing \( \alpha_4\beta_1 \) preferentially home to systemic sites including the skin, nervous system and bone marrow. The \( \alpha_4\beta_7 \) binds the mucosal addressin cell adhesion molecule MAdCAM-1, and therefore, \( \alpha_4\beta_7 \) expressing T cells preferentially migrate to mucosal sites [18]. Lymphocyte up-regulation of \( \beta_1 \) and \( \beta_7 \) is mutually exclusive, and therefore, in the circulation, these integrins define T cells homing to systemic and mucosal sites respectively [19].

We hypothesize that altered homing of mucosally-activated T cells may underlie the aberrant production of plgA observed in IgAN. To address this possibility, we investigated the expression of CD62L and the integrins \( \alpha_4\beta_1 \) and \( \alpha_4\beta_7 \) on peripheral blood T-cell subsets from patients with IgAN, healthy adults and patients with membranous nephropathy (MN). In IgAN, we found an increased percentage of CD4 T cells expressing the systemic HR \( \alpha_4\beta_1 \), paralleled by a decrease in CD62L expression, indicating a higher proportion of systemically homing activated effector and CD4 T cells in IgAN.

**Subjects and methods**

**Materials**

Unless otherwise stated, all reagents and materials were purchased from Sigma Chemical Co. (Poole, Dorset, UK). All antibodies were purchased from Pharmingen (BD Biosciences, Cowley, Oxford, UK), except anti-integrin \( \beta_1 \) (anti-CD29, Serotec, Kidlington, Oxford, UK), and anti-integrin \( \alpha_4\beta_7 \) (Act-1, previously described by Schweighoffer [18]) which was a kind gift from Millenium Pharmaceuticals Inc (Cambridge, MA, USA).

**Subjects**

We studied 38 patients with biopsy-proven IgAN (22 male, mean age 38 years, range 20–57), 46 healthy adults with no history of kidney disease (23 male, mean age 34 years, range 21–57), and 7 patients with biopsy-proven idiopathic membranous nephropathy (MN) (5 male, mean age 44 years, range 28–56). 12 randomly selected IgAN patients (6 male, mean age 34 years, range 20–51) and 11 healthy adults (6 male, mean age 35 years, range 25–50) were studied a second time, a minimum of 3 months after their initial recruitment. All subjects gave informed consent for inclusion in the study.

At the time of the study and during the follow-up period, no subject had an intercurrent illness, and none of the IgAN patients had macroscopic haematuria. The median time from renal biopsy to entry into the study for IgAN patients was 5 years (range 0.5–8). All IgAN patients had microscopic haematuria and/or proteinuria, but proteinuria was <1.5 g/24 h in all cases. All patients with idiopathic MN had <1.5 g/24 h proteinuria. The median serum creatinine in the IgAN patients was 117 \( \mu \)mol/l (range 65–285), and in MN was 104 \( \mu \)mol/l (range 70–170). None of the patients or healthy adults was receiving immunosuppressive treatments at the time of the study or had received treatment in the 24 months prior to study entry.

**Peripheral blood mononuclear cell (PBMC) preparation**

PBMCs were isolated from heparinized venous blood samples by density gradient centrifugation on Histopaque 1077 for 30 min at room temperature at 400 g. Cells were washed twice in ice cold PBS/2 mM EDTA/0.5% BSA (FACS buffer), resuspended in the same buffer at 1 x 10^7/ml, and immediately used for staining.

**Flow immunocytometry**

Cells were labelled with specific combinations of directly fluorochrome-conjugated or unconjugated antibodies. Where unconjugated primary antibodies were used, cells were sequentially labelled with unconjugated antibody followed by species-specific fluorochrome-conjugated secondary antibody. Non-specific and Fc-mediated binding was minimized by using F(ab)2 conjugates and blocking
with normal species-specific sera before staining. Samples were washed in ice cold FACS buffer between each step, all steps were performed on ice and following labelling, cells were immediately analysed by three colour flow immunocytometry.

Lymphocyte subsets were identified by staining with fluorochrome-labelled antibodies against CD19 (B cells), CD3 (T cells), CD4 (helper T cells) and CD8 (cytotoxic T cells). HR expression was assessed by simultaneous staining with antibodies to L-selectin (CD62L), integrins α4 (CD49d) and β1 (CD29), or the α4β7 heterodimer. Appropriate negative controls were prepared by incubating cells with fluorochrome-labelled isotype control antibodies. Propidium iodide (PI) staining was used to exclude dead cells from all analyses.

All data were acquired and analysed with an FACScan flow cytometer coupled to CELLQuest software (Becton Dickinson, San Jose, CA, USA). Lymphocytes were selected according to forward and side scatter parameters, dead cells were excluded and a minimum of 10^4 cells analysed. For each fluorescence channel appropriate negative isotype controls were run with each sample series and the percentage of cells staining positive with each antibody calculated. Over the duration of the experiments, the FACScan was calibrated weekly for fluorescence and light scatter with microbead standards (Dako FluoroSpheres, Dako Ltd, High Wycombe, Bucks, UK).

**Analysis of α4β1 integrin expression**

There is no single antibody available that directly reacts with the whole α4β1 heterodimer, and therefore, it was necessary to carry out double-staining with antibodies directed against the α4 and β1 chains individually to identify cells with the systemic homing phenotype. In all subjects studied, upwards of 50% of CD3 T cells were positive for β1 integrin expression but, as described by others, these positive cells fell clearly into two distinct populations with high and low β1 expression (Figure 1) [19,20]. As expected, identical staining patterns were found when gating on CD4 and CD8 T-cell subsets. Therefore, during flow immunocytometric analysis we calculated the total percentage of cells co-expressing α4 and β1 integrins, the percentage expressing α4 with β1hi, and also the percentage of β1-positive cells that fell into the β1hi subpopulation. We consistently found that >95% of β1hi T cells co-expressed α4, and therefore only present data here on those lymphocytes displaying a β1hi phenotype, as these lymphocytes represent the activated effector and memory T cells, primed for homing to non-mucosal sites.

**Statistical analysis**

Data analysis was by Mann–Whitney U tests, ANOVA, regression analysis and paired t-tests. P values <0.05 were considered significant.

**Results**

**Lymphocyte subsets in IgAN**

Consistent with other studies, no difference was found between patients with IgAN and healthy adults in the
In an initial study of 38 patients with IgAN and 46 healthy adults, there was no difference between the subject groups in the percentage of CD62Lhi CD3 T cells. Compared with healthy adults (open bars; n = 46), we found in patients with IgAN (closed bars; n = 38) a trend to a lower percentage of CD62Lhi CD3 cells, and a significantly increased percentage of z4β7hi CD3 cells. The percentage of z4β7hi CD3 cells was not different across the subject groups.

**CD3 T-cell homing receptor expression**

In an initial study of 38 patients with IgAN and 46 healthy adults, there was no difference between the subject groups in the percentage of α4β1hi CD3 T cells (healthy adults: 48 ± 2.6%; IgAN: 50.5 ± 2.4%), or in the intensity of z4β7 staining in the α4β7hi T-cell subset (data not shown). However, we noted a trend towards a reduced percentage of CD62Lhi CD3 T cells in IgAN (healthy adults: 79.8 ± 1.5%; IgAN: 73.7 ± 2.4%; P = 0.054), and a significant increase in the percentage of α4β7hi CD3 T cells (the systemic homing phenotype) in IgAN (healthy adults: 40.9 ± 1.9%, IgAN: 46.9 ± 2.1%; P = 0.034) (Figure 2). Commensurate with this, the percentage of α4β7-positive cells that fell into the β7hi range of the biphasic distribution was increased in IgAN (healthy adults 53.4 ± 2.1%, IgAN 59.7 ± 2.2%, P = 0.03). There was no difference between healthy adults and IgAN in the intensity of CD62L staining in the CD62Lhi T-cell subset (data not shown). There was also a significant negative correlation between the percentage of CD62Lhi CD3 T cells and α4β7hi CD3 T cells in IgAN (Figure 3), demonstrating the expected inverse relationship between CD62L, the dominant HR of naïve T cells, and β7 integrin, which is up-regulated following lymphocyte encounter with antigen. Finally, there was no correlation between the expression of any homing receptor and the degree of renal impairment (eGFR calculated by the modified MDRD formula) or the rate of urinary protein excretion (protein creatinine ratio) at the time of venous sampling. This was confirmed when data from the second study (as follows) were included incorporating both IgAN and MN patients (data not shown).

These observations suggest that compared with healthy adults, in IgAN, a higher percentage of circulating T cells are activated T cells, and that these are more likely to home to systemic than mucosal effector sites.

**Homing receptor expression by T-cell subsets**

In order to confirm our initial observations and further characterize the phenotype of the increased systemic homing CD3 T cell population in IgAN, we re-studied 23 subjects at a second time point, not less than 3 months later (12 IgAN, 11 healthy adults). In this study, we additionally included seven patients with idiopathic MN, to establish whether abnormal T-cell homing is specific to patients with IgAN, or is also seen in other forms of glomerular disease. In this second study, we analysed the HR expression of CD4 and CD8 T-cell subsets separately.

**Comparison of homing receptor expression by CD4 and CD8 T cells**

Consistent with previous reports in healthy adults, a greater proportion of CD4 T cells expressed CD62L than CD8 T cells (CD4 92.8 ± 1.7%, CD8 72.0 ± 2.7%, P < 0.001). In contrast, there was no difference in the percentage of CD4 and CD8 T cells expressing α4β1, or in the distribution of β7hi staining (Table 1), while the mucosal HR α4β7 was preferentially expressed.
was no difference in the percentage of CD62L hi CD4 T cells (\( P < 0.05 \) for all groups). There was no difference in the percentage of \( \alpha_4 \beta_1 \) CD4 and \( \alpha_4 \beta_2 \) CD8 cells, but in all subject groups, there was a significantly higher percentage of \( \alpha_4 \beta_1 \) CD8 than \( \alpha_4 \beta_2 \) CD4 T cells (\( P < 0.05 \) for all groups).

on CD8 T cells (CD4 41.7 ± 3.2%, CD8 56.9 ± 5.2%, \( P = 0.017 \)).

**Homing receptor expression by CD4 T cells in patients and healthy adults**

In IgAN, the percentage of CD62L hi CD4 T cells was lower than healthy adults (healthy adults 92.8 ± 1.7%, IgAN 84.9 ± 2.6%, \( P < 0.01 \)), while \( \alpha_4 \beta_1 \) expression was higher (healthy adults 43.2 ± 3.1%, IgAN 56.7 ± 3.8%, \( P < 0.01 \)). There was no difference between healthy adults and IgAN in the intensity of CD62L staining in the CD62L hi T-cell subset (data not shown). As before, the increased frequency of cells expressing \( \alpha_4 \beta_1 \) was associated with a shift in the distribution of \( \beta_1 \) staining (percentage of total \( \beta_1 \) positive CD4 cells falling into the \( \beta_1 \) hi subpopulation: healthy adults 60.1 ± 2.0%, IgAN 70.3 ± 2.2%, \( P < 0.001 \)). There was no difference in either the percentage of \( \alpha_4 \beta_1 \) CD4 T cells or in the intensity of \( \alpha_4 \beta_7 \) staining in the \( \alpha_4 \beta_1 \) hi CD4 T-cell subset between IgAN and healthy adults. HR expression by CD4 T cells from patients with MN did not differ significantly from healthy adults (Figure 4).

**Homing receptor expression by CD8 T cells in patients and healthy adults**

In contrast, patients with IgAN did not display any significant alteration in the percentage of CD8 T cells with a CD62L hi, \( \alpha_4 \beta_1 \) or \( \alpha_4 \beta_2 \) phenotype when compared with healthy adults or MN (Figure 5).

**Influence of time on T-cell homing receptor expression**

To establish whether the observed pattern of T cell HR expression was persistent over time, we compared the results obtained from 12 patients and 11 healthy adults who participated in both studies at two different time points, T1 and T2, which were a minimum of 3 months apart. Individual subjects showed remarkable consistency in their T-cell HR expression over time, with a lower percentage of CD62L hi and higher percentage of \( \alpha_4 \beta_1 \) hi T cells being apparent in the IgAN group at both time points (Figures 6 and 7). The proportion of \( \alpha_4 \beta_7 \) T cells equally did not vary significantly between IgAN and healthy adults (\( P < 0.05 \) for all groups).
across the two time points and remained unchanged from healthy adults.

Discussion

In this study, we investigated the possibility that alterations in T-cell homing may be involved in the aberrant pattern of mucosal-type pIgA1 production seen in patients with IgAN. We found a persistent increase in the percentage of CD4 T cells expressing $\alpha_4\beta_1$, which favours their recruitment to non-mucosal sites, and a corresponding decrease in expression of CD62L by CD4 T cells in IgAN. However, in IgAN we found no changes in mucosal homing T-cell populations, characterized by surface expression of the alternative $\alpha_4$ integrin $\alpha_4\beta_7$. Taken together, these findings indicate a higher percentage of circulating T cells are activated effector cells in IgAN and that these T cells are more likely to home to systemic than mucosal effector sites.

L-selectin is uniformly expressed by naïve circulating T lymphocytes and mediates T-cell recruitment into peripheral lymph nodes, but not into extra-lymphoid tissue [21]. It is well-recognized that lymphocyte expression of the integrin chains $\alpha_4$, $\beta_1$ and $\beta_7$ are variable, leading to T-cell subsets with high and low expression [20,22]. Antigen encounter and T-cell activation are marked by up-regulation of $\alpha_4$ along with one of these two $\beta$ chains, leading to distinct populations of effector and memory T cells expressing $\beta_1^hi$ or $\beta_7^hi$ with the capacity to traffic through
non-lymphoid tissues. Expression of z4β1hi is the hallmark of gut-homing lymphocytes enabling these cells to attach to mucosal MAdCAM-1, while z4β1lo (VLA-4) preferentially binds to VCAM-1 and fibronectin, and thereby recruits cells systemically to areas of activated endothelium or exposed extracellular matrix. Co-expression of CD62L with z4 integrins appears to bias T-cell recirculation to trafficking through lymphoid tissues while CD62Llo−/hi T cells display a relative preference for entering extralymphoid sites [19]. The factors controlling the type of integrin HR expressed by activated T cells are not well understood, although evidence is accumulating for the critical role of dendritic cells [23]. Furthermore, it is as yet unclear whether site-specific integrin expression is achieved by up-regulation of appropriate receptors by T cells equally able to express all HR, or preferential ‘selection’ and clonal expansion of T cells precommitted to express specific integrin chains [24].

In all the subjects examined, the CD4 and CD8 T-cell subsets demonstrated consistent patterns of HR expression. As previously demonstrated, the CD8 subset had lower CD62L and increased z4β7 expression when compared with CD4 T cells [25]. We found no difference in the percentage of circulating CD4 or CD8 cells expressing z4β7lo or in the intensity of z4β7 staining between patients and healthy adults. The gut mucosa is the major site of IgA production in man, and there is good evidence for disrupted IgA production in IgAN, with reduced numbers of J chain and IgA1-producing plasma cells and compromised mucosal IgA1 antibody responses to mucosal antigen challenge [2,7]. Our study does not provide any evidence for altered mucosal-homing T-cell populations playing a direct role in reduced mucosal pIgA1 production in IgAN. However, the z4β7-expressing CD4 and CD8 T-cell subsets identified in this study will have been predominantly memory T cells. We cannot, therefore, exclude a selective defect in z4β7 expression in effector T cells in IgAN. Furthermore, mucosal homing is not mediated exclusively by z4β7 and there is increasing evidence to support the importance of a number of chemokine receptors such as CCR9 and CCR10 in lymphocyte trafficking to mucosal epithelial sites [26]. These were not assessed in this particular study, but are the focus of a separate investigation. Equally, we cannot exclude subtle imbalances in either the antigen specificities or functional characteristics of the z4β7 T-cell population we have detected. Also, effective homing of these cells back to appropriate mucosal sites depends on additional local factors such as expression of MAdCAM-1 and synthesis of chemokines such as MEC (mucosae-associated epithelial chemokine/CCL28) and TECK (thymus-expressed chemokine/CCL25) [27].

Few studies have investigated mucosal T-cell populations in situ in IgAN. Increased T-cell activation marker expression and altered V region usage by mucosal γδ T cells have been reported [28,29], indicating that there is, in fact, some disruption of mucosal T-cell function, but the significance of these findings is as yet unclear.

Our major finding in IgAN was an increase in the percentage of circulating CD4 T cells co-expressing high levels of the integrin z4 and β1 chains, the components of the HR heterodimer z4β1 (VLA-4). We also found a reduced proportion of CD62Lhi CD4T cells in IgAN, which showed a significant negative correlation with z4β1hi. Taken together, this suggests that in IgAN there are increased numbers of CD4 T cells capable of homing to non-mucosal sites. As CD62L is often downregulated by antigen-experienced T cells, this is probably a further reflection of increased CD4 activation in this disease [30].

These observations contradict to some extent earlier findings suggesting increased CD62L expression by T cells in IgAN [31,32]. One of these studies reports on lymphocyte HR profiles in children with IgAN, and therefore, it is difficult to compare with adult data as HR expression is known to change with age [33]. The study by Kennel-De March reported increased CD62L density on T lymphocytes in IgAN (unconfirmed in this study). However, consistent with our findings, this study could not demonstrate a significant difference in the proportion of CD62Llo T cells when comparing healthy adults and IgAN subjects. This earlier study examined enriched T and B lymphocytes rather than whole blood and it may be that this relatively prolonged experimental protocol led to changes in the surface phenotype of the lymphocytes and the subtle increase in antigen staining reported. With regard to T cell β1 expression, we have specifically evaluated the β1hi subset of the bimodal β1 staining profile. Comparison of the percentage of z4β1hi-staining T cells in this study (48.0–50.5%) with that seen in the Kennel-De March study (71.3–83.5%) would suggest that the criteria used to define z4β1hi T cells differ considerably making comparisons impossible. Importantly, this earlier study did not examine HR expression in T-cell subsets, and therefore was unable to comment on changes in CD4 CD62L and z4β1 expression. Acknowledging the discrepancy between our findings and earlier reports we randomly selected a proportion of the healthy adults and IgAN subjects and repeated their HR staining. This did not differ significantly across the two time points suggesting that our initial observations were indeed correct. This stability is perhaps not surprising as we were predominantly studying the phenotypes of naïve and memory T-cell populations, which would not be expected to change significantly in the absence of acute infection or inflammation.

We can only speculate as to the likely destination of z4β1hi CD4 T cells in IgAN. The main ligand of z4β1 is VCAM-1 [34,35]. In contrast to the z4β1 ligand MAdCAM-1, which is restricted to mucosal venules where it is constitutively expressed, VCAM-1 can be induced in the vasculature of a wide variety of tissues in inflammatory conditions, but is rarely expressed in the mucosa, even when inflamed [19,36]. VCAM-1, therefore, mediates recruitment of z4β1hi cells to inflamed non-mucosal sites [37–39]. In IgAN there is an increase in pIgA1 antibody production at systemic
sites such as the bone marrow [3,4]. Interestingly, there is good evidence for a key role for VCAM-1/α4β1 interactions in normal cellular recruitment to the bone marrow [40–42]. We would suggest that the increase in systemically homing CD4T cells in IgAN includes a subset of helper T cells capable of supporting a mucosal-type, plgA-dominated immune response at non-mucosal sites such as the bone marrow. It is our belief that the continual release of systemically produced plgA into the blood, perhaps under the control of systemically homing T helper cells, overwhelms normal clearance mechanisms and, along with physical characteristics predisposing to mesangial deposition, results in the glomerular plgA1 accumulation pathognomonic of IgAN. In order to formally test this hypothesis, we are now assessing antigen specific T- and B-cell homing patterns and effector phenotypes during immune responses to mucosally and systemically administered neo- and recall antigens.

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Conflict of interest statement. None declared.

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