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Leukocyte Recruitment to the Inflamed Glomerulus: A Critical Role for Platelet-Derived P-Selectin in the Absence of Rolling

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The renal glomerulus is one of the few sites within the microvasculature in which leukocyte recruitment occurs in capillaries. However, due to the difficulty of directly visualizing the glomerulus, the mechanisms of leukocyte recruitment to glomerular capillaries are poorly understood. To overcome this, we rendered murine kidneys hydronephrotic to allow the visualization of the functional glomerular microvasculature during an inflammatory response. These experiments demonstrated that following infusion of anti-glomerular basement membrane (GBM) Ab, leukocytes became adherent in glomerular capillaries via a process of immediate arrest, without undergoing prior detectable rolling. However, despite the absence of rolling, this recruitment involved nonredundant roles for the P-selectin/P-selectin glycoprotein ligand-1 and $\beta_2$ integrin/ICAM-1 pathways, suggesting that a novel form of the multistep leukocyte adhesion cascade occurs in these vessels. Anti-GBM Ab also increased glomerular P-selectin expression and induced a P-selectin-independent increase in platelet accumulation. Moreover, platelet depletion prevented both the increase in glomerular P-selectin, and the leukocyte recruitment induced by anti-GBM Ab. Furthermore, depletion of neutrophils and platelets also prevented the increase in urinary protein excretion induced by anti-GBM Ab, indicating that their accumulation in glomeruli contributed to the development of renal injury. Finally, infusion of wild-type platelets into P-selectin-deficient mice restored the ability of glomeruli in these mice to support leukocyte adhesion. Together, these data indicate that anti-GBM Ab-induced leukocyte adhesion in glomeruli occurs via a novel pathway involving a nonrolling interaction mediated by platelet-derived P-selectin.

T is well established that for leukocytes to leave the bloodstream and enter sites of inflammation, they must first undergo a sequence of interactions with the endothelium lining blood vessels at the target site (1). In general, leukocytes first make contact with the endothelium via the process of rolling. This interaction allows the leukocytes to respond to activating stimuli and subsequently arrest on the endothelial surface (2). Several studies in which leukocyte rolling has been inhibited or eliminated have demonstrated that the rolling interaction is critical in allowing leukocytes to undergo adhesion (3–6). Moreover, direct examination of the microvasculature using in vivo microscopy has repeatedly demonstrated that these interactions occur almost exclusively in postcapillary venules, primarily because expression of the endothelial adhesion molecules which mediate leukocyte rolling, particularly P- and E-selectin, is restricted to these sites (7, 8). However, before arriving at postcapillary venules, leukocytes must pass through capillaries, undergoing deformation to enable their passage through these narrow vessels (9, 10). Despite the close apposition of the leukocyte and endothelial cell surfaces brought about by this deformation, leukocytes are rarely observed to undergo adhesion in capillaries.

However, there is a growing body of evidence that this paradigm does not apply in all capillary beds. Leukocyte recruitment to capillary-like vessels has been observed in hepatic sinusoids, pulmonary capillaries, and in the glomerulus (11–13). The glomerular capillary bed in particular is a common target of injurious leukocyte recruitment during nephritogenic immune responses (14–16). Despite this, the mechanisms whereby leukocytes adhere in this unique capillary bed are poorly understood. Several adhesion molecules have been observed to contribute to recruitment in this site (17–20). Antagonism of the $\beta_2$-integrin/ICAM-1 adhesion pathway has been observed to be effective at reducing glomerular leukocyte recruitment in several studies, suggesting that conventional pathways which mediate leukocyte arrest are functional in the glomerular microvasculature (17–19, 21). In contrast, the necessity for the rolling step, and indeed the roles in the glomerulus of the adhesion molecules that normally mediate leukocyte rolling remain unclear.

P-selectin inhibition has been shown to reduce glomerular leukocyte recruitment and renal injury, suggesting that P-selectin-mediated rolling interactions contribute to efficient glomerular leukocyte recruitment (20, 22). In contrast, other work has shown that P-selectin-deficient (P-selectin$^{-/-}$) mice have increased levels of glomerular recruitment and renal damage, suggesting that not only is P-selectin not required, it may actually inhibit glomerular leukocyte recruitment (23, 24). None of these studies directly assessed interactions between circulating leukocytes and glomerular endothelial cells. Consequently, the effect of these interventions on rolling and adhesion, and indeed the requirement for rolling within the glomerulus remain unknown. Therefore, the aim of this study was to examine the molecular mechanisms of leukocyte recruitment to the glomerulus, using intravital microscopy to directly assess the glomerular microvasculature. To achieve this aim, we made use of the technique of renal hydronephrosis. This approach overcomes the difficulty of visualizing structures deep in the renal cortex by eliminating much of the renal medulla and rendering the
remaining cortex transparent, while maintaining glomerular perfusion (25). Direct visualization of glomeruli in these experiments has demonstrated that leukocyte recruitment to the glomerulus occurs via a novel pathway involving overlapping roles for the β2-integrin/ICAM-1 pathway, P-selectin, and platelets in the absence of detectable rolling in glomerular capillaries.

Materials and Methods

Animals

C57BL/6 wild-type mice were purchased from the Walter and Eliza Hall Institute (Melbourne, Australia), and P-selectin−/− mice on a C57BL/6 background (The Jackson Laboratory) were bred in-house. All experimental procedures were approved by the Monash University Animal Ethics Committee.

Antibodies

Sheep anti-mouse-glomerular basement membrane (GBM) Ab was prepared as described previously, except that murine cortices were sonicated following homogenization (26). Normal sheep globulin (sheep IgG, prepared from nonimmune sheep serum using the same protocol, served as a control Ab. Abs used for immunohistochemistry were as follows: FITC-conjugated goat anti-mouse C3 (Cappel); FITC-conjugated rabbit anti-sheep IgG (Sigma-Aldrich); polyvalent rabbit anti-human P-selectin (20); RB6-8C5 (anti-Gr-1); and FA-11 (anti-CD68). Abs used in vivo were 2E6, a hamster mAb against murine CD18 (2 mg/kg); YN1/1, a rat mAb against murine ICAM-1 (2 mg/kg); RB40.34, a rat mAb against murine P-selectin (20 μg per mouse; BD Biosciences); 2PH1, a rat mAb against murine P-selectin glycoprotein ligand-1 (PSGL-1) (2 mg/kg; BD Biosciences); and rabbit anti-mouse thrombocyte serum (Accurate Chemical & Scientific).

Unilateral ureteric ligation

Male mice (4–5 wk old) were anesthetized via inhalation of Ethrane (Abbott Australasia). A midline incision was made, and the ureter of the left kidney was ligated with 6/0 nonabsorbable silk and divided. The incision was closed, and 12 wk allowed for the kidney to undergo hydropnephrosis.

Intravital microscopy

Mice were anesthetized by i.p. injection of ketamine hydrochloride and xylazine, as described previously (27). The jugular vein was cannulated for the administration of further anesthetic and other reagents. Animals were maintained at 37°C on a heating pad. The hydropnephrotic kidney was exteriorized through a lateral incision, drained of urine using a 30-gauge needle, and extended over a clear viewing platform using 4/0 silk tied to the kidney capsule. The kidney was superfused with bicarbonate-buffered saline (pH 7.4) (37°C) and covered with a coverslip. The renal microvasculature was observed with an intravital microscope (Axioplan 2 Imaging; Carl Zeiss) with a water immersion objective (40/0.70 NA objective lens). Images were captured with a Leica DC 300F digital camera using Photoshop CS software (Adobe Systems) at predefined exposure and gain levels. The mean fluorescence intensity within the glomerular tuft minus background intensity in unstained tissue was determined using Scion Image (National Institutes of Health Image) (33). For sheep Ig and C3 levels, between five and 35 glomeruli were assessed per mouse, whereas P-selectin expression was quantitated in 20–50 glomeruli per animal. For identification of leukocytes in glomeruli, cryostat sections were prepared from periodate lysine paraformaldehyde-fixed kidneys, and sections were stained for Neutrophils (anti-Gr-1; mAb RB6-8C5) and macrophages (anti-CD68; mAb FA-11) using a three-layer immunoperoxidase technique as described previously (14, 34). To examine platelet accumulation in inflamed glomeruli, mice were injected with anti-GBM Ab, and after 2 h, nonadherent platelets were removed by successive perfusion with PBS and periodate lysine paraformaldehyde. Platelets were detected in cryostat sections using a two-layer staining protocol using rabbit anti-thrombocyte serum (1 μg/ml) followed by FITC-conjugated sheep anti-rabbit IgG (1/50). Individual platelets within glomeruli were counted in 30–50 glomeruli per animal.

Platelet isolation and transfer

Platelets were isolated from mouse whole blood as described previously (35). Platelets from either wild-type or P-selectin−/− mice were transferred into hydropnephrotic P-selectin−/− mice (or wild-type mice treated with anti-P-selectin Ab) via i.v. injection. Platelets from one donor were used to supply platelets for two recipient mice.

Assessment of proteinuria

To examine the contribution of neutrophils and platelets to renal injury, before treatment with anti-GBM Ab, mice were depleted of neutrophils, using RB6-8C5 (anti-Gr-1, 150 μg/mouse, i.p.) (36), or of platelets, using anti-platelet serum as already described. Control anti-GBM Ab-treated mice were treated with identical amounts of rat IgG or rabbit serum, respectively. Subsequently, renal injury was assessed by measurement of proteinuria as described previously. Briefly, mice were placed on metabolic cages for 16 h, and urine was collected throughout this period. urinary protein was assessed via Bradford assay and expressed as mg/24 h (26).

Statistical analysis

All data presented are shown as the mean ± SE. Student’s t tests or one-way ANOVA was performed to compare experimental groups. p values <0.05 were considered significant.

Results

Hydropnephrotic kidneys exhibit a normal response to anti-GBM Ab

The aim of the first series of experiments was to determine whether the process of hydropnephrosis had markedly altered either the ability of anti-GBM Ab to accumulate in the glomerulus or the level of the subsequent inflammatory response. The dose of anti-GBM Ab used (20 mg) was chosen based on pilot experiments to determine the lowest dose capable of consistently inducing renal injury

3 Abbreviations used in this paper: GBM, glomerular basement membrane; PSGL-1, P-selectin glycoprotein ligand 1.
FIGURE 1. Comparison of the response to inflammatory stimulation in hydrenephrotic and contralateral (nonhydrenephrotic) kidneys. Immunohistochemistry was used to compare sheep Ig deposition \((n = 6)\) (A), complement deposition \((C3) (n = 5–8)\) (B), P-selectin expression \((n = 5/group)\) (C), and neutrophil recruitment \((n = 10)\) (D) in hydrenephrotic and nonhydrenephrotic kidneys. Anti-GBM Ab was administered, then tissues were prepared for immunohistochemistry 60 min later for A–C, whereas for D, tissue was prepared 120 min after anti-GBM Ab administration. A–C were stained using fluorescence immunohistochemistry, and image analysis was performed to quantitate glomerular expression. Data represent intensity units above background. Gr-1-positive cells in glomeruli \((D)\) were counted in sections stained using conventional immunohistochemistry. Data are shown as mean ± SEM. *, Denotes \(p < 0.05\) relative to sheep Ig-treated kidneys.

as determined by analysis of urinary protein excretion. Comparison of hydrenephrotic and contralateral nonhydrenephrotic kidneys from the same mice 1 h after anti-GBM Ab administration demonstrated that the amount of anti-GBM Ab bound by glomeruli did not differ between hydrenephrotic and contralateral kidneys (Fig. 1A). In addition, both C3 deposition (Fig. 1B) and the increase in expression of P-selectin (Fig. 1C) induced by anti-GBM Ab were comparable in hydrenephrotic and nonhydrenephrotic kidneys. Examination of the types of leukocytes in normal and hydrenephrotic kidneys revealed that Gr-1−ve (neutrophils) and CD68+ve (monocytes) leukocytes were rarely observed in untreated glomeruli (data not shown). Two hours after anti-GBM Ab administration, the number of Gr-1+ve cells in glomeruli increased significantly in both normal and hydrenephrotic kidneys (Fig. 1D). Anti-GBM Ab treatment did not increase the number of CD68+ve cells in glomeruli in either kidney (data not shown). Together, these data indicate that hydrenephrosis did not dramatically alter deposition of anti-GBM Ab or the ability of the glomerular vasculature to respond to anti-GBM Ab and induce neutrophil recruitment.

We next used intravital microscopy to examine the process of anti-GBM Ab-induced leukocyte recruitment. Before anti-GBM Ab, leukocytes were visible passing rapidly through the glomerular capillary loops. However, no leukocytes were adherent within glomeruli. Following anti-GBM Ab administration, there was a significant increase in leukocyte adhesion within glomeruli at 60 min, with a further increase at 120 min (Fig. 2). The absence of marked leukocyte accumulation in control mice treated with sheep Ig demonstrated that the processes of hydrenephrosis, surgical exteriorization, and brief periods of fluorescent illumination used were not sufficient to induce leukocyte recruitment.

Rolling is not required for leukocyte recruitment to the glomerulus

Evidence from tissues such as the liver has indicated that the necessity for leukocyte rolling can be bypassed in some tissues, particularly those with unique microvasculature architecture (11). Therefore, we examined glomeruli in hydrenephrotic kidneys during the anti-GBM Ab-induced response to determine whether leukocyte rolling was detectable. In animals in which all leukocytes were stained with rhodamine 6G, rotational movement of leukocytes along the endothelial surface in inflamed glomeruli was not...
observed. In contrast, leukocytes were commonly observed to deform to pass through glomerular capillaries. In addition, some leukocytes were observed to arrest transiently (<1 s) before detaching and re-entering the bloodstream, whereas others were observed to undergo immediate arrest and remain adherent.

To study this process in more detail, experiments were performed with CFSE-labeled isolated neutrophils infused directly into the renal circulation. Following anti-GBM Ab treatment, neutrophils commonly underwent immediate arrest on passage through glomerular capillaries, in many cases subsequently undergoing rapid deformation to the shape of the surrounding vasculature (Fig. 3). In mice treated with anti-GBM Ab, the rate of primary arrest was greater than double that observed in mice treated with sheep Ig (Fig. 4A). Given the possibility that the process of neutrophil isolation altered the adhesive characteristics of these cells, we examined their behavior in the cremasteric microvasculature, in which leukocytes routinely roll and adhere in postcapillary venules. When infused directly into the inflamed cremaster muscle, neutrophils passed through capillaries without arrest, but readily underwent rolling and adhesive interactions in postcapillary venules (Fig. 4B). These findings demonstrate that the inability of these cells to roll in glomerular capillaries was not due to a loss of this capacity associated with the isolation procedure. These observations support the contention that the conventional multistep paradigm of leukocyte recruitment is not required for leukocyte adhesion in the glomerular microvasculature.

Leukocyte recruitment to glomeruli is CD18 and ICAM-1-dependent

Previous work has implicated the $\beta_2$ integrin/ICAM-1 pathway in mediating leukocyte recruitment in experimental glomerulonephritis. Similarly, in the current study, inhibition of either CD18 or ICAM-1 reduced leukocyte recruitment to basal levels, at 60 and 120 min, an effect not seen in mice treated with isotype control Abs (Fig. 5). The effect of anti-CD18 on neutrophil recruitment was also assessed in nonhydronephrotic contralateral kidneys using immunohistochemistry. Anti-CD18 also caused a significant
reduction in the numbers of Gr-1+ve cells in glomeruli in nonhydronephrotic kidneys (anti-GBM Ab alone: 1.16 ± 0.11 neutrophils/glomerular cross-section (n = 10) vs anti-GBM + anti-CD18: 0.76 ± 0.03 neutrophils/glomerular cross-section (p < 0.05; n = 8)).

Leukocyte recruitment to glomeruli is dependent on P-selectin/PSGL-1

We next examined the role of the P-selectin/PSGL-1 pathway in anti-GBM Ab-induced glomerular leukocyte recruitment. Blockade of P-selectin or PSGL-1 in wild-type mice reduced leukocyte recruitment to baseline levels (Fig. 6A). Similar results were obtained in anti-GBM Ab-treated P-selectin−/− mice (Fig. 6A). This was confirmed using immunohistochemical analysis of kidneys from anti-P-selectin Ab-treated mice, which showed that the number of glomerular neutrophils was reduced significantly in both contralateral and hydronephrotic kidneys (Fig. 6B). Finally, similar observations were obtained in intravital microscopy experiments in which isolated CFSE-labeled neutrophils were transferred into mice treated with anti-GBM Ab and anti P-selectin (wild-type: 0.52 ± 0.10 neutrophils/glomerulus (n = 7); wild-type + anti-P-selectin: 0.10 ± 0.06 (n = 4)) (Fig. 6, C and D). It is noteworthy that this role for P-selectin was observed in the absence of detectable leukocyte rolling.

Platelet-derived P-selectin mediates anti-GBM Ab-induced leukocyte recruitment

Given the fact that capillary endothelial cells lack the capacity to express P-selectin (7, 8), it is conceivable that platelets were acting as a source of glomerular P-selectin expression. To assess this possibility, we first examined glomerular platelet accumulation in response to anti-GBM Ab, using immunohistochemistry. Anti-GBM Ab infusion significantly increased the number of platelets detectable within glomeruli, in both contralateral and hydronephrotic kidneys (Fig. 7). In nonhydronephrotic kidneys, platelet accumulation did not require P-selectin because this process was not reduced by P-selectin blockade (Fig. 7, C and D). However, in hydronephrotic kidneys, P-selectin blockade did result in a small but significant reduction in platelet accumulation (Fig. 7F). We next examined the effect of platelet depletion on anti-GBM Ab-induced glomerular P-selectin expression. Following treatment with platelet-depleting serum, which reduced circulating platelet counts by over 97% without altering circulating leukocyte counts (data not shown and Ref. 28), glomerular P-selectin expression in anti-GBM Ab-treated mice was reduced to a level comparable to that seen in sheep Ig-treated mice (Fig. 8). The effects of this treatment were indistinguishable in hydronephrotic and contralateral kidneys (Fig. 8, D and F). This suggested that platelets were acting as the dominant source of P-selectin in this system. Therefore, we next examined the effect of platelet depletion on glomerular...
leukocyte recruitment. Platelet-depleted mice showed minimal leukocyte recruitment in response to anti-GBM Ab (Fig. 9A), indicating that platelets are critical to this model of glomerular leukocyte recruitment.

Given the fact that both P-selectin and platelets contribute to glomerular leukocyte recruitment, and platelet accumulation does not require P-selectin, this raised the possibility that platelets were acting as the source of P-selectin necessary for leukocyte recruitment. To test this hypothesis, we performed platelet transfer experiments between wild-type and P-selectin 

/ / / mice and assessed anti-GBM Ab-induced leukocyte adhesion. In anti-GBM Ab-treated wild-type mice pretreated with anti-P-selectin Ab, leukocyte adhesion remained low following infusion of P-selectin / / platelets (Fig. 9B). In contrast, infusion of wild-type platelets into anti-GBM Ab-treated P-selectin / / mice restored adhesion to levels similar to that seen in wild-type mice (Fig. 9B), indicating that platelet P-selectin is critical for anti-GBM Ab-induced leukocyte adhesion within glomerular capillaries.

To determine whether the observed glomerular accumulation of neutrophils and platelets contributed to glomerular injury, we examined the effects of anti-GBM in mice depleted of neutrophils and platelets, using urinary protein excretion as a readout of glomerular injury. As previously observed, anti-GBM Ab induced a significant increase in proteinuria at 24 h (Fig. 10) (20). Depletion of neutrophils with anti-Gr-1 eliminated the anti-GBM Ab-induced increase in protein excretion. Similarly, anti-GBM Ab failed to increase protein excretion in mice depleted of platelets (Fig. 10). These data indicate that neutrophils and platelets recruited to glomeruli in response to anti-GBM Ab are important contributors to the resultant glomerular injury.

Discussion

Recruitment of leukocytes to the glomerulus is a critical step in the development of glomerulonephritis (14–16). This is remarkable in that the glomerular microvasculature is essentially a capillary plexus, and in most vascular beds, leukocyte recruitment does not occur in capillaries. Given the difficulty of directly visualizing the glomerulus in living animals, the exact nature of the leukocyte-endothelial cell interactions responsible for recruitment to this bed have been difficult to elucidate. Evidence from histological studies has demonstrated a role for adhesion molecule-mediated leukocyte recruitment to glomeruli (17–21, 37). Moreover, findings such as the inhibitory effect of P-selectin blockade on leukocyte recruitment have suggested that the conventional sequence of rolling preceding adhesion applies in glomerular vessels (20, 22). However, this has never been demonstrated directly. Therefore, to determine the nature of the interactions that enable leukocyte recruitment to glomerular capillaries, we visualized glomeruli in the posthydro nephrotic kidney during a glomerular inflammatory response. These experiments demonstrated that leukocyte recruitment to inflamed glomeruli can occur without an initial rolling interaction. In contrast, leukocytes undergo immediate arrest in glomerular capillaries. However, despite the absence of detectable leukocyte rolling, the P-selectin/PSGL-1 pathway plays a key role in mediating leukocyte arrest in glomerular capillaries, indicating that leukocyte
recruitment to the glomerulus occurs via a novel pathway involving selectin-mediated interactions other than conventional rolling.

Previous studies have suggested that platelets contribute to glomerular injury, but their effects on leukocyte recruitment are less consistent (38, 39). The data in the present study indicate that in this model of glomerular inflammation, platelets recruited to the glomerulus play a key role in promoting leukocyte recruitment and glomerular injury, via provision of P-selectin that subsequently mediates leukocyte adhesion. It is noteworthy that platelets have been observed to promote recruitment in inflamed postcapillary venules in a number of tissues (28, 35, 40), in some cases acting as a source of P-selectin important in mediating platelet-leukocyte interactions (35, 40). However, these studies all examined interactions in postcapillary venules, where leukocyte rolling is critical to recruitment. The present study is the first to demonstrate a key role for platelet P-selectin in mediating leukocyte recruitment to inflamed capillaries.

It is established that in postcapillary venules, preformed P-selectin is present in Weibel-Palade bodies of endothelial cells and can be rapidly mobilized to the endothelial surface in response to inflammatory stimuli (41, 42). In contrast, capillary endothelial cells have rarely been observed to express P-selectin, even in response to strong inflammatory stimulation (8, 41). Similarly, in resting glomerular capillaries, P-selectin expression is undetectable, suggesting that glomerular endothelial cells do not express preformed P-selectin (20, 24). However, glomerular P-selectin expression increases in response to stimulation with anti-GBM Ab and in other models of inflammation (20, 24, 43–45). There is evidence that glomerular endothelial cells have the capacity to express P-selectin (45). However, in anti-GBM glomerulonephritis, studies of chimeric mice demonstrated that glomerular P-selectin expression occurred only in mice in which P-selectin was restricted to platelets (24). These findings support the present findings that in anti-GBM Ab-induced glomerular inflammation, platelets are the key source of glomerular P-selectin expression.

Despite the absence of detectable leukocyte rolling, our data also indicate that recruitment in glomeruli involves nonredundant roles for selectins and leukocyte integrins. One interpretation of these findings is that the conventional multistep cascade remains functional under these conditions, but occurs within a subsecond time scale. It is established that in response to appropriate leukocyte-activating stimuli such as chemoattractants, β2 integrins can be activated to a functionally active form extremely rapidly (46). The source of this putative stimulus in this model of glomerular inflammation remains unclear. Previous work has indicated that the complement pathway is not essential for leukocyte recruitment and full expression of disease in this model, suggesting that complement-derived chemoattractants are not responsible (20). Alternatively, signals mediated via leukocyte-expressed selectin ligands such as PSGL-1 may serve this function, because ligation or cross-linking of PSGL-1 has been shown to promote β2 integrin-mediated leukocyte adhesion (47).
GLOMERULAR LEUKOCYTE RECRUITMENT AND P-SELECTIN

To visualize the glomerular microvasculature, we used the technique of hydronephrosis (13, 25, 48, 49). Given the possibility that the process of hydronephrosis may have impacted upon glomerular function, we examined various parameters to assess the inflammatory response in glomeruli of hydronephrotic kidneys. Endpoints such as glomerular localization of anti-GBM Ab, accumulation of neutrophils and platelets, P-selectin up-regulation, and C3 deposition did not differ between contralateral and hydronephrotic kidneys. These findings support the contention that the mechanisms of leukocyte recruitment revealed by direct visual inspection of glomeruli in hydronephrotic kidneys accurately reflect the mechanisms functioning in unaltered kidneys. It is noteworthy that a previous study using this approach to examine the role of selectins in P-selectin-independent leukocyte trapping in narrow vessels, because despite leukocytes being capable of undergoing arrest in hepatic sinusoids, leukocyte rolling is not observed in these narrow vessels (51). Our observations indicate that a similar mechanism functions in unaltered kidneys. It is noteworthy that this recruitment is not due to adhesion molecule-independent leukocyte trapping in narrow vessels, because ICAM-1 is required for FMLP-induced leukocyte adhesion in hepatic sinusoids (11). Similarly, recent data demonstrate a role for the αc integrin and vascular adhesion protein-1 in adhesion of Th1 and Th2 lymphocytes, respectively, in sinusoids in the inflamed liver, demonstrating that recruitment to this capillary bed retains a requirement for an adhesion molecule-mediated leukocyte-endothelial cell interaction (51). Our observations indicate that a similar process occurs in the glomerulus. Despite the fact that leukocytes must deform to transit the narrow glomerular capillaries, leukocyte adhesion in these vessels requires a complex adhesion molecule-mediated interaction between the leukocyte and endothelial cells. The complexity of this interaction is increased by the key role of platelets that accumulate in glomerular capillaries and provide a source of one of the critical adhesion molecules in this response, P-selectin.

Disclosures

The authors have no financial conflict of interest.

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