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IL-10 Regulates Thrombus-Induced Vein Wall Inflammation and Thrombosis

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Vein wall inflammation associated with venous thrombosis is mediated by an imbalance in proinflammatory as compared with antiinflammatory molecules. We hypothesize that IL-10 is an important antiinflammatory cytokine that influences vein wall inflammation and thrombus propagation during venous thrombosis. To test this hypothesis a model of inferior vena caval thrombosis was used. Studies were performed at sacrifice 2 days after thrombus induction and included leukocyte morphometrics, myeloperoxidase activity, vein wall permeability, thrombus weight, and IL-10 ELISA analysis from the vein wall. IL-10 was elevated in the vein wall during venous thrombosis. Neutralization of IL-10 increased inflammation, while supplementation with rIL-10 demonstrated a dose- and time-dependent decrease in inflammation. Interestingly, a low 2.5-μg rIL-10 dose given at time of initiation of thrombosis most significantly decreased inflammation. Thrombus weight was importantly diminished by reconstitution of IL-10. These studies support an important role for IL-10 in the regulation of thrombus-associated inflammation and thrombosis and suggest that IL-10 could be used as a therapeutic agent in the treatment of venous thrombosis. The Journal of Immunology, 1998, 161: 1471–1476.

Venous thrombosis is a persistent clinical problem, contributing to significant morbidity and mortality in our society (1–2). In the United States, clinically recognized venous thrombosis affects nearly 260,000 people each year in patients hospitalized in acute-care facilities (1). Pulmonary embolism remains the most immediate life-threatening sequela causing death in more than 100,000 patients each year in the United States and contributes to death in another 100,000 (3–4). In addition, chronic venous insufficiency with resultant skin stasis changes, skin ulceration, and the postphlebitic syndrome also contributes to significant disability and patient morbidity (1).

Work from our laboratory using a rodent model of stasis-induced venous thrombosis has suggested a relationship between venous thrombosis and vein wall inflammation (phlebitis) (5) and confirmed the original observations by Stewart et al. of early neutrophil infiltration in the pathogenesis of venous thrombosis (6). This work demonstrated that the active vein wall proinflammatory response is characterized by predictable cellular trafficking with early neutrophil infiltration followed by monocyte/macrophage extravasation in response to venous thrombosis. The mechanisms regulating the interaction between these two processes has not been fully elucidated. However, vein wall leukocyte emigration has been correlated with the expression of early adhesion molecules such as P-selectin (7) and with various proinflammatory cytokines and chemokines, emphasizing the role of directed leukocyte migration and a cytokine cascade in the pathogenesis of the vein wall inflammatory response (8). While venous thrombosis has been associated with an increase in net inflammation, we hypothesize that this may be due to an imbalance that favors proinflammatory, as compared with antiinflammatory, mediators.

IL-10 is a potent antiinflammatory cytokine. In this study, we identify IL-10 as an important endogenous cytokine that regulates inflammation associated with venous thrombosis. A significant production of IL-10 from the vein wall was measured in response to venous thrombosis. Neutralization of IL-10 increased thrombus-associated vein wall inflammation and thrombosis, while exogenous IL-10 supplementation decreased thrombus-associated vein wall inflammation with concomitant reduction in thrombosis. Our findings demonstrate that IL-10 plays an important regulatory role in stasis-induced venous thrombosis and the associated vein wall inflammatory response.

Materials and Methods

Animal model and tissue analysis

Briefly, Sprague Dawley rats, weighing 250 to 300 g were anesthetized by inhalation of isoflurane (1–2%) and oxygen (100%) anesthesia. Aseptic midline laparotomy was accomplished, and inferior vena cava (IVC)3 thrombosis was performed, as previously described, with IVC ligation just below the level of the renal veins and concomitant ligation of IVC-draining side branches (9–11). Infrarenal IVC thrombosis is achieved in >95% of animals. Two days after thrombus induction, all animals were sacrificed and the infrarenal IVC below the ligature site were harvested, weighed, and grossly examined for the presence of clot. Thrombus weight was normalized to IVC length. For specimens undergoing vein wall morphometric analysis, a portion of the intact vein wall with thrombus was fixed in 10% formaldehyde for 24 h and then placed into a 70% alcohol solution for 6, 6 h before thrombus induction; HPF, high power field; T0, at the time of thrombus induction; ΔOD, change in optical density; T+6, 6 h after thrombus induction.

4 Abbreviations used in this paper: IVC, inferior vena cava; SA, serum albumin; MPO, myeloperoxidase; T−6, 6 h before thrombus induction; HPF, high power field; T0, at the time of thrombus induction; ΔOD, change in optical density; T+6, 6 h after thrombus induction.

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the vein wall only were assayed for IL-10 content and myeloperoxidase (MPO) analysis. All animals used in this study were housed and cared for in the University of Michigan Unit for Laboratory Animal Medicine under the direction of a veterinarian according to the Principles of Laboratory Animal Care (National Society for Medical Research) and Guide for the Care and Use of Laboratory Animals (National Institutes of Health Publication No. 80–23, revised 1985).

**Histopathologic analysis and leukocyte morphometric analysis**

To assess leukocyte infiltration, standard histologic analysis and morphometrics were performed as previously described (8). After staining the paraffin-embedded slides with hematoxylin and eosin, morphometric analysis was performed under high power light microscopy by counting each section of tissue for specific leukocyte cell types. Each vein wall was assessed for the number and type of cells, beginning at the thrombus-vein wall interface and extending the width of one high power field (HPF, ×1000). Five HPF sections of each vein wall were analyzed. Using standard morphologic criteria, including cell size, cytoplasmic content, and nuclear size, cells were classified as neutrophils, monocytes/macrophages, or lymphocytes.

**Myeloperoxidase assay**

The MPO assay was used to detect the presence of neutrophils in the vein wall using a modification of a previously described technique (12–15). Briefly, after the animals were sacrificed, the IVC vein wall was placed into a 50-mM potassium phosphate buffer solution (pH 6.0) with 5% hexadecyltrimethyl ammonium bromide (Sigma, St. Louis, MO). The vein wall was homogenized, sonicated, and centrifuged at 10,000 × g for 15 min at 4°C. The supernatant was assayed for MPO activity using a spectrophotometric reaction with o-dianisidine hydrochloride (Sigma) at 490 nm. The results were derived by observing the change in optical density (ΔOD) per minute. To improve accuracy, 6 IVC walls were pooled for each MPO determination in the IL-10 neutralization and supplementation studies.

**IL-10 ELISA**

IL-10 was measured by specific ELISA as previously described (8). Briefly, tissue homogenization of vein wall segments was undertaken in 1× PBS using a hand-held homogenizer. Immunoreactive IL-10 levels were quantitated using a double ligand method. Flat-bottom 96-well microtiter plates (Nunc Immuno-Plate 1 96-F, Denmark, Netherlands) were coated with 50 μl/well rabbit anti-IL-10 Ab (1 ng/μl in 0.6 M NaCl, 0.26 M H2BO3, and 0.08% NaOH, pH 9.6) for 16 h at 4°C and then washed with PBS, pH 7.5, 0.05% Tween 20 (wash buffer). Microtiter plate nonspecific binding sites were blocked with 2% BSA in PBS and incubated for 60 min at 37°C. Plates were then rinsed three times with wash buffer, and diluted 1:5 and 1:10 plasma specimen (50 μl) in duplicate was added, followed by incubation for 60 min at 37°C. Plates were then washed three times, followed by the addition of 50 μl/well biotinylated rabbit anti-IL-10 Ab (3.5 μg/ml in PBS, pH 7.5, 0.05% Tween 20, and 2% PBS), and then plates were incubated for 45 min at 37°C. Plates were again washed three times, streptavidin-peroxidase conjugate was added (100 μg/ml, Bio-Rad Laboratories, Richmond, CA), and the plates were incubated for 30 min at 37°C. Plates were again washed three times, and the chromogenic substrate o-phenylenediamine dihydrochloride (Bio-Rad Laboratories) 100 μl/well was added. Plates were then incubated at room temperature to the desired extinction, and the reaction was terminated with 50 μl/well 3 M H2SO4 solution. Plates were then read at 490 nm in an ELISA plate reader. Standards were 10 log dilutions of IL-10 from 1 pg/ml to 100 ng/ml. The sensitivity of the ELISAs was ≈ 50 pg/ml.

**Statistical evaluation**

Mean ± SE and unpaired student’s t test comparing experimental to control groups were used where appropriate. Analysis of variance (ANOVA) was performed to determine whether differences existed within treatment groups, such as the three different IL-10 dosage groups and the three different IL-10 time of administration groups. Individual t tests between dosages and between times were run only if ANOVA values suggested differences between the three groups. Significance was defined at a level of p ≤ 0.05 or p ≤ 0.01.

**Results**

**IL-10 is elevated in the vein wall during venous thrombosis**

Venous thrombosis was induced, and levels of IL-10 in the vein wall (n = 6) were compared with sham operated controls (n = 6) (laparotomy and dissection of the IVC but no ligature). Animals were sacrificed 2 days after thrombus induction, the wall of the IVC was removed, and IL-10 was measured by ELISA. In the vein walls associated with thrombus, IL-10 was 4550 ± 3750 pg/ml compared with 812 ± 812 pg/ml in the sham control vein walls. This was paralleled by elevated morphometric analysis of leukocytes and MPO assays that were all significantly elevated in thrombosed IVC as compared with sham controls. Concerning leukocytes, thrombosed (n = 10) as compared with sham control (n = 10) values were: neutrophils 55 ± 5 vs 3 ± 1 per 5 HPFs; monocytes 42 ± 2 vs 18 ± 1 per 5 HPFs; lymphocytes 4 ± 1 vs 1 ± 1 per 5 HPFs; total inflammatory cells 101 ± 5 vs 22 ± 1 per 5 HPFs; all p < 0.01 (Fig. 1). MPO analysis revealed a 15× increase in activity in the thrombosed veins (n = 10, 239 ± 4 ΔOD/minute) as opposed to the sham control veins (n = 10, 16 ± 3 ΔOD/minute), p < 0.01.

**Treatment with anti-IL-10 in vivo leads to augmentation of thrombus-associated inflammation**

To determine whether IL-10 was involved in the regulation of net inflammation associated with thrombosis, rats were passively immunized with either anti-IL-10 or normal rabbit serum as control i.v. 1 h before thrombus induction. This treatment resulted in a reduction of endogenous IL-10 from 4,550 pg/ml (n = 6) to 1,733 pg/ml (n = 6). Two days after thrombus induction, anti-IL-10–treated animals (n = 6) revealed a statistically significant increase in vein wall neutrophils (p < 0.01) and total inflammatory cells (p < 0.05), as compared with control Ab-treated (n = 6) animals (Fig. 2, A and B). Additionally, anti-IL-10–treated rats (n = 6) exhibited a 36% increase in MPO activity compared with control (n = 6) rats (49 ΔOD/minute vs 36 ΔOD/minute).

**Exogenous administration of IL-10 inhibits inflammation in both a dose- and time-dependent fashion**

To evaluate the antiinflammatory potential of IL-10 in venous thrombosis, rats received i.v. recombinant IL-10 (rIL-10; Peprotec, Rocky Hill, NJ) in both a dose- and time-dependent manner. Corresponding controls (n = 18) were given sterile pyrogen-free 0.25% serum albumin (SA) in similar volumes. Recombinant IL-10 was administered at 0.05, 2.5 μg (n = 12), 10 μg (n = 5), or 40 μg (n = 6) i.h before thrombus induction (16). Differences between groups were noted by the ANOVA for neutrophils and total inflammatory cells (p < 0.01). A statistically significant advantage to giving rIL-10 at the lowest dose (2.5 μg) was found in decreasing vein wall neutrophils and total inflammatory cells, with a significant difference (p ≤ 0.05) between 2.5 μg and 10 μg, and 2.5 μg and 40 μg for both neutrophils and total inflammatory cells (Fig. 3, A and B). The 2.5-μg dose was also significantly different.
from combined SA controls for neutrophils (33 ± 8 vs 57 ± 6 per 5 HPFs, p < 0.05), total inflammatory cells (60 ± 9 vs 87 ± 6 per 5 HPFs, p < 0.05), and monocytes (22 ± 1 vs 27 ± 2 per 5 HPFs, p < 0.05).

In a time-dependent manner, rIL-10 was administered i.v. at 2.5 μg either 6 h prior (n = 6) to thrombus induction (T−6), at the time (n = 6) of thrombus induction (T0), or 6 h after (n = 6) thrombus induction (T+6). Differences between groups were noted by ANOVA for neutrophils and total inflammatory cells (p < 0.01). A statistically significant advantage to giving rIL-10 at a dose of 2.5 μg at the time of thrombus induction (T0) was found compared with 6 h prior (T−6) to thrombus induction or 6 h after (T+6) thrombus induction (Fig. 4. A and B). A significant difference between T0 and T−6 was noted for neutrophils (19 ± 1 vs 59 ± 8 per 5 HPFs, p < 0.01) and total inflammatory cells (40 ± 3 vs 87 ± 6 per 5 HPFs, p < 0.01). The T0 time was significantly different from combined SA controls (n = 18) for neutrophils (19 ± 1 vs 64 ± 4 per 5 HPFs, p < 0.01), monocytes (18 ± 2 vs 25 ± 2 per 5 HPFs, p < 0.05), and total inflammatory cells (40 ± 3 vs 92 ± 4 per 5 HPFs, p < 0.01), while the T+6 time point was significantly different from combined SA controls for neutrophils (36 ± 15 vs 64 ± 4 per 5 HPFs, p < 0.05) and total inflammatory cells (69 ± 13 vs 92 ± 4 per 5 HPFs, p < 0.05). Additionally, the T0 time point produced the lowest MPO value (n = 6, 127 ± 7 ΔOD/min), with an 8% increase at T+6 (n = 6, 137 ± 9 ΔOD/min) and an even greater 14% increase at T−6 (n = 6, 144 ± 15 ΔOD/min).

Exogenous administration of IL-10 inhibits thrombosis

Since we have previously identified a correlation between inflammation and venous thrombosis and since IL-10 inhibits inflammation, we next assessed whether IL-10 would inhibit venous thrombosis. Wet thrombus weight (measured at time of sacrifice) was evaluated with rIL-10 administered at the optimal dose and time interval as established above (2.5 μg at T0). Importantly, there was a statistically significant 18% decrease in gross thrombus weight with rIL-10 administration compared with SA control (n = 9, 95 ± 6 mg vs n = 9, 116 ± 7 mg), p = 0.027. Thrombus weight corrected to IVC length demonstrated a similar trend with a 12% decrease (91 ± 4 mg vs 103 ± 5 mg, p = 0.072).

Discussion

We have previously utilized a rat model of stasis-induced venous thrombosis and described the pathophysiology of the vein wall inflammatory response induced during thrombus formation (5, 8), confirming the original observations of neutrophil infiltration by Stewart et al. (6). One of the key features of this response is the presence of neutrophils early after thrombus initiation, followed by monocyte/macrophage vein wall infiltration. Neutrophils, initially found adherent to the endothelium, cause endothelial disruption, exposing the collagen-rich basement membrane and leading to further thrombus propagation. This is followed by leukocyte transendothelial migration, leading to additional vein wall injury.

Although proinflammatory cytokines contribute to modulation of the thrombotic/phlebitis relationship, it seems likely that the initiation, maintenance, and eventual resolution of phlebitis is dependent on a complex balance of proinflammatory and antiinflammatory molecules. Importantly, the regulating role of the antiinflammatory cytokines has not been addressed in venous thrombosis. However, numerous diverse models of inflammation have suggested the importance of the antiinflammatory cytokine IL-10 and its role in down-regulating the inflammatory response (17–23).

In the present study, we describe the role of IL-10 in modulating the interrelationship between venous thrombosis and vein wall inflammation. IL-10 was found present in the thrombosed IVC vein...
wall in response to venous thrombosis and was correlated to other parameters of inflammation. In addition, IL-10 neutralization resulted in heightened vein wall inflammation, whereas exogenous administration of IL-10 was antiinflammatory. Administration of IL-10 at the time of IVC thrombosis induction was the best time point for limiting vessel wall inflammation. Since the half-life of i.v. administered IL-10 has been reported to be between 2.3 and 3.7 h (24), this may explain the lack of significant antiinflammatory effect when given 6 h before thrombus induction. In fact, a dose-response curve in two rats given rIL-10 at 2.5 μg in our laboratory revealed a peak serum level by ELISA 1 h after administration, but no detectable IL-10 at or after 4 h.

IL-10 is a naturally occurring antiinflammatory cytokine critical for influencing the inflammatory and coagulation response. This 35-kDa protein, produced by lymphocytes, monocytes/macrophages, neutrophils, mast cells, and epithelial cells, acts by inhibiting the synthesis of proinflammatory cytokines in addition to IL-1, TNF, and IL-6 (17–23, 25). In our venous thrombosis model, we have noted by immunohistochemical staining that IL-10 is produced primarily by monocytes and neutrophils in the thrombus and in the vein wall. IL-10 suppresses T cell proliferation (26), macrophage microbial activity (17), and the release of oxygen free radicals and inhibits nitric oxide-dependent microbicidal activity of leukocytes (27). IL-10 inhibits cytokine production from stimulated eosinophils (28), stimulated monocytes (29), and stimulated neutrophils (26, 30), while decreasing chemokine mRNA half-life (31) and up-regulating IL-1 receptor antagonist from stimulated neutrophils (32). In an ex vivo system of LPS-challenged human blood, IL-10 elevations were noted within the first 6 h of LPS administration, and the addition of neutralizing Abs to IL-10 increased the levels of leukocyte-derived cytokines. Furthermore, patients with septicemia demonstrate a significant elevation in IL-10 (33). Additionally, IL-10 has in vitro effects on endothelial cells. IL-10 has been found to inhibit the expression of IL-6 and IL-8 from stimulated HUVEC (34) and to inhibit the adhesion of leukocytes to stimulated HUVEC by down-regulating the expression of ICAM-1 and VCAM-1 (35). In other studies, in a paradoxical fashion, IL-10 has been found to induce the expression of E-selectin on HUVEC and human dermal microvascular endothelial cells (36) and to enhance VCAM-1 expression (but not ICAM-1, E-selectin, or major histocompatibility Ags) on HUVEC in the presence of PHA-activated peripheral blood monocytes (37).

We found that the inhibition of inflammation and IL-10 administration were best at a low dose (2.5 μg) when given at the time of thrombus induction. Recent studies in mice confirm that exogenous IL-10 at low dose (1 μg) confers resistance to what is normally a lethal dose of LPS (38). This protective effect occurred when IL-10 was given simultaneously or 30 min after LPS challenge. In a mouse model of staphylococcal enterotoxin, IL-10 was protective when given either before or simultaneously (39, 40). Additionally, mice pretreated 2 h before 25 min of supraceliac aortic occlusion with either 0.2 μg, 2 μg, 5 μg, or 20 μg rhIL-10 were found to be protected against adverse neutrophil-mediated lung injury at the lower doses, while essentially no protection was noted at the highest dose of 20 μg (16). This is similar to the results in which the highest dose (40 μg) was not protective against inflammation and in fact potentiated the inflammatory response, suggesting an in vivo desensitization of IL-10 responses at high levels of IL-10. Alternatively, at higher doses of IL-10, the paradoxical proinflammatory aspects of IL-10 may predominate.

In the context of coagulation regulation, IL-10 has been found to inhibit the production of tissue factor on the surface of monocytes (41–43), down-regulate the expression of mRNA for fibrinogen (44), and, in human endotoxemia, modulate the fibrinolytic system and
inhibit coagulant responses including the generation of prothrombin fragment F1 + 2 and thrombin-antithrombin complexes on volunteer exposure to LPS (45). These findings suggest a role for IL-10 in the regulation of thrombus generation. It is unclear whether these properties of IL-10 are a direct effect of this cytokine’s ability to induce proteins that inhibit tissue factor or procoagulant activity or are due to indirect effects of IL-10 inhibition of cytokine production. Tissue factor expression on the surfaces of monocytes in response to adhesion molecule expression contributes to thrombus formation and propagation (46). In addition, thrombin formation after a stimulating event, such as venous thrombosis with venous stasis, endothelial hypoxia, and vein wall injury, leads to the up-regulation of early adhesion molecules (such as P-selectin) that contribute to the amplification of vein wall inflammation and thrombus propagation (47). In this investigation, utilizing an assessment of thrombus load, i.e., thrombus weight, importantly we have shown that IL-10 plays a role in thrombus formation as related to vein wall inflammation. Animals treated with rIL-10 at the 2.5-μg dose given at the time of thrombus induction revealed a statistically significant decrease in thrombus weight.

FIGURE 4. A, rIL-10 times of administration and morphometrics; significant differences between T0 and T−6 for neutrophils and total inflammatory cells, T0 and control SA for neutrophils, monocytes and total inflammatory cells, and T+6 and control SA for neutrophils and total inflammatory cells. B, Note the significant decrease in neutrophils in the IVC in a rat treated with rIL-10, 2.5 μg given i.v. at the time of thrombus induction (A) compared with T+6 (B) and T−6 (C). n = neutrophils; w = vein wall; t = thrombus; arrows indicate thrombus/vein wall interface. Hematoxylin and eosin, ×1000 (oil).
Our findings demonstrate the importance of the anti-inflammatory cytokine IL-10 in regulating the interaction between stasis-induced venous thrombosis and the associated vein wall inflammatory response. IL-10 is present in high quantity in the vein wall in response to venous thrombosis. IL-10 depletion by neutralization resulted in increased vein wall leukocyte infiltration (especially neutrophils) confirmed by MPO analysis. Exogenous IL-10 supplementation produced a decrease in inflammation at a dose of 2.5 μg when given at the time of thrombus induction. IL-10 administration 6 h before initial thrombus formation even at the proper dose appeared to produce a paradoxical increase in leukocyte infiltration confirmed by MPO analysis; likewise, its administration at doses of 10 μg and 40 μg given 1 h before thrombus induction increased leukocyte infiltration. These results stress the importance of appropriate dosing and timing when administering IL-10 to achieve its desired antiinflammatory effects. Importantly, IL-10 administration also decreased thrombosis weight. The present results suggest that further studies on the ability of rIL-10 to limit inflammation and thrombus formation during venous thrombosis are warranted.

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References


