Online Table I. Activation and Signaling Pathways of Human Platelets Mediate Both Hemostasis and Inflammation[1-17]

Agonist(s) or Ligand(s)	Surface Receptor(s)	Receptor Class	Hemostatic Activities	Inflammatory Activities
Thrombin; Synthetic thrombin receptor activating peptides (TRAPs); Matrix metalloproteinase 1; others	Protease-activated receptors (PAR1, PAR4 in humans; PAR3, PAR4 in mice)	G Protein-Coupled Receptor (GPCR)	Inside-out signaling of integrin $\alpha_{IIb}\beta_3$; fibrinogen binding; aggregation; degranulation; clot retraction; TXA_2 synthesis; tissue factor synthesis	Release of chemokines and antibacterial peptides; surface translocation of P-selectin; synthesis of IL-1β and tissue factor; formation of platelet-leukocyte aggregates; triggering of platelet-dependent leukocyte signaling; altered surface display of toll-like receptors
ADP	P2Y receptors ($P2Y_1$, $P2Y_{12}$)	GPCR	Triggering, amplification of platelet aggregation; stabilization of platelet aggregates; TXA_2 synthesis; degranulation	Formation of platelet-leukocyte aggregates; synthesis of IL-1β
Thromboxane A_2 (TXA_2; stable TXA_2 mimetics)	TXA_2 receptor	GPCR	$\alpha_{IIb}\beta_3$ activation; fibrinogen binding; aggregation; adhesion; potentiation of thrombin signaling	Synthesis of IL-1β; release of CD40L

Platelet-activating factor (PAF); PAF-like oxidatively modified phospholipids	PAF receptor (PAFR) (Human but not mouse platelets express PAFR)	GPCR	Weak agonist for aggregation, adhesion; synergistic amplification of platelet activation by thrombin, ADP	Potent agonist for formation of platelet-neutrophil and platelet-monocyte aggregates; IL-1β synthesis
Collagen	GPVI (Collagen is also recognized by integrin $\alpha_2\beta_1$ on platelets)	Immunoreceptor	Association with GPIb-IX-V; activation of $\alpha_{IIb}\beta_3$; degranulation; release of inorganic polyphosphates (PolyP) with procoagulant and proinflammatory actions	Synthesis of IL-1β (not yet known if this is mediated by GPVI, integrin $\alpha_2\beta_1$, or both); shedding of proinflammatory microparticles; release of PolyP
Fibrinogen (Fg)	Integrin $\alpha_{IIb}\beta_3$ (integrin $\alpha_{IIb}\beta_3$ also binds other ligands, including fibrin, fibronectin, von Willebrand factor, vitronectin, and thrombospondin)	Integrin	Outside-in signaling triggering or contributing to: tight platelet adhesion and spreading on extracellular matrix; TXA_2 synthesis; fibrin clot stabilization and retraction; generation of platelet procoagulant activity and microparticles; degranulation; synergistic signaling with thrombin, other agonists; signaling to translation control pathways	Degranulation; amplification of signal-dependent translation

This list of agonist – and receptor-mediated hemostatic and inflammatory activities and responses is illustrative and not comprehensive. Additional examples, and details of intracellular pathways and mechanisms, are included in the supplemental references. Other inflammatory activities of platelets induced by pathways or agonists that trigger primary hemostatic responses are likely to be discovered.

Online Table II. Functional Responses of Human and Mouse Platelets Induced by LPS In Vitro[18-28]

Platelet Preparation	LPS	Functional Response(s)	Reference
Washed human platelets	*S. minn.* R595, 10-250 µg/mL	Potentiation of serotonin release induced by IgG aggregates or immune complexes	18
Human PRP	*E. coli* 0111:B4, 1-100 ng/mL	Did not directly induce or potentiate aggregation triggered by ADP, epinephrine (epi), or arachidonic acid (AA)	19
Human whole blood	*E. coli* 0111:B34, 0.1-100 ng/mL	Potentiated aggregation triggered by ADP, epi, AA; primed platelet-PMN aggregate formation; primed PAF synthesis	19
Human platelet rich plasma (PRP)	*E. coli* 0111:B4, ≤10 ng/mL	Did not directly induce aggregation or P-selectin translocation, or potentiate these responses to ADP, PAF, collagen	20
Gel filtered mouse platelets in buffer ~~or~~ with 10% autologous serum	*E. coli* 0111:B4, 5 µg/mL	Did not induce P-selectin translocation (30 min); induced adhesion of platelets to immobilized fibrinogen under flow	21

Human PRP or washed human platelets	Several *E. coli* LPS types; 1 µg/mL diluted in plasma	PAC-1 binding; CD40L upregulation; binding of fibrinogen; adhesion to cultured microvascular endothelial cells (no adhesion of washed platelets)	22
Isolated human platelets in Hank's Balanced Salt Solution	*E. coli* 0111:B4, 5-100 µg/mL	Did not induce platelet aggregation (~5 min) or P-selectin expression: induced attachment of platelets to neutrophils immobilized on protein-coated coverslips under flow; induced neutrophil extracellular trap (NET) formation and neutrophil degranulation	23
Human platelets isolated by negative immunoselection; PRP	*E. coli* 0111:B4, ~~10 ng – 1 µg~~100 ng/mL in 0.5% serum or recombinant CD14+LBP	Did not directly induce rapid shape change or aggregation; augmented rapid (5 min) ADP-induced aggregation in PRP; induced time-dependent actin polymerization, P-selectin translocation, P-selectin-dependent platelet-neutrophil interaction, CD40L upregulation (1-3 hr); time-dependent splicing of *IL-1β* pre-mRNA, IL-1β protein synthesis	24

Washed human platelets or PRP	Several different LPS types; (1-100 µg/mL)	Did not induce rapid aggregation of washed platelets but potentiated aggregation of platelets stimulated with subthreshold concentrations of thrombin, collagen; directly induced ADP release (10 min), P-selectin translocation (30 min)	25
Washed mouse platelets	*E. coli* 0111:B4, 10 µg/mL	Potentiated thrombin-induced aggregation, secretion	25
Human platelets isolated by negative immunoselection	*E. coli* 0111:B4, 100 ng/mL + rCD14, LBP	Shedding of microparticles; splicing of *IL-1β* pre-mRNA, synthesis of IL-1β protein; signaling of cultured endothelial cells	26
Human platelets isolated by negative immunoselection	*E. coli* 0111:B4, 10 ng/mL – 1 µg/mL	Did not induce P-selectin translocation (60 min); induced splicing of *tissue factor* (TF) pre-mRNA and generation of TF procoagulant activity (30 min – 4 hr)	27
Human PRP	LPS from *S. typhimurium*, 1 µg/mL	Did not induce thrombin generation. In contrast, histones triggered platelet activation and thrombin generation that were partially blocked by anti-TLR4 antibody.	28

See main text and cited references for additional details

Online Table III. Activated Human Platelets Have Diverse Mechanisms for Release or Surface Display of Inflammatory Factors[1-3, 16, 29-32]

Inflammatory Factor	Mechanism of Release or Surface Display	Inflammatory Activities
TxA_2	Rapid synthesis and paracrine release	See Table 1
PAF	Rapid synthesis; retained on platelet plasma membrane	See Table 1
Fibrinogen	Degranulation (alpha granules) and secretion	See Table 1
Platelet factor 4 (PF4; CXCL4)	Degranulation (alpha granules) and secretion	Chemotactic for neutrophils, monocytes; promotes monocyte survival and differentiation to macrophages; heterodimerization with RANTES to promote monocyte recruitment to endothelium; T-cell and monocyte trafficking, cytokine production in experimental cerebral malaria; plasmodium killing
RANTES (CCL5)	Degranulation (alpha granules) and secretion	Chemotactic for eosinophils ; signaling of monocyte inflammatory gene expression; recruitment of T-cells to endothelium; heterodimerization with PF4 with recruitment of monocytes to endothelium

P-selectin	Translocation to platelet plasma membrane from alpha granules	Binding to P-selectin glycoprotein 1 (PSGL-1) on neutrophils, monocytes, lymphocytes, and dendritic cells, mediating platelet-leukocyte interactions; signaling of gene expression and other responses of leukocytes by engaging PSGL-1
Serotonin	Degranulation (dense granules) and secretion	Modulation of endothelial barrier function; activates monocytes and prevents monocyte apoptosis; accessory signal for T-cells; alters T-cell trafficking
Inorganic Polyphosphates (PolyP)	Degranulation (dense granules) and release	PolyP trigger bradykinin generation in plasma and bradykinin-dependent increased capillary permeability, plasma leakage, and edema
ADP	Degranulation (dense granules) and secretion	Alterations in endothelial barrier function; modulation of monocyte activation, apoptosis; accessory signaling of T-cell activation
Human β-defensin 1	Release from novel cytoplasmic compartment in response to *S. aureus* α-toxin	Induction of neutrophil extracellular trap formation; bacterial killing
TLR9	Translocation from novel cytoplasmic compartment	Signaling and platelet activation if engaged by bacterial, viral DNA or other microbial factors

CD40 ligand (CD40L; CD154)	CD40L present on plasma membrane and in subcellular compartment(s) in basal state; cleavage of transmembrane CD40L at plasma membranes of activated platelets, release	Signaling of lymphocytes, monocytes, endothelial cells, platelets via CD40; adaptive immune responses; immune amplification
Interleukin 1β (IL-1β)	Signal-dependent pre-mRNA splicing and mRNA translation; translocation to plasma membranes of activated platelets; release in microvesicles and in soluble form	Activation of endothelial cells resulting in adhesion molecule and chemokine expression; induction of vascular smooth muscle cell cytokine production; triggering of chemokine release by synovial fibroblasts

Additional details regarding mechanisms and inflammatory activities of these platelet factors are included in the main text and cited references. This is an abbreviated list, and represents only a small fraction of the factors released or displayed by activated platelets.

Online Table IV. Examples of Signal Dependent Translation by Human Platelets that Yields Proteins with Relevance to Thrombosis and Inflammation[1, 2, 12, 27, 33-44]

mRNA or Pre-mRNA Transcript	Mechanisms of Signal-Dependent Translation	Protein Product	Functional Response(s)
Bcl-3	Translation of constitutive mRNA in activated platelets controlled by mammalian target of rapamcyin (mTOR)	B cell lymphoma 3 (Bcl-3)	Clot retraction in vitro
PAI-1	Basal expression that is enhanced by thrombin-stimulated translation of *PAI-1* mRNA	Plasminogen activator inhibitor-1 (PAI-1)	Release of PAI-1; association with tissue plasminogen activator in vitro
Il-1β	Signal-dependent splicing of pre-mRNA in activated platelets controlled by cdc-like Kinase 1 (CLK1); translation of the mature, processed mRNA transcript	IL-1β	Release of Il-1β in microparticles, solution; endothelial signaling in vitro (Platelet-derived IL-1β is reported to have inflammatory activities in vivo. See text.)
TF	Same as for *Il-1β*	Tissue factor (TF)	Release of TF in microparticles; clot time shortening in vitro
TIMP-2	Translation of constitutive mRNA by activated platelets	Tissue inhibitor of metalloproteinase 2 (TIMP2)	Time-dependent secretion of TIMP2 in vitro; Functional activity not tested

Experiments involving metabolic labeling of newly-synthesized proteins with radiolabeled amino acids and separation of the products by electrophoresis indicate that multiple proteins are produced when human platelets are activated under appropriate conditions. Many of these products are not yet identified, but others in addition to those on this list have been reported [36, 40, 44]. Also see main text and references.

Online Table V. Platelet Activities in Selected Inflammatory Vasculopathies

Syndrome, Disorder, or Disease Involving Vascular Inflammation	Platelet Activities in Clinical Studies and/or Experimental Models
Sepsis [1-3, 23, 27, 45-73]	Platelet activation may be ubiquitous in clinical sepsis. Platelet-fibrin thrombi and platelet sequestration in microvessels are central manifestations. Thrombocytopenia (multifactorial) is common and is a prognostic feature. Disseminated intravascular coagulation (DIC) occurs. Microbial factors (LPS, other TLR ligands) and host factors generated in sepsis (thrombin, PAF, others) can directly activate platelets (see Supplemental Tables 1 and 2). Reported platelet activities include: variable aggregation, adhesion, secretion depending on the clinical study; formation of platelet-neutrophil and platelet-monocyte aggregates; enhancement of adhesion of neutrophil aggregates to human endothelium in vitro; expression of *tissue factor* mRNA and tissue factor activity by platelets from septic subjects. Plasma from septic patients induces binding of platelets to neutrophils and NET formation in vitro, consistent with triggering of NET formation by LPS-stimulated platelets (Table 2). Platelet-neutrophil binding induced by plasma from septic subjects was blocked by an inhibitor that interrupts binding of MD2 to TLR4. Recent observations indicate that platelet-monocyte aggregates correlate with negative outcomes in elderly patients with sepsis (Rondina M, et al, manuscript submitted). Studies of controlled challenge of human volunteers with LPS are consistent with activation of platelets in sepsis. Mouse and other animal models are generally consistent with clinical studies of human platelets in sepsis, and indicate that platelets mediate microvascular thrombosis, NET formation, increased endothelial permeability, and lymphoid apoptosis.

Malaria[1, 2, 31, 32, 74-90]

Thrombocytopenia is common in human malaria caused by *Plasmodium falciparum*, *P. vivax*, and *P. knowlesi*. Inflammatory vasculopathy is a feature of severe malaria, which includes cerebral and pulmonary malaria and multiple organ failure. Cytoadherence ("sequestration") of parasitized red blood cells (PRBC) and accumulation of platelets and leukocytes – particularly monocytes – with generation of cytokines, dysregulation of hemostasis, and endothelial barrier disruption are thought to contribute to the vasculopathy. Platelets sequestered in microvessels in contact with leukocytes, PRBC, and a hemoglobin-derived malarial toxin (hemozoin) have been observed in autopsy specimens. Platelets bind to PRBC and form aggregates in vitro; this "clumping" is associated with severe malaria. Platelets act as cellular bridges between PRBC and activated human endothelial cells in vitro. PRBC (*P. falciparum*) activate human platelets in vitro, inducing binding of PAC-1 antibody, surface translocation of P-selectin, PF4 release. PF4 has been detected in plasma samples from patients infected with *P. falciparum*; few other studies of patient samples have been reported. Mouse models of severe malaria have controversial features, but generally support the idea that platelets contribute to malarial vasculopathy as immune effectors. While there is evidence that platelets contribute to vascular inflammation in severe malaria they may be protective and have anti-parasite activities early in the infection.

Dengue[1, 2, 91-102]	Severe thrombocytopenia, dysregulated coagulation, bleeding, capillary leak, systemic inflammation with increased plasma cytokines, and/or systemic hypoperfusion occur in some patients, resulting in syndromes that have been called dengue hemorrhagic fever and dengue shock syndrome. Platelet-monocyte and platelet-neutrophil aggregates form in the blood of patients and non-human primates infected with dengue. In vitro experiments indicate that the dengue flavivirus directly infects human platelets but precise contributions of platelets to vasculopathy and vascular instability in severe dengue syndromes are under investigation.
Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS)[1-3, 103-119]	Increased pulmonary capillary permeability and diffuse alveolar inflammation are hallmarks of ALI/ARDS, which are common causes of critical illness. Systemic vascular involvement and multiple organ failure are frequent complications. Sepsis is a common precipitating condition. (Also see text and Supplemental Table 2.) Platelets, leukocytes, and fibrin accumulate in lung microvessels in patients with ALI/ARDS based on imaging and autopsy studies. Clinical observations and experimental models indicate that platelets contribute to disrupted alveolar capillary barrier function, alveolar edema, sequestration of neutrophils and monocytes in pulmonary vessels, microvascular thrombosis, and alveolar inflammation. See also Transfusion-related ALI, below.

Transfusion-related Acute Lung Injury (TRALI)[1, 2, 104, 107, 120-126]	TRALI is a particular syndrome of ALI/ARDS that occurs within hours of transfusion of blood products, including platelets. LPS and platelets or platelet products trigger ALI in "two hit" animal models. CD40L in stored human blood products may prime neutrophils for endothelial injury based on in vitro studies. Platelets and neutrophils are sequestered and NETs form in lungs of mice with TRALI induced by challenge with an MHC antibody after LPS priming; targeting platelet activation with aspirin or inhibitors of integrin $\alpha_{IIb}\beta_3$ reduces accumulation of NETs in alveolar vessels, accumulation of NET-associated platelets, lung edema, and pulmonary vascular permeability in this model. TxA_2 (see Supplemental Table 1) mediates increased permeability of LPS-primed endothelial cells challenged with NETs in vitro.
Deep Vein Thrombosis (DVT)[127-139]	DVT and its complications, including pulmonary thromboembolism (PTE), are common vascular disorders. Inflammatory syndromes and neoplasia are frequent precipitating conditions. DVT and PTE are usually acute or subacute conditions, but chronic sequelae including post-phlebitic syndrome and chronic thromboembolic pulmonary hypertension also occur. A variety of clinical and experimental observations indicate that DVT has inflammatory components and may in many cases contribute to inflammatory vasculopathy and that platelets are involved. Activated platelets, platelet-leukocyte aggregates, and platelet microparticles have been detected in the blood of patients with DVT, venous stasis ulceration, and/or chronic thromboembolic pulmonary hypertension. Animal models demonstrate the inflammatory nature of clots and critical contributions by platelets, and that platelets and leukocytes act together to promote coagulation. A recently-described mouse model indicates that interactions between platelets, monocytes, and neutrophils together with tissue factor synthesis and NET formation drive venous thrombosis. Clinical studies utilizing radiolabeled

	fluorodeoxygluclose and positron emission tomography (PET) imaging demonstrate that clots in DVT are metabolically active, consistent with active contributions by inflammatory effector cells.
Sickle Cell Disease Vasculopathy and Vaso-Occlusion[123, 140-148]	Sickle cell vasculopathy has inflammatory components and involves accumulation of myeloid leukocytes and platelets in vessels, in addition to sickled erythrocytes. Activated endothelial cells can recruit adherent leukocytes in murine models of this disease; the leukocytes can then secondarily capture erythrocytes and platelets, leading to vascular occlusion. Mice in a sickle cell disease model have increased pulmonary and systemic inflammatory responses to LPS. Platelet-neutrophil aggregate formation mediated by P-selectin occurs in mice in a sickle cell model and patients with sickle cell disease; hypoxia and reoxygenation induces additional platelet-neutrophil aggregates to form and parallel activation of both platelets and neutrophils. The platelet transcriptome is altered in human sickle cell disease, resulting in changes in the arginine metabolic pathway.
Rheumatoid Vasculopathies and Vasculitis[1-3, 149-158]	Clinical and experimental evidence indicates that local, regional, and in some cases systemic vasculopathies are key features of rheumatic diseases. Triggers for vascular inflammation in rheumatic syndromes alter vessels in an organ – and syndrome – specific fashion. Many rheumatic syndromes are associated with increased frequency of DVT and/or accelerated atherogenesis and complications of atherosclerosis. Circulating activated platelets and markers of platelet activation have been detected in blood samples from patients with several rheumatic conditions. The platelet transcriptome is altered in patients with systemic lupus erythematosus (SLE), and alterations in Type 1 interferon-regulated genes and proteins are associated with development of vascular disease. Platelet-derived CD40L may be a key immune modulator in SLE. In a study with relevance to progressive systemic sclerosis involving patient samples and rodent models, platelet-derived serotonin was reported to link vascular

disease and tissue fibrosis. Platelets likely contribute to a variety of syndromes of microangiopathy, vasculitis, and inflammation-induced thrombosis, but many are incompletely studied because they are relatively uncommon.

Transplant Vasculopathies[159-163]

Platelets contribute to the pathogenesis of transplant vasculopathy and may be involved in acute organ rejection and chronic allograft vasculopathy. Platelets and fibrin in vessels were reported in tissue from patients with hyperacute and acute rejections, and platelet aggregates were observed in capillaries in antibody-mediated and cell-mediated renal transplant rejection in clinical studies. Interactions of platelets with monocytes, B and T lymphocytes, and dendritic cells may be involved, depending on the specific syndrome and time after transplantation. Experimental observations indicate that platelet-endothelial interactions dependent on complement occur, and that platelets recruit leukocytes to areas of alloantibody deposition and mediate sustained leukocyte-endothelial interactions in vivo. In a murine model, human platelet-derived CD40L induced endothelial activation and acute rejection of cardiac allografts. In a porcine-primate renal xenotransplant model, platelet-leukocyte aggregates formed, platelet aggregates and fibrin were detected in kidney vessels, and expression of tissue factor by recipient platelets triggered consumptive coagulopathy.

Atherosclerosis and Predisposing Conditions[2, 3, 5, 14, 164-178]

Atherosclerosis is a chronic inflammatory vasculopathy. Contributions of platelets to initiation and progression of atherosclerotic lesions and to atherothrombotic complications are well-known and have been extensively reviewed. Emerging evidence indicates that platelets may link inflammation and progressive vascular involvement in predisposing conditions that include diabetes, obesity, and smoking.

Acute Coronary Syndromes (ACS), Coronary Intervention, Reperfusion Vasculopathy[2, 5, 9, 166, 179-191]

Platelets are key effector cells in coronary thrombosis resulting from atherosclerotic plaque rupture, a pivotal vascular event that precipitates myocardial infarction and other ACS. Inflammatory and hemostatic activities of platelets contribute to atherothrombotic sequellae. Megakaryocytes and platelets are reported to be hyperactive in ACS. Circulating platelet-monocyte aggregates are an early marker of acute myocardial infarction, and are a sensitive index of platelet activation in experimental and clinical ACS and coronary intervention. Platelets also bind to and interact with neutrophils in ACS. Platelet-leukocyte interactions can induce cytokine expression in ACS, and can mediate systemic inflammation in these disorders. Platelet expression of the transcript for myeloid-related protein-14 may be a novel signature that identifies acute coronary events. Integrin $\alpha_{IIb}\beta_3$ is involved in platelet-leukocyte interactions and surface of expression of leukocyte integrins in ACS. Beneficial effects of anti-platelet therapies, which are central interventions in the management of these complications of atherosclerosis, may result from interruption of inflammatory activities of platelets in addition to inhibition of coronary thrombosis. Platelets also have key activities in iatrogenic vasculopathy after interventions to open obstructed coronary vessels such as angioplasty and stenting; platelets accumulate rapidly after coronary angioplasty or stent placement and bind leukocytes. Platelets are central in the pathogenesis of restenosis together with leukocytes and vascular wall cells. Platelets also contribute to reperfusion injury after coronary intervention and following cardiopulmonary bypass,. ~~These contributions~~ likely involving inflammatory activities of these cells.

Cerebrovascular Disease and Stroke[9, 192-206]	Platelet activation likely contributes in a variety of ways to vascular inflammation, thrombus formation, and vascular occlusion in cerebrovascular disease, and to thromboinflammatory amplification in cerebral ischemia and stroke. Analysis of clinical samples indicates that platelets are activated in patients with acute, subacute, and remote cerebrovascular ischemia and intracerebral hemorrhage. Platelet activation and platelet-leukocyte interactions occur and may be critical in acute stroke preceded by infection. Platelet-monocyte aggregates form in cerebrovascular disease, and in vitro experiments indicate that interaction of platelets, monocytes, and exposed collagen can induce metalloproteinase expression at sites of cerebrovascular plaque rupture. Platelet induced metalloproteinases, cytokines that are induced by platelet-monocyte interactions such as monocyte chemotactic protein 1, and CD40L-CD40 may be key molecular effectors and pathways that can be modified by targeted intervention in both platelets and leukocytes. The blood transcriptome is altered in stroke, potentially reflecting changes in the platelet transcriptome in part. Increased formation of platelet-monocyte aggregates and CD40L levels were associated with worsened outcomes after ischemic stroke in a recent report.
Atherosclerotic Peripheral Arterial Disease[207, 208]	Contributions of platelets to peripheral vascular diseases have been recently reviewed. Altered platelet reactivity has been detected in a large number of clinical studies, with indices and assays including enhanced responses to thrombin, ADP, or collagen; spontaneous platelet aggregation; circulating platelet-leukocyte aggregates; and basal P-selectin display and/or activation of integrin $\alpha_{IIb}\beta_3$. Some studies include patients with diabetes or other predisposing conditions.

Thromboangiitis Obliterans[209-214]

Thromboangiitis obliterans (TAO), or Buerger's Disease, is an uncommon inflammatory vasculopathy of arteries and veins linked to smoking that usually affects young adults and is a cause of amputation and other morbidities. Small studies suggest that platelet activation and shedding of platelet microparticles are associated with exacerbation of TAO. Analogs of prostacyclin – a major inhibitor of platelet activation – are beneficial in management of TAO. Platelet activation and platelet-leukocyte aggregation mediated by PAF-like oxidized lipids occur in experimental animals subjected to cigarette smoke, suggesting potential mechanisms to drive vascular inflammation in TAO. Human cigarette smokers were reported to have increased CD40L on platelets, increased plasma CD40L, and circulating platelet-monocyte aggregates. Nevertheless, individual mechanistic contributions of platelets and leukocytes are not yet defined in this vasculopathy.

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