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Biology and immunopathogenesis of vasculitis

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Key Points

- The interplay between leukocytes and endothelium is important in inflammatory processes in general and in the pathogenesis of vasculitis in particular.
- Cytokine-induced endothelial cell activation and leukocyte–endothelium interactions are coordinated processes underlying differential leukocyte recruitment to sites of inflammation
- Immune complex formation and deposition underlie the small-vessel vasculitides in immunoglobulin A vasculitis (Henoch-Schönlein purpura), anti–glomerular basement membrane disease, cryoglobulinemic vasculitis, and hypocomplementemic urticarial vasculitis.
- Clinical and experimental data suggest but do not prove that antineutrophil cytoplasmic antibodies (ANCAs) directed against proteinase 3, and myeloperoxidase are pathogenic in the ANCA-associated small-vessel vasculitides.
- Toll-like receptor–mediated dendritic cell activation in the adventitia followed by interferon-γ–producing T helper cell 1 and interleukin-17–producing T helper cell 17 responses to as yet undefined antigen(s) is the major pathogenic event in the medium- and large-vessel vasculitides.

INTRODUCTION

Vasculitis is a condition characterized by inflammation of blood vessels. Its clinical manifestations depend on the location and size of the involved vessels as well as on the nature of the inflammatory process. The vasculitides are localized or systemic diseases with a variable clinical expression. At the Chapel Hill Consensus Conference (CHCC) in 1993, a classification of vasculitides was proposed based largely on the size of the vessels involved, the histopathologic features of the lesions, and clinical findings.[1] By consensus, definitions were proposed for the individual diseases, but it was not the aim of the conference to develop classification criteria (see Chapter 161). Nevertheless, these definitions have been used since then for classifying vasculitis into specific categories. The nomenclature of the vasculitides was revised in 2012, with inclusion of various conditions not mentioned in the original CHCC nomenclature and an attempt to classify vasculitides also based on underlying condition and probable etiology (Box 162.1).[2]

As mentioned, vasculitis concerns inflammation of the blood vessel wall. The vascular endothelium, being at the interface of the circulating bloodstream and the structural components of vascular and perivascular tissue, plays a major role in vasculitis. Cells from the innate and adaptive immune system have to adhere to and pass the endothelium to evoke inflammation in the vessel wall. The endothelium is an active player in this process. Endothelial cells (ECs) differ in morphology and function depending on their location in the body. Macrovascular ECs are different from microvascular ECs, and various artery-derived ECs are not identical to venous ECs. Because various forms of vasculitis differ in their involvement of the vascular tree and their location, characteristics of the respective endothelia may be relevant for our understanding of the systemic vasculitides.

THE ENDOTHELIUM

The endothelium constitutes a single layer of cells that covers the inner side of blood vessels. It functions as a passive lining of the vasculature and is also actively involved in many physiologic and pathophysiologic processes. The endothelium is not a homogeneous layer of cells throughout the body, but its characteristics and functions differ depending on the size and location of the vessels. They can trans differentiate in function and activity after contact with stimuli that are generated locally or systemically.

Larger blood vessels consist of ECs (intima), smooth muscle cells (media), connective tissue, and vaso vasorum (adventitia). The three layers are separated by the internal and external elastic lamina.

The endothelium in these vessels actively participates in orchestrating adjustments in vascular tone to match local tissue perfusion with oxygen demand by endothelial release of a diverse family of compounds including nitric oxide, other reactive oxygen species (ROS), and arachidonic acid metabolites in particular thromboxane A2 and prostaglandin H2.[3] In autoimmune diseases, the endothelial release of ROS is thought to mediate both dilation and parenchymal inflammation, leading to cellular dysfunction, thrombosis, and fibrosis.[4] Microvascular ECs of a different origin (e.g., glomerular ECs) are available for in vitro studies.[5]

In the microvascular bed, ECs reside on a basal lamina with sparsely distributed pericytes around them. These pericytes have important functions in maintaining the integrity of the microvasculature.[6] Loss of pericytes results in endothelial hyperplasia and increased permeability of the endothelium.[7]

The endothelium has the following main functions:

- Providing a semipermeable barrier for transport of soluble molecules
- Maintaining hemostatic balances
- Controlling local blood flow (e.g., via nitric oxide, ROS, and endothelin-1)
- Regulating coordinated trafficking of leukocytes;
- Participating in neovascularization

Although the molecular base and localization of these functions differ, changes in these functions occur in a coordinated way upon stimulation, in particular via proinflammatory cytokines, during inflammation.

ENDOTHELIAL CELL ACTIVATION

Endothelial cells can be activated either via direct mechanisms, by microbes binding to pattern recognition receptors (PAMPS), or by vascular damage activating the damage-associated receptors (DAMPS) and by indirect mechanisms in which the adaptive immune system is involved. An example of an indirect activating mechanism is via vascular immune complex deposition.[8] After activation, ECs show a quick rise in Ca2+ levels mediated via the G protein–coupled receptors. As a next step, ECs exocytose the content of their storage granules, the so-called Weibel-Palade bodies. These granules release P-selectin, von Willebrand factor, factor VII, and angiopoietin-2. This release results in a rapid interaction among the activated endothelium, platelets, and neutrophils, facilitating leukocyte rolling and adhesion.

A more sustained inflammatory response is mediated by the release of proinflammatory cytokines by leukocytes, in particular tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1).

Tumor necrosis factor-α exerts its effect by binding to TNF receptor (TNFR) 1 or TNFR2 and, IL-1α and IL-1β bind to the IL-1 receptor type 1 (IL-1R1) on ECs. Receptor binding activation initiates signaling via nuclear factor κB (NF-κB), p38 mitogen-activated protein kinases (MAPK), extracellular signal–regulated kinases or classical MAP kinases ERK1/ERK2, phosphoinositide 3-kinase PI3K/protein kinase B (PKB) (also known as Akt), and the c-Jun NH2-terminal kinase (JNK) pathway (Fig. e162.1). Although the upstream signaling pathways activated by IL-1R1 deviate from those evoked by TNF-α, both pathways overlap to a large extent.[9]

Activation by TNF-α and IL-1 results in the expression of E-selectin by ECs, which interact with the tetrasaccharide sialyl-Lewis X expressed on leukocytes, facilitating rolling and adherence to the endothelium. Firm arrest of leukocytes on the endothelium is facilitated by endothelial expression of the adhesion molecules vascular cell adhesion molecule (VCAM)-1 and intercellular adhesion molecule (ICAM)-1, -2 and -3, which bind to the integrins very late antigen (VLA)-4 and leukocyte function antigen (LFA)-1, respectively, on neutrophils and monocytes.[10,11]

Besides producing and upregulating adhesion molecules that regulate leukocyte recruitment, EC-activating stimuli also affect hemostatic balance. In particular, they induce the production and expression of tissue factor by ECs, resulting in a procoagulant state during inflammation. During inflammation, proangiogenic factors—that is, vascular endothelial growth factor (VEGF) and fibroblast growth factor 2 (FGF-2)—also are produced and interact with ECs, which results in angiogenesis, particularly during chronic inflammatory responses. Hypoxic conditions at the site of

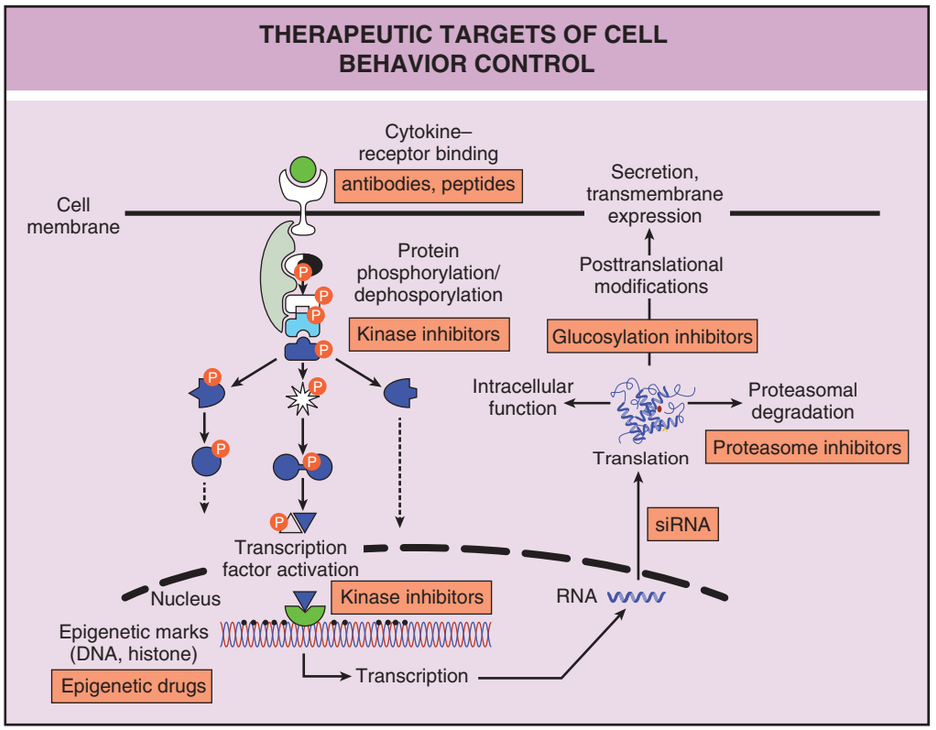

FIG. E162.1 Schematic representation of the various levels in cell behavior control that can be therapeutically targeted by drugs. For many angiogenesis and inflammation-related processes, the initiation of endothelial engagement in the disease starts with growth factor or cytokine binding to its transmembrane receptor. This initiates a cascade of (kinase based) signaling, which eventually leads to changes in gene transcription and protein expression. A broad array of drugs has been developed to counteract these processes and interfere at different levels, ranging from growth factor/cytokine-receptor binding to kinase-based substrate phosphorylation and dephosphorylation pathways to epigenetic pathways involving DNA and histone modifications (depicted in red boxes). The complexity of these pathways and their (micro)environmentally controlled traits justify detailed in vivo studies into the exact status and the factual effects of drugs on these pathways. *(From Langenkamp E, Kamps JA, Mrug M, et al. Innovations in studying in vivo cell behavior and pharmacology in complex tissues—microvascular endothelial cells in the spotlight. Cell Tissue Res 354:647-669, 2013. Fig 2.)*

BOX 162.1 NAMES FOR VASCULITIDES ADOPTED BY THE 2012 INTERNATIONAL CHAPEL HILL CONSENSUS CONFERENCE ON THE NOMENCLATURE OF VASCULITIDES

Large-vessel vasculitis (LVV)

- Takayasu arteritis (TAK)
- Giant cell arteritis (GCA)

Medium-vessel vasculitis (MVV)

- Polyarteritis nodosa (PAN)
- Kawasaki disease (KD)

Small-vessel vasculitis (SVV)

- Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV)
  - Microscopic polyangiitis (MPA)
  - Granulomatosis with polyangiitis (Wegener granulomatosis) (GPA)
  - Eosinophilic granulomatosis with polyangiitis (Churg-Strauss vasculitis) (EGPA)
- Immune complex SVV
  - Anti–glomerular basement membrane (anti-GBM) disease
  - Cryoglobulinemic vasculitis (CV)
  - Immunoglobulin A vasculitis (Henoch-Schönlein purpura) (IgAV)
  - Hypocomplementemic urticarial vasculitis (anti-C1q vasculitis)

Variable-vessel vasculitis (VVV)

- Behçet disease (BD)
- Cogan syndrome (CS)

Single-organ vasculitis (SOV)

- Cutaneous leukocytoclastic angiitis
- Cutaneous arteritis
- Primary central nervous system vasculitis
- Isolated aortitis
- Others

Vasculitis associated with systemic disease

- Lupus vasculitis
- Rheumatoid vasculitis
- Sarcoid vasculitis
- Others

Vasculitis associated with probable etiology

- Hepatitis C virus–associated cryoglobulinemic vasculitis
- Hepatitis B virus–associated vasculitis
- Syphilis-associated aortitis
- Drug-associated immune complex vasculitis
- Drug-associated ANCA-associated vasculitis
- Cancer-associated vasculitis
- Others

inflammation induce the expression of hypoxia-inducible factor 1 (HIF-1), a transcription factor that induces the expression of genes involved in angiogenesis.[12]

Several signal-transducing pathways are involved in EC activation, and insight into these pathways has stimulated the development of drugs that interfere with these pathways (as shown in Fig. e162.1). Activation of NF-κB, a central signaling molecule, mediates expression of not only the adhesion molecules E-selectin, ICAM-1, and VCAM-1 but also induces the production of the proinflammatory cytokine IL-6, the polymorphonuclear neutrophil (PMN) recruiting and activating chemokine IL-8, inducible nitric oxide synthase (iNOS), cyclooxygenase-2, and others. At the same time, protective genes are expressed with antiapoptotic and downregulatory activity on ECs. This prevents the activated ECs from going into apoptosis.

Nevertheless, activated ECs, probably in an early apoptotic state, may detach and be present in the bloodstream as circulating ECs. Increased levels of circulating ECs have been reported in active cytomegalovirus infection and in different forms of vasculitis. In antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis, their level correlates with disease activity.[13] These circulating ECs were also shown to inhibit endothelial progenitor cells and, for this reason, to contribute to vascular damage, because these endothelial progenitor cells play a major role in repairing injured vessels.[14]

LEUKOCYTE–ENDOTHELIUM INTERACTION

Local recruitment of cells participating in the immune response is essential for immune homeostasis. As mentioned earlier, the coordinated upregulation of adhesion molecules on activation of ECs is essential in starting an inflammatory reaction. P-selectin, constitutively present in Weibel-Palade storage granules, is rapidly translocated to the EC membrane. This allows the first interaction with circulating neutrophils via P-selectin glycoprotein ligand 1 (PSGL-1), the principal ligand for P-selectin on the neutrophil membrane. This interaction results in tethering of the PMN on the EC surface. This is rapidly followed, within a couple of hours, by transcription and translation of E-selectin, which appears next on the EC membrane. E-selectin interacts with sialyl Lewis^X on the PMN. This interaction, together with the binding of L-selectin on PMNs to its ligands on activated ECs, results in a state of rolling of PMNs over the endothelial surface (Fig. e162.2). The rolling neutrophil is now locally activated by signaling molecules, produced by the activated endothelium, that bind to G protein–coupled chemokine (**chemo**tactic small cyto**kines**) receptors on the neutrophil. These molecules include platelet-activating factor, which is rapidly synthesized and has a phospholipid structure, and the chemokines CXCL8 (or IL-8), CXCL1, CXCL2, and CXCL5, which bind to the chemokine receptor CXCR2 to activate neutrophils and promote their adhesion to the endothelium.[15] Neutralization of CXCL2 in the interstitium effectively reduced neutrophil recruitment after recruitment by immune complexes through a CXCL2-driven feed forward loop.[16] Not only CXCL2 but also fractalkine (FKN, CX3CL1) is a very important chemokine needed for the recruitment and adhesion of neutrophils and monocytes on ECs.

As part of this activation and adhesion process by cytokines and chemokines of PMNs, β_2 integrins, ligands for a group of adhesion molecules that next appear on activated ECs, undergo conformational alterations, resulting in changes in avidity and affinity, and are now able to interact with these adhesion molecules that 4 to 12 hours after activation appear on the EC membrane. The β_2 integrins on leukocytes include the CD11a/CD18 and lymphocyte function–associated antigen 1 (LFA-1) complex that interacts with ICAM-1 and ICAM-2 on activated ECs (see Fig. e162.2). Together with VCAM-1, these molecules belong to the immunoglobulin superfamily. VCAM-1 is the ligand for VLA-4, also indicated as the α_4 integrins, which is expressed on lymphocytes. After these latter ligand–ligand interactions, leukocytes adhere firmly to the endothelium in an activated state.[17]

The cytoskeletons of the leukocytes are reorganized in such a way that the leukocytes are spread out over the ECs. In this form, leukocytes extend pseudopodia and pass through gaps between ECs. This process of leukocyte extravasation requires active involvement of molecules located at the junctions of ECs. At least six molecules are involved in junctioning two ECs by homophilic interaction. These include vascular EC-specific cadherin (VE-cadherin); the junction adhesion molecules JAM-A, JAM-B, and JAM-C; platelet-EC adhesion molecule-1 (PECAM-1), CD99; and EC selective adhesion molecule (ESAM).[15]

When through the endothelium, the leukocyte must penetrate the basement membrane. The mechanism for penetration is disputed but may involve proteolytic digestion of the membrane, mechanical force, or both.[10] The entire process of blood vessel escape is known as *diapedesis*.

The transmigration of leukocytes can occur via junctions between adjacent ECs, the paracellular route, as well as through the body of ECs, the transcellular route.[10]

Leukocyte–EC interaction preferentially occurs in postcapillary venules. It is noteworthy that many forms of small-vessel vasculitis are manifested by leukocytoclastic vasculitis localized in postcapillary venules, particularly in the skin. Here, PMNs do not pass the basement membrane but become fully activated followed by apoptosis and necrosis within the vessel wall. The role of immune complexes and ANCAs in this process is discussed later in the section on small-vessel vasculitis.

ROLE OF AGING IN LEUKOCYTE-ENDOTHELIAL INTERACTION

Vasculitis, like ANCA-associated vasculitis (AAV) and giant cell arteritis (GCA), is an age-associated disease, and therefore alterations of the immune response, termed *immunosenescence,* likely contribute to an increased susceptibility of older adults. Especially the reported chronic low degree of inflammation (termed *inflamm-aging*), evidenced by increased serum levels of inflammatory cytokines and acute phase proteins, might prime both ECs and leukocytes. In addition, expression of receptors important for tethering, rolling, adhesion, and transmigration also change during aging.[18]

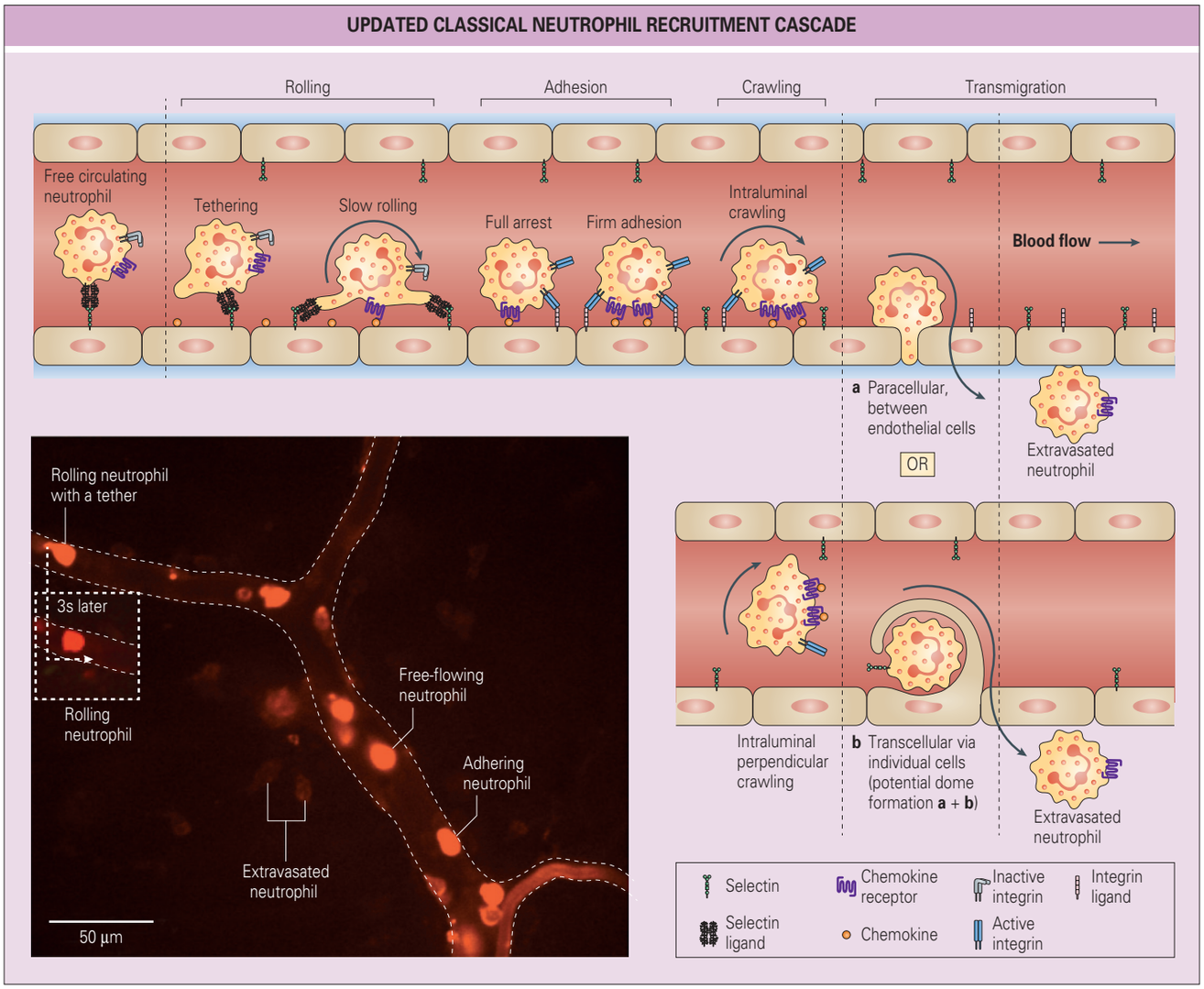

FIG. E162.2 Shown are the sequential steps of neutrophil recruitment from the vasculature to the tissue. Two possible methods of transmigration are acknowledged: paracellular (between endothelial cells; a) and transcellular (through endothelial cells; b). Major groups of adhesion molecules are marked. Rolling is mostly selectin-dependent, whereas adhesion, crawling, and transmigration depend on integrin interactions. Chemokines lining the luminal part of endothelium activate rolling neutrophils, thus inducing conformational changes of neutrophil surface integrins and allowing for subsequent events. Crawling neutrophils follow the chemokine gradient along endothelium, which guides them to the preferential sites of transmigration. The intravital microscopy image shows a skin postcapillary venule with neutrophils (LY6G+ cells) labelled in red (phycoerythrin antibody conjugate; 10 µg). Mouse skin was infected with *Staphylococcus aureus*, and the image was taken 2 hours later. It captured neutrophils at different stages of migration: freely circulating cells, rolling cells extending tethers, adhering neutrophils and the cells that extravasated out of the blood vessel. *(From Kolaczkowska E, Kubes P: Neutrophil recruitment and function in health and inflammation. Nat Rev Immunol 13:159-175, 2013. Fig 1.)*

ENDOTHELIUM, COAGULATION, AND INFLAMMATION

Tissue factor is upregulated in ECs activated by, among others, proinflammatory cytokines. Tissue factor is a transmembrane protein that initiates coagulation. In the resting state, endothelium has antithrombotic characteristics based on the expression of thrombomodulin, heparan sulfate proteoglycans that bind and activate antithrombin III, prostacyclin, ecto-adenosine diphosphatase, and receptors for fibrinolytic agents (e.g., plasminogen and tissue plasminogen activator). One of the first steps in EC activation is the translocation of Platelet(P)-selectin from the Weibel-Palade bodies to the membrane of ECs. Interaction of P-selectin with P-selectin glycoprotein ligand 1 PSGL-1 on leukocytes induces the upregulation of tissue factor, which initiates the coagulation cascade. The prothrombotic state of activated ECs is further highlighted by the loss of thrombomodulin and heparan sulfate proteoglycans. Indeed, elevated levels of serum thrombomodulin occur in many forms of vasculitis and have been proposed as markers of disease activity.[3]

DAMAGE AND REPAIR: ANGIOGENESIS

Chronic inflammation and angiogenesis synergize with each other, witnessed by the fact that inflammatory cells can directly release proangiogenic factors, such as VEGF, angiopoietins, FGF-2, platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), and matrix metalloproteinases, that can act on the vasculature. In addition, neovascularization sustains inflammation by providing oxygen and nutrients to meet the metabolic needs of the cells present at the inflammation site.[19]

IMMUNOPATHOGENESIS OF SMALL-VESSEL VASCULITIDES

Based on the 2012 CHCC classification,[2] the small-vessel vasculitides show vasculitic involvement of arterioles, capillaries, or venules. Larger vessels may be involved as well. Within this category, two groups are identified: the immune complex–mediated small-vessel vasculitides and the ANCA-associated vasculitides. The former group encompasses immunoglobulin A (IgA) vasculitis (Henoch-Schönlein purpura) and cryoglobulinemic vasculitis as the two most prevalent conditions and, in addition, anti–glomerular basement membrane (anti-GBM) disease and hypocomplementemic urticarial vasculitis (anti-C1q vasculitis); the second group consists of granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA; Churg-Strauss syndrome).

IMMUNE COMPLEX–MEDIATED SMALL-VESSEL VASCULITIDES

Since 1970, immune complexes have been considered as pathogenic factors in many forms of vasculitis. In some of the vasculitides associated with probable etiology (see Box 162.1) in particular, immune complexes consisting of microbial antigens or drugs and their cognate antibodies may be operative in pathogenesis. Although immune deposits—that is, immunoglobulin and complement—have been detected by direct immunofluorescence, the antigens involved in the complexes have been identified only in a minority of cases. Nevertheless, small-vessel vasculitis in the presence of immune deposits should always raise suspicion of an underlying disorder, either one of the systemic rheumatic diseases or an infectious disorder. In particular, infective endocarditis may mimic idiopathic small-vessel vasculitides. Chronic immune stimulation during infections may result in polyclonal B-cell stimulation with production of autoantibodies such as ANCA. Within the spectrum of idiopathic vasculitides, the 2012 CHCC classification defined IgA vasculitis, anti-GBM disease, cryoglobulinemic vasculitis, and hypocomplementemic urticarial vasculitis as disorders that are characterized by the presence of immune deposits within the vessel wall.

Immunoglobulin A vasculitis (Henoch-Schönlein purpura)

Immunoglobulin A vasculitis is defined by the CHCC as "a vasculitis with IgA1-dominant immune deposits affecting small vessels (predominantly capillaries, venules, or arterioles); often involves skin and gastrointestinal tract and frequently causes arthritis; glomerulonephritis indistinguishable from IgA nephropathy may occur."[2] This definition implies that IgA1-containing complexes are the primary pathogenic factor in this disease. Indeed, deposition of polymeric IgA1 in combination with complement C3 has been found in capillaries and postcapillary venules in the skin, gastrointestinal tract, and glomeruli in IgA vasculitis (Fig. 162.1). Within the kidney, IgA1 deposits are found in the glomerular capillary wall and in the mesangium, with the mesangium being the main location of IgA1 deposits. Data relating to the pathogenesis of IgA vasculitis are derived also from studies of IgA nephropathy because no major biologic differences have been found between the two diseases.[20,21]

Abnormal glycosylation of IgA, particularly in the hinge region of the molecule, has been implicated as a causal factor for abnormal clearance and formation of complexes of IgA with fibronectin, lectin, IgG, and IgA1 itself (resulting in polymeric IgA1). These complexes could be pathogenic factors in nephritis as part of IgA vasculitis and IgA nephropathy by activating mesangial cells[20] (Fig. 162.2).

How do increased levels of IgA or abnormally structured IgA result in immune complex–mediated vasculitis? Both immune complex deposition from the circulation and in situ complex formation may play a role. Subendothelial deposition results in endothelial activation, upregulation of adhesion molecules, neutrophil recruitment via IL-8, endocapillary proliferation, and crescent formation in the kidneys. Polymeric IgA or IgA complexes may activate these neutrophils additionally. (For more information on Henoch-Schönlein purpura and IgA vasculitis, see Henoch-Schönlein Purpura / Immunoglobulin-A Vasculitis Chapter 169.)

Anti–glomerular basement membrane disease

Anti-GBM disease is defined by the CHCC as "vasculitis affecting glomerular capillaries, pulmonary capillaries, or both, with basement membrane deposition of anti–basement membrane autoantibodies; lung involvement causes pulmonary hemorrhage, and renal involvement causes glomerulonephritis with necrosis and crescents."

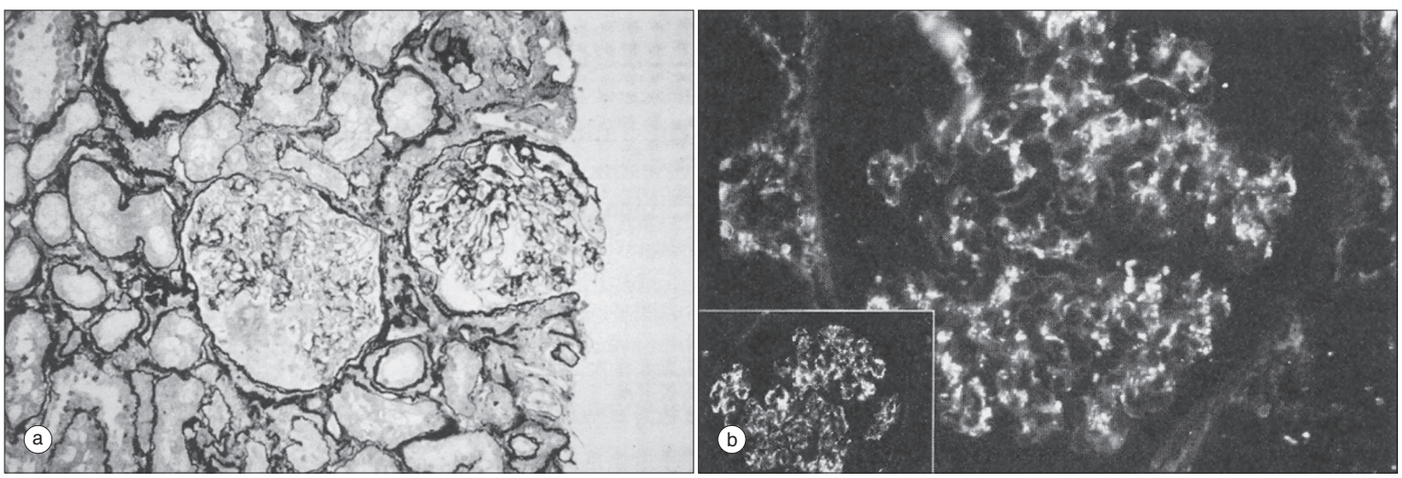

FIG. 162.1 Nephritis in immunoglobulin A (IgA) vasculitis (Henoch-Schönlein nephritis). **(a)** Renal biopsy was performed in a 45-year-old woman with recurrent cutaneous vasculitis and episodes of gastrointestinal vasculitis of 2 years' duration because of recent-onset erythrocyturia and severe proteinuria. The specimen shows a focal and segmental extracapillary crescentic glomerulonephritis of recent origin (silver methenamine, hematoxylin and eosin stain, ×50). **(b)** Staining with monoclonal anti-IgA1 antibodies shows diffuse glomerular and granular deposits in the mesangia and locally in the capillary wall. *Inset:* staining for C3 shows a similar pattern (immunofluorescence, anti-IgA, ×125).

The autoantibodies in anti-GBM disease are directed against the α3 chain of the C-terminal globular (NC1) domain of a tissue-specific type IV collagen (α3(IV)NC1).[22] The same epitopes are recognized in all patients. In direct immunofluorescence testing of renal tissue from patients with anti-GBM disease, a linear pattern of GBM staining is seen for IgG and complement C3. The pathogenicity of these autoantibodies has been demonstrated by eluting IgG class antibodies from kidneys of patients with anti-GBM disease and injecting the eluates in monkeys. This resulted in deposition of the antibodies and complement at the GBM and glomerulonephritis but without crescent formation. Further studies demonstrated that DRB1*1501 (expressed in 75%–90% of patients with anti-GBM disease) which is co-expressed with monomorphic DRA1*0101 to form class II molecule DR2, plays an important role in the development of anti-α3NC1 B- and T-cell responses, which are required for lesion development, including crescent formation in human anti-GBM disease.[23]

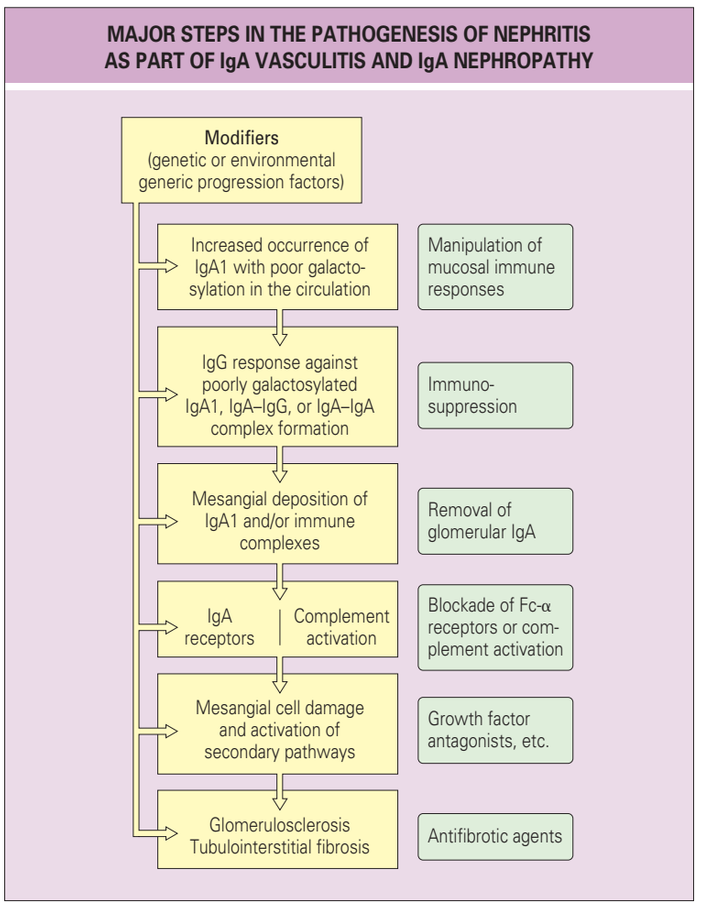

FIG. 162.2 Each of the key steps *(center)* in the pathogenesis of nephritis in immunoglobulin A (IgA) vasculitis and IgA nephropathy likely is affected by potent genetic or environmental modifiers. Potential therapeutic consequences are shown on the *right*. *(Reproduced with permission from Floege J. The pathogenesis of IgA nephropathy: what is new and how does it change therapeutic approaches? Am J Kidney Dis 2011;58:992-1000.)*

Cryoglobulinemic vasculitis

Cryoglobulinemic vasculitis is defined according to the 2012 CHCC classification as "vasculitis with cryoglobulin immune deposits affecting small vessels (predominantly capillaries, venules, or arterioles) and associated with cryoglobulins in serum; skin, glomeruli and peripheral nerves are often involved."

The main element in the pathogenesis of this disorder is the presence of cryoglobulins that are cold-precipitable immunoglobulins. Three types of cryoglobulins are detectable:

1. Type I, found in 10% to 15% of patients, consists of monoclonal IgM-Rheumatoid Factor (RF) and originates in the context of a lymphoproliferative or myeloproliferative disease.
2. Type II, occurring in 50% to 60% of patients, consists of monoclonal IgM-RF and polyclonal IgG.
3. Type III, found in 30% to 40% of patients, consists of polyclonal IgM-RF and polyclonal IgG.

Type II and type III cryoglobulins are collectively referred to as *mixed cryoglobulins*. These mixed cryoglobulins have been detected during chronic bacterial and viral infections and as part of (systemic) autoimmune diseases, in particular in Sjögren syndrome. The remaining idiopathic cases are designated as *essential* mixed cryoglobulinemia. Many cases of essential mixed cryoglobulinemia are related to hepatitis C virus (HCV) infection.[24-26]

The percentage of HCV-related cases differs among geographic areas, ranging from 40% to 100%, with a 90% association in the Mediterranean countries.

The etiopathogenesis of essential mixed cryoglobulinemia without HCV infection has not been clarified, but polyclonal B-cell activation and antigen- or superantigen-driven B-cell activation have been suggested. The clinical manifestations of (HCV-related) mixed cryoglobulinemia are purpura, arthritis and arthralgia, peripheral neuropathy, and nephritis. The full-blown spectrum of the disease is seen in association with type II cryoglobulins. HCV proteins are present in the dermis and epidermis, but vascular damage develops in the presence of IgM and IgG molecules only in conjunction with complement deposition. Endothelial activation with upregulation of adhesion molecules attracts neutrophils, which leads to leukocytoclastic vasculitis. Within the kidney, subendothelial cryoglobulin deposition results in membranoproliferative glomerulonephritis type I, occurring in 20% to 30% of patients (Fig. 162.3). Here also, HCV core proteins can be detected. Vasculitis of small- and medium-sized renal arteries occurs in one third of patients. Focal, immune complex–mediated glomerulonephritis may occur in type III cryoglobulinemia and is much milder than in type II cryoglobulinemia. Neuropathy has

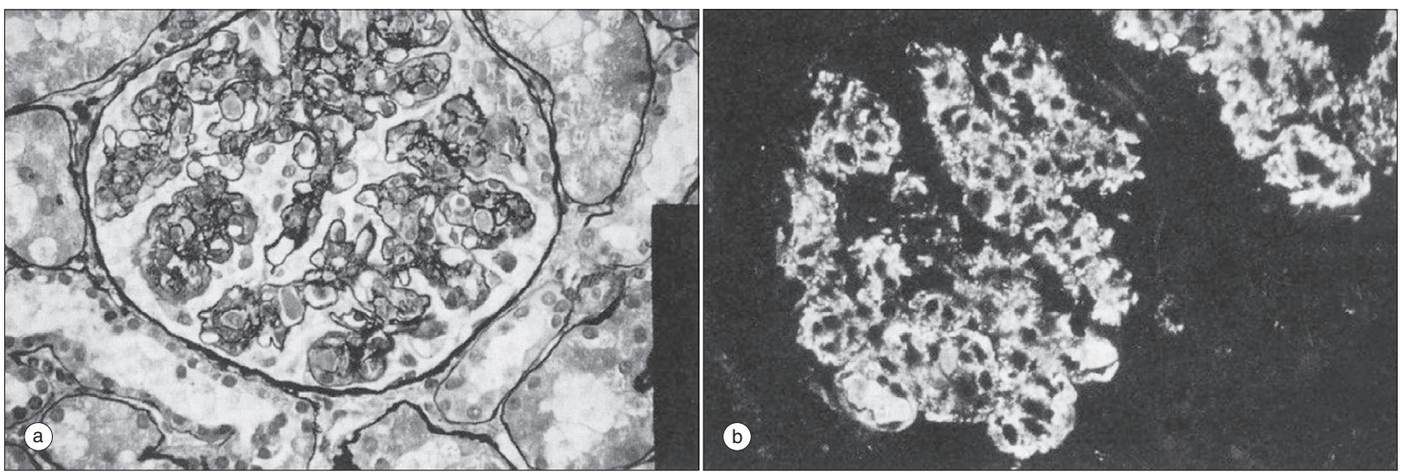

FIG. 162.3 Essential type II cryoglobulinemia. **(a)** Diffuse proliferation of mesangial cells and subendothelial deposition of eosinophilic material with or without mesangial (matrix) interposition (silver methenamine, hematoxylin and eosin stain, ×125). **(b)** Anti-C3 polyclonal antibodies. Diffuse glomerular granular deposition of immune complexes consisting of immunoglobulin G (IgG), IgM, and C1q (not shown) as well as C3 in the mesangial area is seen as well as subendothelial deposition and occasionally intracapillary aggregates (immunofluorescence, ×125).

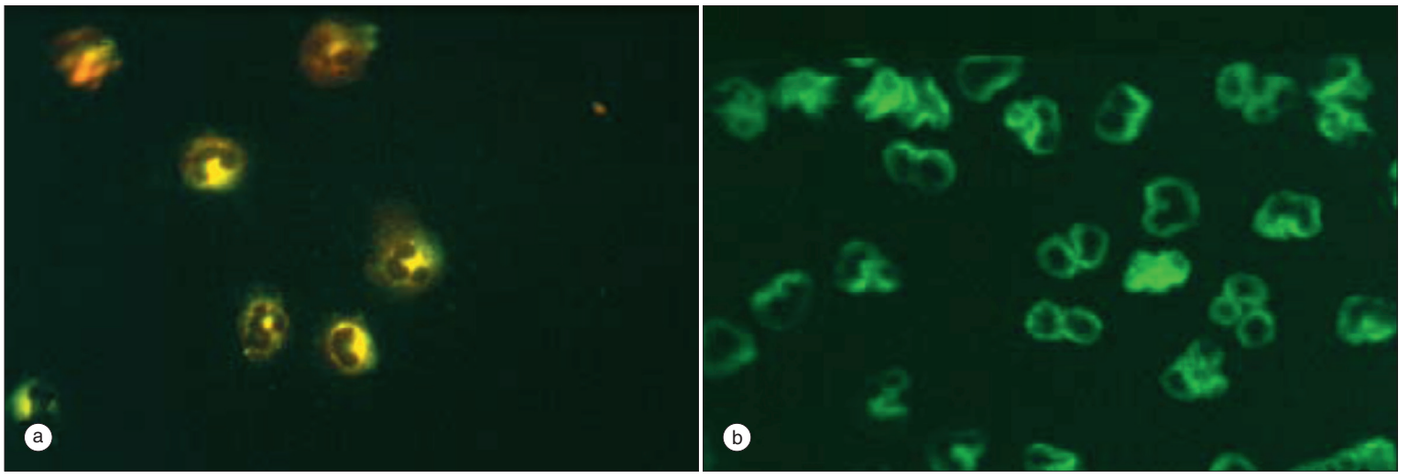

FIG. 162.4 Staining of cytoplasmic components of ethanol-fixed neutrophils by indirect immunofluorescence using a serum sample from a patient with active antineutrophil cytoplasmic antibody (ANCA)–associated granulomatous vasculitis and antibodies to proteinase 3. **(a)** A characteristic granular pattern of fluorescence (c-ANCA) is seen. **(b)** This fluorescence pattern is different from the perinuclear pattern that can be produced by serum samples from patients with antimyeloperoxidase antibodies (p-ANCA). *MPO,* Myeloperoxidase.

Table 162.1

Disease associations of PR3-ANCA and MPO-ANCA

Disease entity	Sensitivity of PR3-ANCA (%)	Sensitivity of MPO (%)
Granulomatosis with polyangiitis	66	24
Microscopic polyangiitis	26	58
Idiopathic crescentic glomerulonephritis	30	64
Eosinophilic granulomatosis with polyangiitis	<5	40

ANCA, *Antineutrophil cytoplasmic antibody;* MPO, *myeloperoxidase;* PR3, *proteinase 3.*

been considered to result from vasculitis of the vasa nervorum (see also Chapter 171).

Hypocomplementemic urticarial vasculitis (anti-C1q vasculitis)

Hypocomplementemic urticarial vasculitis (HUV) is defined by the 2012 CHCC as "vasculitis accompanied by urticaria and hypocomplementemia affecting small vessels and associated with anti-C1q antibodies; glomerulonephritis, arthritis, obstructive pulmonary disease, and ocular inflammation are common." Lesions show leukocytoclastic vasculitis with deposition of immunoglobulins and complement. Whereas normocomplementemic urticarial vasculitis is mostly idiopathic, HUV can be associated with systemic autoimmune diseases such as systemic lupus erythematous and Sjögren syndrome; infectious diseases, in particular hepatitis B and C; use of medication; malignancies; and other conditions.[27]

ANTINEUTROPHIL CYTOPLASMIC ANTIBODY–ASSOCIATED VASCULITIDES

Unlike IgA vasculitis and cryoglobulinemic vasculitis, inflammatory lesions in ANCA-associated vasculitides—that is, GPA, MPA, and EGPA—are generally, but not always, devoid of immune deposits. These disorders are characterized by the presence of autoantibodies against cytoplasmic constituents of neutrophils and monocytes, designated as ANCAs (Fig. 162.4). ANCAs in the vasculitides are directed either against proteinase 3 (PR3), a third serine protease besides elastase and cathepsin G that is found in neutrophil granules, or against myeloperoxidase (MPO).[28,29] Three lines of evidence suggest, but do not prove, that PR3-ANCAs and MPO-ANCAs are involved in the pathogenesis of their associated disorders.

First, PR3-ANCA and MPO-ANCA are closely associated with GPA, MPA, and EGPA. Diagnostic sensitivity and specificity, as derived from several studies, are given in Table 162.1. In EGPA, MPO-ANCAs are associated with typical vasculitic lesions, but in the absence of ANCAs, eosinophilic infiltration, generally without apparent small-vessel vasculitis, predominates.[30] Furthermore, an increase in levels of ANCAs has been shown to precede relapses of the associated disease. The predictive value of an increase in ANCA titer in patients with GPA as measured by indirect immunofluorescence (IIF) was reported as 57% and for PR3-ANCAs measured by enzyme-linked immunosorbent assay (ELISA) as 71%.[31] Otherwise, 43% of patients with a rise in ANCAs by IIF and 29% with a rise in PR3-ANCAs by ELISA did not experience relapse. These data, however, have not been confirmed in other studies.[32,33] Also, patients who persistently test positive for PR3-ANCAs after induction of remission have a higher chance of ensuing relapses. Glycosylation and maturation of ANCA probably play an essential role in why certain ANCAs are pathogenic and others not.[34,35] Anti-PR3 IgG1 ANCA Fc galactosylation, sialylation, and bisection were found to be reduced compared with total IgG1 in GPA,[36] and this was related to the presence of inflammatory cytokines. Also, newer techniques demonstrated that MPO-ANCA can be present in ANCA-negative disease, can react against a sole linear sequence, and can activate neutrophils.[37]

Thus PR3-ANCAs and MPO-ANCAs are certainly strongly associated with GPA, MPA, and, to a lesser extent, EGPA, but the association between changes in levels of ANCA and disease activity, particularly in relation to relapsing disease, is far from absolute.

Second, in vitro studies showed that ANCAs are able to stimulate neutrophils, primed with low doses of proinflammatory cytokines, to produce ROS and release lytic enzymes. In various in vitro systems, ANCAs are able to induce adherence of neutrophils to ECs and to stimulate neutrophils to lyse ECs or to induce detachment of these cells. The interaction between ANCAs and neutrophils occurs via binding of their $F(ab')_2$ fragment to PR3 or MPO expressed on the neutrophil surface as well as by binding of their Fc fragments to Fcγ receptors on the neutrophils. Thus, both the availability of the autoantigens on the surface of neutrophils, in particular PR3, and the neutrophil-activating potential of ANCA appear to be involved in necrotizing vasculitis based on in vitro studies.[38,39]

The third and strongest argument for pathogenicity of ANCAs is derived from experimental studies in animals.[40] In these studies, an MPO-directed immune response was induced by immunizing MPO-deficient mice with mouse MPO. IgG or splenocytes of these mice were transferred into immunodeficient mice or wild-type mice. This resulted in the development of (focal) necrotizing glomerulonephritis and pulmonary capillaritis, which was augmented by the simultaneous injection of lipopolysaccharide (Fig. 162.5). Furthermore, the alternative pathway of complement has been demonstrated to be an essential factor for lesion development because mice deficient in factor B or factor C5 of the complement system did not develop lesions. This model strongly suggests a direct pathogenic effect of MPO-ANCAs. Also, a rat model of anti–MPO-associated vasculitis demonstrated the in vivo potential of anti-MPO to interfere with leukocyte–endothelial interaction and to cause microvascular damage.

In summary, although it is difficult to prove, the currently available data certainly suggest that ANCAs are pathogenic (Fig. 162.6).

IMMUNOPATHOGENESIS OF MAJOR SMALL-VESSEL VASCULITIDES

Granulomatosis with polyangiitis

The cause of GPA is not known. The initial phase of the disease is frequently characterized by ongoing (destructive) inflammation in the upper airways.

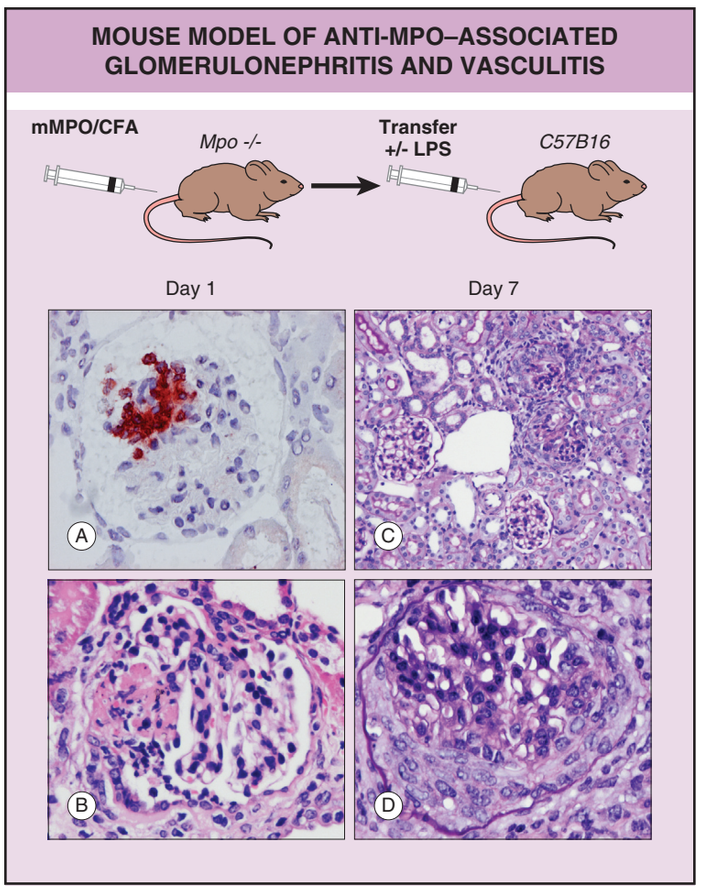

FIG. 162.5 Histopathology in the MPO-ANCA mouse model. The model is induced by intravenous injection of purified anti-mouse MPO IgG derived from mouse MPO-immunized MPO-deficient mice. Administration of the anti-MPO antibodies in C57Bl6 mice induces crescentic glomerulonephritis. Disease severity can be enhanced by co-administration of LPS. A: acute glomerular infiltration of neutrophils (day 1, immunohistochemistry) and B: glomerular capillary necrosis (H&E stain, magnification x200). C and D: glomerular crescent formation (day 7, PAS stain, magnification x200 [C] x400 [D]). *(Modified from Heeringa P: Animal models of vasculitis. In Oxford Textbook of Vasculitis 3rd edition eds Ball GV, Fessler BJ and Bridges SL, 93-100, 2014.)*

This localized form of the disease may persist, but the disease may also progress to (or directly manifest as) a generalized form. Relapses also frequently start with otorhinolaryngologic symptoms, and smoldering disease is mostly apparent in this region as well. This suggests that the initial trigger is localized in the upper airways. Friedrich Wegener, after whom the disease was previously named, considered the disease to be a pathergic reaction to an environmental factor. This factor has not yet been identified, but chronic nasal carriage of *Staphylococcus aureus* is present in 60% of patients with GPA compared with 20% of control participants and is associated with a relapsing course.[41] Whether this association is based on a causal relationship is presently not clear. GPA is strongly associated with the presence of PR3-ANCAs (see Table 162.1).

PR3-ANCAs are strongly associated with GPA, although MPO-ANCAs may occur as well (see Table 162.1). Within cohorts of patients with ANCA-associated vasculitis, patients who test positive for PR3-ANCAs show more granulomatous inflammation, more widespread organ involvement, and a faster decline in renal function than patients who test positive for MPO-ANCA. In addition, data from animal experiments suggest a direct pathogenic effect of MPO-ANCAs but not of PR3-ANCAs (see earlier). Thus, both clinically and experimentally, PR3-ANCA-associated disease differs from MPO-ANCA–associated vasculitis. However, this clinical distinction between PR3-ANCA– and MPO-ANCA–associated disease is far less apparent in cohorts from east Asian countries.

The granulomatous inflammatory lesions in GPA indicate involvement of cellular immune responses. Although the targets of these immune responses are not yet known, persistent T-cell activation with predominance of effector memory T cells is present in GPA also during remission. Relapses coincide with an increase in levels of soluble IL-2R, which reflects increase in T-cell activation. In terms of cytokine production, type 1 helper T (Th1) cells seem to predominate, although this has not been consistently found. Effector memory T cells, probably with a cytokine pattern consistent with type 17 helper T cell (Th17) cells, are continuously present also during quiescent disease and localize in target tissues such as the kidneys when the disease becomes active. One explanation why the effector memory T cells remain active in GPA, even in remission could be the B7-1/B7-2–CD28/CTLA-4 pathway and the PD-1 pathway, which are both important in the activation of T cells. PD-1–deficient mice develop autoimmune disease, including arthritis and glomerulonephritis, and PD-1 upregulation has been reported in AAV.[42] Moreover, development of GPA has been described in patients treated with CLTA4 and PD-1 blockade.[43] Another explanation could be the direct activation of T cells by PR3-expressing neutrophils.[44] Not only T cells but also B cells play a direct role in the pathogenesis of GPA. Two types of B cells can be distinguished, that is, B regulatory and B effector cells. Especially the latter proinflammatory cytokine–producing B cells may contribute to the AAV pathogenesis.[45-48]

In conclusion, current data suggest an exogenous trigger as the inducing agent in GPA followed by immune activation with generation of PR3-ANCAs as well as effector T and B cells.[49,50]

Microscopic polyangiitis

Microscopic polyangiitis, in contrast to classic polyarteritis nodosa (PAN), is an ANCA-associated disease characterized by small-vessel vasculitis with frequent involvement of the kidneys (pauci-immune NCGN) and, somewhat less frequently, the lungs (pulmonary capillaritis). Their combined involvement results in a renal-pulmonary syndrome. ANCAs are directed against MPO in the majority of patients (see Table 162.1). After injection of immunoglobulin fractions with MPO-ANCAs into naïve rats in a rat model of MPO ANCA, endothelial injury with postcapillary venular hemorrhage was observed[51,52] and nasal insufflation of MPO409–428 as a therapeutic desensitization approach attenuated anti–MPO GN in mice.[53] All of these data strongly suggest a direct pathogenic role for MPO-ANCAs in MPA based on studies that show similarities between clinical and histopathologic findings in MPA and lesion development in in vivo experimental models. Also, the occurrence of MPA in a neonate born to a mother with MPO-ANCAs strongly suggests that transplacental transfer of IgG-class MPO-ANCAs can induce this disease.[54]

Interestingly, anti-GBM antibodies are found in around 30% of patients with MPO-ANCA–associated vasculitis. This subset of patients has more severe renopulmonary disease and a poorer prognosis than patients with MPO-ANCAs only.[55]

Eosinophilic granulomatosis with polyangiitis

Within the spectrum of ANCA-associated vasculitides, ANCAs occur less frequently in EGPA. Around 40% of patients test positive, in most cases for MPO-ANCAs. The presence of ANCAs in EGPA is associated with small-vessel vasculitis clinically apparent as purpura, mononeuritis multiplex, necrotizing glomerulonephritis, and pulmonary hemorrhage. This suggests that EGPA includes two disease entities, one associated with ANCAs and characterized by small-vessel vasculitis and the other being ANCA negative and characterized by tissue infiltration by eosinophils. Different environmental and genetic factors, namely human leukocyte antigen DRB1*04 (HLA-DRB1*04) and *07 alleles and the related *HLADRB4* gene, give an increased risk of eGPA. The disease is regarded as a Th2-mediated disease with an important direct pathogenic role of eosinophils. Studies showed that Th17 and B cells also play a role in the pathogenesis of eGPA.[56]

IMMUNOPATHOGENESIS OF VASCULITIDES OF MEDIUM- AND SMALL-SIZED ARTERIES

Among the vasculitides of medium- and small-sized arteries, classic PAN, and Kawasaki disease are the major disorders.

POLYARTERITIS NODOSA

The 2012 CHCC defined classic PAN as "necrotizing arteritis of medium or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules, and not associated with ANCA." This definition excludes any vasculitic condition in which arterioles, capillaries, and venules are involved. For this reason, many conditions previously described as PAN are now designated as MPA, which makes classic PAN a very rare disorder. Classic PAN is characterized by segmental necrotizing arterial lesions frequently with microaneurysm formation and resulting in ischemia, infarction, and hemorrhage.[57] Frequently, it presents as an isolated finding (e.g., as small bowel infarction). Hepatitis B virus (HBV)–related PAN, formerly observed

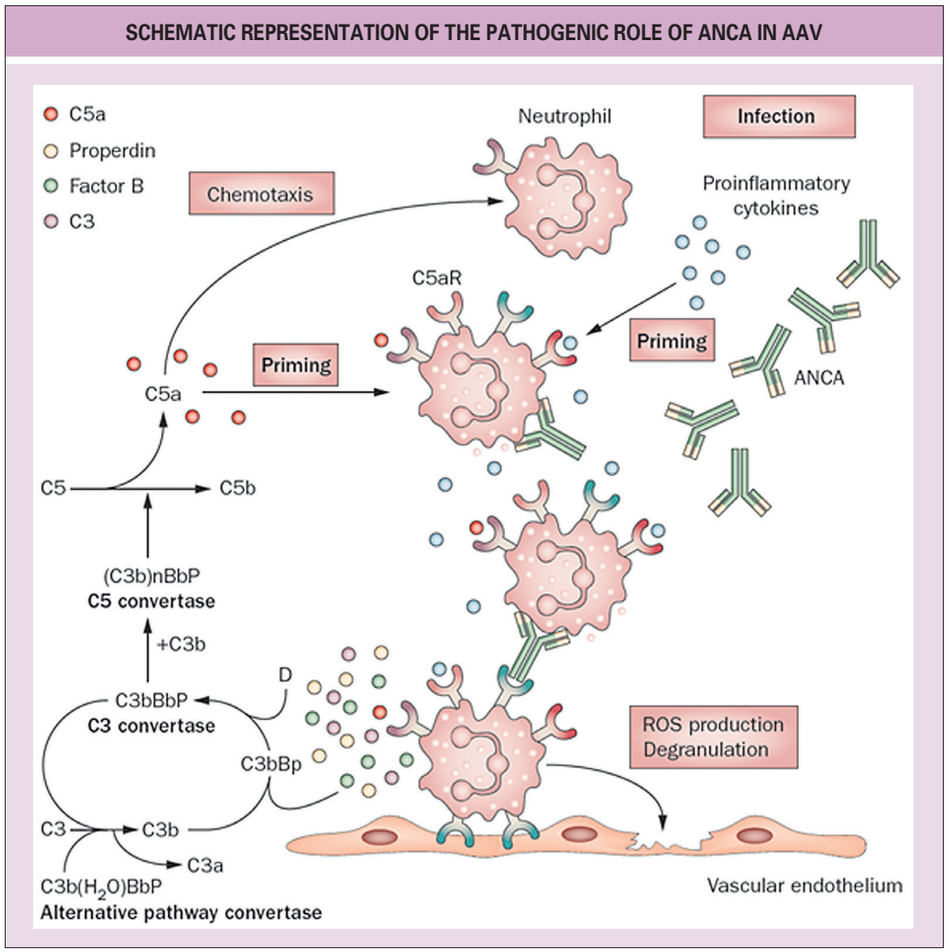

FIG. 162.6 In antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV), local infection, such as with *Staphylococcus aureus,* results in priming of neutrophils via proinflammatory cytokines. This results in the surface expression of the ANCA antigens, allowing ANCAs to bind to and further activate neutrophils that are rolling along the endothelium. Activation results in firm binding to the endothelium and release of lytic enzymes and reactive oxygen species (ROS), which damage the vessel wall. Also, the alternative pathway of complement is activated with generation of the powerful neutrophil chemoattractant C5a. This amplification loop contributes to the necrotizing inflammation of the vessel wall. *(From Chen M, Kallenberg CG. ANCA-associated vasculitides—advances in pathogenesis and treatment. Nat Rev Rheumatol 2010;6:653-66, with permission.)*

in one third of patients with PAN, is now rare. This condition presents as an acute disease occurring within 6 months of an HBV infection. Abdominal signs, malignant hypertension with renal failure, and orchitis are predominant. The immunopathogenesis of classic PAN, including HBV-related PAN, has been studied to a limited extent. ANCAs are absent; immune deposits are detected particularly in HBV-related PAN. When viral replication has stopped and seroconversion has occurred, the disease does not progress or relapse. This strongly suggests that HBV-related PAN is caused by immune complex formation in antigen excess. In HBV-negative PAN, immune deposits are frequently absent, and its immunopathogenesis is presently unclear. Shear stress at arterial bifurcation points may be involved in the location of the lesions and microaneurysm formation.[58]

KAWASAKI DISEASE

Kawasaki disease is an acute, self-limiting form of vasculitis occurring in childhood. It starts with fever, conjunctivitis, erythema of the lips and oral mucosa, and cervical lymphadenopathy, together with an acute-phase response. The clinical presentation as well as the epidemiology of the disease strongly suggests an infectious origin, but despite many efforts, a particular microbial pathogen has not been identified. A few pathologic observations, obtained from postmortem studies, show endothelial activation with subendothelial infiltration of mononuclear cells, in particular cytotoxic T cells and monocytes and macrophages in the coronary arteries, which are a site of predilection in this medium-sized artery vasculitis. The finding of oligoclonal IgA-producing plasma cells around inflamed coronary arteries also suggests a microbial cause, more specifically a respiratory virus. Thus, at present, Kawasaki disease is considered to arise from an aberrant immune response to as yet undefined microorganisms in a genetically susceptible host.[59]

IMMUNOPATHOGENESIS OF LARGE-VESSEL VASCULITIDES

In contrast to the necrotizing vasculitides affecting the small- and medium-sized vessels, the large-vessel vasculitides are not dominated by polymorphonuclear cell infiltration but show a cellular immune response with infiltration of monocytes, macrophages, and T cells. The two major diseases in this group are GCA and Takayasu arteritis.

GIANT CELL ARTERITIS

Giant cell arteritis is defined by the 2012 CHCC as "arteritis, often granulomatous, usually affecting the aorta and/or its major branches, with a predilection for the branches of the carotid and vertebral arteries; often involves the temporal artery; onset usually in patients older than 50; often associated with polymyalgia rheumatica."

Giant cell arteritis is characterized histopathologically by mononuclear infiltrates in all layers of the arterial wall. Macrophages and T cells are present in granuloma formation, and multinucleated giant cells are localized close to the fragmented internal elastic lamina. Proliferation of the intima results in occlusive vasculopathy.

Weyand and Goronzy attributed an initiating and central role to dendritic cells (DCs) in the immunopathogenesis of GCA.[60] Immature DCs, lacking the costimulatory molecules CD80 and CD86, are present in the adventitia of arteries and, because of a lack of costimulation, tolerize T cells that recognize (auto)antigens presented by these DCs localized in the adventitial area. Immature DCs can be activated in vitro and in vivo by stimulants such as lipopolysaccharide via Toll-like receptor 4 (TLR-4), which results in, among others, the expression of costimulatory molecules (CD80/86) and the capacity to activate T cells. Whereas DCs in the adventitia of arteries from healthy control participants are immature, temporal arteries from patients with polymyalgia rheumatica without inflammatory changes display mature DCs in their adventitia. It has been shown that DCs from patients with GCA, in contrast to adventitial DCs from control participants, are able to activate T cells derived from GCA lesions, as shown in experiments in mice with severe combined immunodeficiency in which the respective temporal arteries were implanted and T cells adoptively transferred. Thus, in situ maturation of DCs in the adventitia seems an initial event in the immunopathogenesis of GCA. The second element is constituted by CD4+ T cells that interact with these mature DCs. The crucial question of what these T cells recognize

has not been answered. Activated DCs in the adventitial layer of the temporal artery express high levels of major histocompatibility complex (MHC) class II and CD80/CD86 and produce cytokines and chemokines such as CCL19, CCL20, and CCL21 and express receptors for these chemokines as well. This causes the DCs to remain in situ instead of migrating into regional lymph nodes and allows the local interaction with CD4+ T cells.[61]

Recruited CD4+ T cells mainly expressing CCR6 and CD161 are polarized into Th17 cells (in the presence of IL-6, IL-1β and IL-23), Th1 cells (in the presence of IL-12 and IL-18), or both, which leads to a chronic inflammatory response. Th17 cells produce IL-17, which triggers IL-23 and IL-12 production by resident cells, thus stabilizing the Th17 lineage via IL-23 and increasing Th1 polarization via IL-12. As a third step, macrophages are recruited probably also via chemokine gradients, and after being activated by interferon-γ (IFN-γ), they produce IL-1β and IL-6, responsible for the systemic symptoms in GCA, ROS, nitric oxide via upregulation of iNOS, and metalloproteinases. IFN-γ induces the generation of multinucleated giant cells that contribute to the production of PDGF and, in particular, VEGF, which stimulate neoangiogenesis. Th1 and Th17 immunity seems responsible for the early phase and Th1 immunity for the more chronic smoldering inflammation.[62,63] The response to injury of the arterial vessel wall determines the level of occlusion of affected arteries and the occurrence of ischemic lesions. VEGF production results in neovascularization in the media and intima, which allows further proliferation of myofibroblasts, a process that is also dependent on PDGF production (Fig. e162.3).

Besides this cellular immune response that results in arteritis of the extracranial branches of the aorta, a systemic inflammatory response is characteristic of GCA as well (see also Chapter 166).

TAKAYASU ARTERITIS

Takayasu arteritis is defined by the 2012 CHCC as "arteritis, often granulomatous, affecting the aorta and its major branches." Onset usually in patients younger than 50 years of age. This disease occurs far more frequently in people from Japan, Southeast Asia, India, and Mexico than in Europeans, in whom GCA predominates. *IL12B* has been shown to be a susceptibility gene beyond ethnicity, and HLA-B*52:01 and *67:01 and HLA-DQB1/DRB1 are associated with Takayasu.[64] In Takayasu arteritis, as in GCA, all three layers of the vessel wall are involved, and the disease probably also starts in the adventitia. Immunohistopathologic analysis of the infiltrates in acute phases of the disease points toward a cellular immune response with infiltration of both Th1 and Th17 cells, natural killer (NK) cells, and CD8+ cytotoxic T cells. Th1 cells producing IFN-γ induce activation of macrophages and the formation of giant cells. Th17 cells contribute to the inflammatory lesions by activating neutrophils. NK cells and γd T cells interact via their Natural-Killer Group 2, member D receptor with MHC class I polypeptide-related sequence A antigens on vascular smooth muscle cells, which results in cytotoxicity via their production of perforin[65] (Takayasu Arteritis Chapter 165).

CONCLUSION

ECs and leukocytes are the most important players in the development of vasculitis. All vessels in the body can be affected. Why vasculitis develops in certain vascular beds depends on the initiating factors involved. These factors can be present in the circulation as immuncomplexes, IgA (complexes), and ANCA or be present at the vascular side as stress or danger signals activated DCs. Danger signals such as infectious triggers or damage probably initiate the vasculitis at the adventitial (large vessels) or endothelial (small vessels) side, and cytokines and chemokines direct the migration of leukocytes to the vessels. Repair mechanisms such as angiogenesis and proliferation often amplify the inflammatory cascade and amplify damage.

REFERENCES

1. Jennette JC, Falk RJ, Andrassy K, et al. Nomenclature of systemic vasculitides. proposal of an international consensus conference. *Arthritis Rheum*. 1994;37(0004-3591; 2):187-192.
2. Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised international chapel hill consensus conference nomenclature of vasculitides. *Arthritis Rheum*. 2013;65(1):1-11.
3. Kazmi RS, Boyce S, Lwaleed BA. Homeostasis of hemostasis: the role of endothelium. *Semin Thromb Hemost*. 2015;41(6):549-555.
4. Gutterman DD, Chabowski DS, Kadlec AO, et al. The human microcirculation: regulation of flow and beyond. *Circ Res*. 2016;118(1):157-172.
5. Langenkamp E, Molema G. Microvascular endothelial cell heterogeneity: general concepts and pharmacological consequences for anti-angiogenic therapy of cancer. *Cell Tissue Res*. 2009;335(1):205-222.
6. Winkler EA, Bell RD, Zlokovic BV. Central nervous system pericytes in health and disease. *Nat Neurosci*. 2011;14(11):1398-1405.
7. Hellstrom M, Gerhardt H, Kalen M, et al. Lack of pericytes leads to endothelial hyperplasia and abnormal vascular morphogenesis. *J Cell Biol*. 2001;153(3):543-553.
8. Medzhitov R. Innate immunity: quo vadis? *Nat Immunol*. 2010;11(7):551-553.
9. Langenkamp E, Kamps JA, Mrug M, et al. Innovations in studying in vivo cell behavior and pharmacology in complex tissues–microvascular endothelial cells in the spotlight. *Cell Tissue Res*. 2013;354(3):647-669.
10. Nourshargh S, Alon R. Leukocyte migration into inflamed tissues. *Immunity*. 2014;41(5):694-707.
11. Reglero-Real N, Colom B, Bodkin JV, et al. Endothelial cell junctional adhesion molecules: role and regulation of expression in inflammation. *Arterioscler Thromb Vasc Biol*. 2016;36(10):2048-2057.
12. Flamant L, Toffoli S, Raes M, et al. Hypoxia regulates inflammatory gene expression in endothelial cells. *Exp Cell Res*. 2009;315(5):733-747.
13. Woywodt A, Streiber F, de Groot K, et al. Circulating endothelial cells as markers for ANCA-associated small-vessel vasculitis. *Lancet*. 2003;361(9353):206-210.
14. Clarke LA, Hong Y, Eleftheriou D, et al. Endothelial injury and repair in systemic vasculitis of the young. *Arthritis Rheum*. 2010;62(6):1770-1780.
15. Kolaczkowska E, Kubes P. Neutrophil recruitment and function in health and inflammation. *Nat Rev Immunol*. 2013;13(3):159-175.
16. Li JL, Lim CH, Tay FW, et al. Neutrophils self-regulate immune complex-mediated cutaneous inflammation through CXCL2. *J Invest Dermatol*. 2016;136(2):416-424.
17. Pober JS, Sessa WC. Evolving functions of endothelial cells in inflammation. *Nat Rev Immunol*. 2007;7(10):803-815.
18. Wulfert FM, van Meurs M, Kurniati NF, et al. Age-dependent role of microvascular endothelial and polymorphonuclear cells in lipopolysaccharide-induced acute kidney injury. *Anesthesiology*. 2012;117(1):126-136.
19. Arroyo AG, Iruela-Arispe ML. Extracellular matrix, inflammation, and the angiogenic response. *Cardiovasc Res*. 2010;86(2):226-235.
20. Floege J, Moura IC, Daha MR. New insights into the pathogenesis of IgA nephropathy. *Semin Immunopathol*. 2014;36(4):431-442.
21. Davin JC, Coppo R. Henoch-Schonlein purpura nephritis in children. *Nat Rev Nephrol*. 2014;10(10):563-573.
22. Turner N, Mason PJ, Brown R, et al. Molecular cloning of the human goodpasture antigen demonstrates it to be the alpha 3 chain of type IV collagen. *J Clin Invest*. 1992;89(2):592-601.
23. Foster MH, Buckley ES, Chen BJ, et al. Uncommon structural motifs dominate the antigen binding site in human autoantibodies reactive with basement membrane collagen. *Mol Immunol*. 2016;76:123-133.
24. Ramos-Casals M, Stone JH, Cid MC, et al. The cryoglobulinaemias. *Lancet*. 2012;379(9813):348-360.
25. Terrier B, Cacoub P. Cryoglobulinemia vasculitis: an update. *Curr Opin Rheumatol*. 2013;25(1):10-18.
26. Damoiseaux J. The diagnosis and classification of the cryoglobulinemic syndrome. *Autoimmun Rev*. 2014;13(4-5):359-362.
27. Jachiet M, Flageul B, Deroux A, et al. The clinical spectrum and therapeutic management of hypocomplementemic urticarial vasculitis: data from a french nationwide study of fifty-seven patients. *Arthritis Rheumatol*. 2015;67(2):527-534.
28. Chen M, Kallenberg CG. ANCA-associated vasculitides–advances in pathogenesis and treatment. *Nat Rev Rheumatol*. 2010;6(11):653-664.
29. Damoiseaux J, Andrade LE, Fritzler MJ, et al. Autoantibodies 2015: from diagnostic biomarkers toward prediction, prognosis and prevention. *Autoimmun Rev*. 2015;14(6):555-563.
30. Chaigne B, Dion J, Guillevin L, et al. Pathophysiology of eosinophilic granulomatosis with polyangitis (Churg-Strauss). *Rev Med Interne*. 2016;37(5):337-342.
31. Boomsma MM, Stegeman CA, van der Leij MJ, et al. Prediction of relapses in Wegener's granulomatosis by measurement of antineutrophil cytoplasmic antibody levels: a prospective study. *Arthritis Rheum*. 2000;43(9):2025-2033.
32. Kemna MJ, Damoiseaux J, Austen J, et al. ANCA as a predictor of relapse: useful in patients with renal involvement but not in patients with nonrenal disease. *J Am Soc Nephrol*. 2015;26(3):537-542.
33. Fussner LA, Hummel AM, Schroeder DR, et al. Factors determining the clinical utility of serial measurements of antineutrophil cytoplasmic antibodies targeting proteinase 3. *Arthritis Rheumatol*. 2016;68(7):1700-1710.
34. Holland M, Yagi H, Takahashi N, et al. Differential glycosylation of polyclonal IgG, IgG-fc and IgG-fab isolated from the sera of patients with ANCA-associated systemic vasculitis. *Biochim Biophys Acta*. 2006;1760(4):669-677.
35. Espy C, Morelle W, Kavian N, et al. Sialylation levels of anti-proteinase 3 antibodies are associated with the activity of granulomatosis with polyangiitis (Wegener's). *Arthritis Rheum*. 2011;63(7):2105-2115.
36. Wuhrer M, Stavenhagen K, Koeleman CA, et al. Skewed fc glycosylation profiles of anti-proteinase 3 immunoglobulin G1 autoantibodies from granulomatosis with polyangiitis patients show low levels of bisection, galactosylation, and sialylation. *J Proteome Res*. 2015;14(4):1657-1665.
37. Roth AJ, Ooi JD, Hess JJ, et al. Epitope specificity determines pathogenicity and detectability in

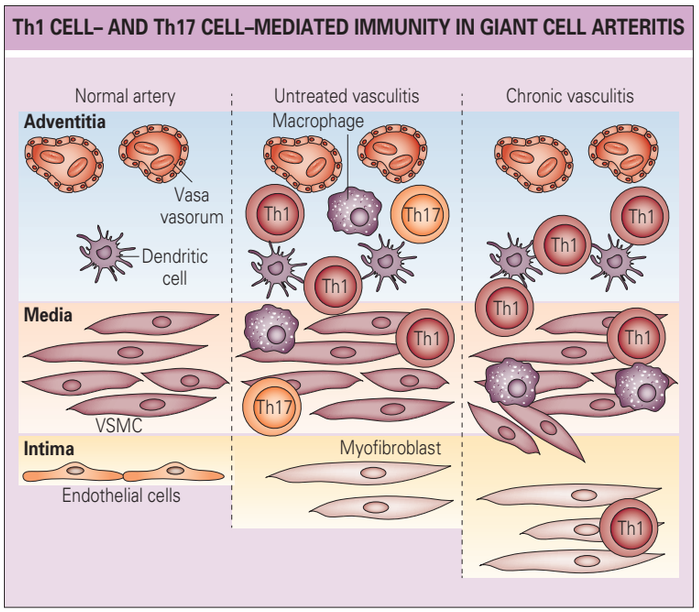

FIG. E162.3 The walls of human arteries are multilayered, with an endothelial barrier in the intima, sheets of vascular smooth muscle cells (VSMCs) in the media, and the vasa vasorum network in the adventitia. Endogenous vascular dendritic cells populate the adventitia *(left)* and are responsible for the recruitment of T cells and macrophages into the tissue niche. In early and untreated vasculitis, interferon-γ (IFN–γ)–producing type 1 helper T (Th1) cells and interleukin-17 (IL-17)–secreting type 17 helper T (Th17) cells are abundant, surrounded by macrophages *(middle)*. Corticosteroid therapy diminishes Th17 cells but cannot clear Th1 cells from the vascular lesions *(right)*. Dysregulated VSMCs migrate toward the lumen and lay down to form lumen-stenosing intimal hyperplasia. *(From Weyand CM, Goronzy JJ: Immune mechanisms in medium and large-vessel vasculitis. Nat Rev Rheumatol 9:731-40, 2013. Fig 1.)*

ANCA-associated vasculitis. *J Clin Invest*. 2013;123(4):1773-1783.
38. Jennette JC, Falk RJ, Hu P, et al. Pathogenesis of antineutrophil cytoplasmic autoantibody-associated small-vessel vasculitis. *Annu Rev Pathol*. 2013;8:139-160.
39. Kettritz R. How anti-neutrophil cytoplasmic autoantibodies activate neutrophils. *Clin Exp Immunol*. 2012;169(3):220-228.
40. Gan PY, Ooi JD, Kitching AR, et al. Mouse models of anti-neutrophil cytoplasmic antibody-associated vasculitis. *Curr Pharm Des*. 2015;21(18):2380-2390.
41. Stegeman CA, Tervaert JW, Sluiter WJ, et al. Association of chronic nasal carriage of *Staphylococcus aureus* and higher relapse rates in Wegener granulomatosis. *Ann Intern Med*. 1994;120(0003-4819; 1):12-17.
42. Wilde B, Hua F, Dolff S, et al. Aberrant expression of the negative costimulator PD-1 on T cells in granulomatosis with polyangiitis. *Rheumatology (Oxford)*. 2012;51(7):1188-1197.
43. van den Brom RR, Abdulahad WH, Rutgers A, et al. Rapid granulomatosis with polyangiitis induced by immune checkpoint inhibition. *Rheumatology (Oxford)*. 2016;55(6):1143-1145.
44. Millet A, Martin KR, Bonnefoy F, et al. Proteinase 3 on apoptotic cells disrupts immune silencing in autoimmune vasculitis. *J Clin Invest*. 2015;125(11):4107-4121.
45. Lepse N, Abdulahad WH, Rutgers A, et al. Altered B cell balance, but unaffected B cell capacity to limit monocyte activation in anti-neutrophil cytoplasmic antibody-associated vasculitis in remission. *Rheumatology (Oxford)*. 2014;53(9):1683-1692.
46. Bunch DO, McGregor JG, Khandoobhai NB, et al. Decreased CD5(+) B cells in active ANCA vasculitis and relapse after rituximab. *Clin J Am Soc Nephrol*. 2013;8(3):382-391.
47. Unizony S, Lim N, Phippard DJ, et al. Peripheral CD5+ B cells in antineutrophil cytoplasmic antibody-associated vasculitis. *Arthritis Rheumatol*. 2015;67(2):535-544.
48. Land J, Abdulahad WH, Sanders JS, et al. Regulatory and effector B cell cytokine production in patients with relapsing granulomatosis with polyangiitis. *Arthritis Res Ther*. 2016;18:84-016-0978-1.
49. Sanders JS, Abdulahad WH, Stegeman CA, et al. Pathogenesis of antineutrophil cytoplasmic autoantibody-associated vasculitis and potential targets for biologic treatment. *Nephron Clin Pract*. 2014;128(3-4):216-223.
50. Dumoitier N, Terrier B, London J, et al. Implication of B lymphocytes in the pathogenesis of ANCA-associated vasculitides. *Autoimmun Rev*. 2015;14(11):996-1004.
51. Little MA, Al-Ani B, Ren S, et al. Anti-proteinase 3 anti-neutrophil cytoplasm autoantibodies recapitulate systemic vasculitis in mice with a humanized immune system. *PLoS ONE*. 2012;7(1):e28626.
52. van Timmeren MM, Heeringa P. Pathogenesis of ANCA-associated vasculitis: recent insights from animal models. *Curr Opin Rheumatol*. 2012;24(1):8-14.
53. Gan PY, Tan DS, Ooi JD, et al. Myeloperoxidase peptide-based nasal tolerance in experimental ANCA-associated GN. *J Am Soc Nephrol*. 2016;27(2):385-391.
54. Bansal PJ, Tobin MC. Neonatal microscopic polyangiitis secondary to transfer of maternal myeloperoxidase-antineutrophil cytoplasmic antibody resulting in neonatal pulmonary hemorrhage and renal involvement. *Ann Allergy Asthma Immunol*. 2004;93(4):398-401.
55. Rutgers A, Slot M, van Paassen P, et al. Coexistence of anti-glomerular basement membrane antibodies and myeloperoxidase-ANCAs in crescentic glomerulonephritis. *Am J Kidney Dis*. 2005;46(2):253-262.
56. Greco A, Rizzo MI, De Virgilio A, et al. Churg-Strauss syndrome. *Autoimmun Rev*. 2015;14(4):341-348.
57. Bonsib SM. Polyarteritis nodosa. *Semin Diagn Pathol*. 2001;18(1):14-23.
58. De Virgilio A, Greco A, Magliulo G, et al. Polyarteritis nodosa: a contemporary overview. *Autoimmun Rev*. 2016;15(6):564-570.
59. Newburger JW, Takahashi M, Burns JC. Kawasaki disease. *J Am Coll Cardiol*. 2016;67(14):1738-1749.
60. Weyand CM, Goronzy JJ. Immune mechanisms in medium and large-vessel vasculitis. *Nat Rev Rheumatol*. 2013;9(12):731-740.
61. Ma-Krupa W, Jeon MS, Spoerl S, et al. Activation of arterial wall dendritic cells and breakdown of self-tolerance in giant cell arteritis. *J Exp Med*. 2004;199(0022-1007; 2):173-183.
62. Deng J, Younge BR, Olshen RA, et al. Th17 and Th1 T-cell responses in giant cell arteritis. *Circulation*. 2010;121(7):906-915.
63. Samson M, Audia S, Fraszczak J, et al. Th1 and Th17 lymphocytes expressing CD161 are implicated in giant cell arteritis and polymyalgia rheumatica pathogenesis. *Arthritis Rheum*. 2012;64(11):3788-3798.
64. Terao C, Yoshifuji H, Mimori T. Recent advances in Takaysu arteritis. *Int J Rheum Dis*. 2014;17(3):238-247.
65. Serra R, Butrico L, Fugetto F, et al. Updates in pathophysiology, diagnosis and management of Takayasu arteritis. *Ann Vasc Surg*. 2016;35:210-225.