Franco Dammacco · Domenico Ribatti
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Systemic Vasculitides: Current Status and Perspectives

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To be fully aware of one's own ignorance is an irrepressible incitation to the pursuit of knowledge.

Preface

This volume seeks to provide a comprehensive overview of the systemic vasculitides, an extremely heterogeneous group of diseases characterized by inflammation and necrosis of different-sized blood vessels. With a few exceptions (e.g., HCV-related cryoglobulinemic vasculitis and HBV-positive polyarteritis nodosa), the etiology of these clinical conditions remains unknown. In spite of their relatively low prevalence, the systemic vasculitides have been the object of recent, intensive, basic, and clinical studies. For this reason, it can be safely stated that this group of diseases is one of the most rapidly progressing areas of clinical medicine, as evidenced by the dramatic achievements in terms of clinical remission and overall prognostic improvement.

The pathophysiology of the vasculitides is multifactorial and thus in most cases poorly defined. Among the many potential influences on disease expression, sex, ethnicity, and genetic as well as environmental factors are likely to play a role. In addition, the vascular damage characteristic of the systemic vasculitides may be the result of autoimmune responses, such as antineutrophil cytoplasmic autoantibodies, anti-endothelial cell autoantibodies, immune complex deposition, an immune response to foreign antigens or infectious agents, and T-lymphocyte responses with granuloma formation.

The general aims of this book are:

(i) To provide an in-depth update of the major pathogenetic, genetic, and clinical advances in the field encompassing the vasculitides, including, for each condition, a summary of the most cogent information scattered in the medical literature but not always readily retrievable
(ii) To describe not only conventional treatments, but also the more recently developed and tested drugs as well as efforts at patient-tailored therapies, especially for patients with refractory and relapsing disease
(iii) To point out future directions of research that, while challenging, are likely to be profitable in terms of improved diagnosis and therapy

If this book serves as a stimulating resource for basic and clinical researchers and specialists in related disciplines, as well as practicing physicians and advanced medical students interested in this fascinating branch of medicine, our efforts as editors will have been fully rewarded. The lion's share of the merit should, however, be given to the international contributors who accepted our invitation to collaborate in this project and who, in doing so, were able to impart the knowledge gained during their multiyear experience in this field.

Bari, Italy

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Part I
Biology of Blood Vessels, Experimental Models and Nomenclature of Vasculitides

Chapter 1
Morphofunctional Aspects of Endothelium

Domenico Ribatti

Abstract Blood vessels represent an essential component of all organs. The vascular tree develops early during embryogenesis and progresses into a highly branched system of vascular channels lined by endothelial cells (ECs) and surrounded by mural cells. A highly hierarchical vascular architecture is established which comprises distinct arterial, capillary and venous segments as well as organ- and tissue-specific vascular beds. EC heterogeneity plays a role in directing disease processes to distinct vascular territories and characterization of the molecules involved in creating vascular heterogeneity might eventually allow refinement of diagnostic and therapeutic strategies aimed at targeting distinct segments of the vascular tree.

Keywords Endothelial cells • Vascular heterogeneity • Vascular diseases

1.1 Endothelial Cell Heterogeneity and Organ Specificity

Endothelial cells (ECs) form a continuous monolayer between the blood and the interstitial fluid. The EC surface in an adult human is composed of approximately 1.6×10^{13} cells and covers a surface area of approximately 7 m^2 [1]. Quiescent ECs generate an active antithrombotic surface through the expression of tissue factor pathway inhibitors, heparan sulphate proteoglycans that can interfere with thrombin-controlled coagulation, and thrombomodulin that facilitate transit of plasma and cellular constituents throughout the vasculature. Perturbations and dysfunctions (Table 1.1) induce ECs to create a prothrombotic and antifibrinolytic microenvironment.

An increase of blood flow into a capillary induces local recruitment of smooth muscle cells and leads to a differentiation into an artery or vein, while cessation of blood flow causes vessel regression [2].

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Table 1.1 Consequences of endothelial dysfunctions

Inflammation
Fibrosis
Cardiovascular diseases
Pulmonary hypertension
Atherosclerosis
Hyperlipidemia
Thrombosis
Immune reactions
Peripheral vascular diseases
Angiogenesis

There are differences between ECs derived from various microvascular beds/organs, ascribed to genetic and microenvironmental influences [3], including extracellular matrix components, locally produced pro- and anti-angiogenic molecules, interactions with neighboring cells, and mechanical forces. Interactions may occur through the release of cytokines and the synthesis and organization of matrix proteins on which the endothelium adheres and grows. Moreover, ECs release and express on the cell surface many signaling molecules that can affect the density of developing neighboring tissue cells [4].

ECs lining the capillaries of different organs are morphologically distinct. The vasculature of liver, spleen and bone marrow sinusoids is highly permeable because vessels are lined by discontinuous ECs, capillaries in the brain and retinal capillaries, dermis, bone tissue, skeletal muscle, myocardium, testes and ovaries are continuous, and ECs in endocrine glands and kidney are fenestrated. EC heterogeneity is also appreciable in individual organs. For example, the kidney contains fenestrated ECs in its peritubular capillaries, discontinuous ECs in its glomerular capillaries, and continuous ECs in other regions. The phenotype of ECs is unstable and likely to change when they are removed from their microenvironment [5]. Endothelial heterogeneity is also responsible for different responses across different vascular beds to pathological stimuli and disease states [6].

Antigens are differentially expressed on ECs of certain organs and tissues [7]. For example, the von Willebrand factor (vWF) marker is expressed at higher levels on the venous rather than on the arterial side of the capillary circulation, while it is largely absent from sinusoidal ECs. Moreover, vWF may play a role in tumor cell dissemination, as significantly higher levels have been reported in metastatic cancers [8].

1.2 Arterial and Venous Endothelial Cell Distinctions

The discovery that members of the ephrin family are differentially expressed in arteries (Fig. 1.1) and veins from very early stages of development is an indication that artery-vein identity is intrinsically programmed. Ephrin-B2 is expressed in arterial ECs, large arteries within the embryo, and in the endocardium of the developing

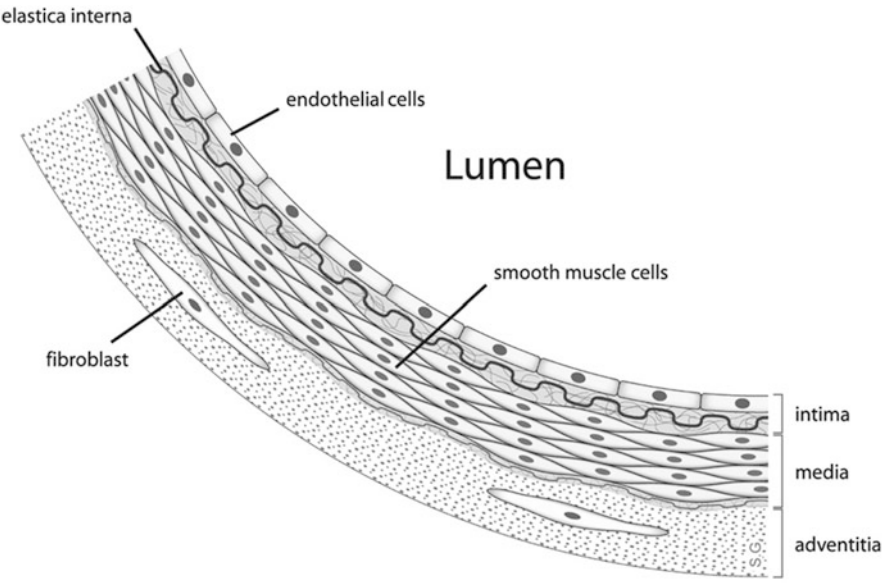

Fig. 1.1 Schematic drawing showing the general organization of the wall of an arterial vessel (Reproduced from "Endotelijalna ćelija" by D. Rosenbach at English Wikipedia)

heart, while the receptor for Ephrin-B2, Eph-B4, displays a reciprocal expression pattern in embryonic veins, large veins and also in the endocardium. Remodelling of the primary vascular plexus into arteries and veins was arrested in both Ephrin-B2 and Eph-B4 mutants, suggesting important roles for Ephrin-B2/Eph-B4 interactions on arterial and venous ECs differentiation, respectively [2].

Other specific markers for the arterial system include neuropilin-1 (NRP-1) and members of the Notch family, Notch-3, DDL4 and GRIDLOCK (Grl), while venous markers include NRP-2 Notch signalling is necessary for remodelling the primary plexus into mature vascular beds and maintaining arterial fate, and is essential for the homeostatic functions of fully differentiated arteries. During vascular development, defects in signalling through the Notch pathway, including ligands such as Jagged-1, Jagged-2, and Delta-like-4 and receptors, such as Notch-1, Notch-2, and Notch-4, disrupt normal differentiation into arteries or veins, resulting in loss of artery specific markers [9].

Le Noble et al. [10] studying arterial-venous differentiation in the developing yolk sac of the chick embryo, observed that prior to the onset of flow, EC expressing arterial and venous specific markers are localized in a posterior-arterial and anterior-venous pole. Ligation of one artery by means of a metal clip, lifting the artery, and arresting arterial flow distal to the ligation site could morphologically transform the artery into a vein. When the arterial flow was restored by removal of the metal clip, arterial maker was re-expressed, suggesting that the genetic fate of arterial EC is plastic and controlled by hemodynamic forces.

1.3 Vascular Diversity in Pathological Conditions

Endothelium plays a major role in the pathophysiology of different conditions, including inflammation and cancer. EC activation by inflammatory cytokines results in the increased expression of adhesion molecules, including E-selectin, intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1) [11].

It has long been recognized that systemic vasculitides impact distinct segments and branches of the vascular tree, and smooth muscle cells and dendritic cells are involved in the pathogenesis of these diseases. Necrotizing sarcoid granulomatosis, Takayasu's arteritis, and giant cell arteritis cause macrovascular compromise, while cryoglobulinemic vasculitis affects microcirculation. Some diseases such as Behçet's syndrome (a small vessel vasculitis that can affect venules) and Wegener's granulomatosis (an ANCA-associated vasculitis generally affecting small arteries and veins) compromise the whole pulmonary vasculature. Churg-Strauss syndrome (a necrotizing ANCA-associated vasculitis) targets medium-sized arteries and veins of the macrocirculation, whereas microscopic polyangiitis impacts arterioles, capillaries and venules of the microcirculation [12].

A dual role of angiogenesis in vasculitides has been proposed. On the one hand, angiogenesis may be a compensatory response to ischemia and to the increased metabolic activity in acute phase of the disease. On the other hand, ECs of newly-formed vessels express adhesion molecules and produce colony-stimulating factors and chemokines for leukocytes [12].

Tumor vessels exhibit chaotic blood flow, have focal regions that lack ECs or basement membrane. Qualitative differences exist in the tumor vasculature at different stages [13]. Distinct tumor vessels may need specific vascular growth factors and cytokines at defined tumor stages. There are vascular tumors that derive from ECs and express unique autonomous properties. In infantile hemangioma, molecular profiling has provided evidence for a placental derivation of ECs [14]. Kaposi's sarcoma, an AIDS-defining vascular tumor, involves a phenotypically unique spindle cell that appears to derive from lymphatic ECs [15]. The vasculature of tumors tends to acquire characteristics similar to those of the host environment. The microvasculature of murine mammary carcinoma, rhabdomyosarcoma, and human glioblastoma implanted s.c. in nude mice become extensively fenestrated [16]. On the contrary, the same tumors implanted in the brain acquire a microvasculature resembling more closely the brain microvasculature phenotype.

Differential pattern of expression of angiogenic genes accompany and are probably responsible for the host-environment-induced differences in vascularisation. St. Croix et al. [17] have identified markers specifically induced in ECs from human colorectal carcinoma through a comparison of gene expression profiles of ECs isolated from human colorectal carcinoma and normal human colorectal tissue. Ria et al. [18] have identified genes differentially expressed in multiple myeloma ECs compared to ECs of monoclonal gammopathy of undetermined significance. Deregulated genes are involved in extracellular matrix formation and bone remodeling, cell adhesion, chemotaxis, angiogenesis, resistance to apoptosis, and cell-cycle regulation.

Coronary artery disease is one example of a disease that targets the arterial ECs. In response to hypercholesterolemia, myocardial ECs increase the expression of adhesion molecules, which leads to intimal thickening and plaque formation. ECs lack preferential cell alignment and often show a polygonal morphology in zones of disturbed vascular flow, such as regions susceptible of atherogenesis including the aortic arch or heart valves. Up-regulation of genes associated with endoplasmic reticulum processing of proteins, endoplasmic reticulum stress and unfolded protein response, contribute to enhanced endothelial permeability via focally increased EC proliferation in these regions [19, 20].

Selective EC activation may be responsible for the development of some brain pathologies, including blood–brain barrier dysfunction linked to Alzheimer's disease [21].

1.4 Concluding Remarks

EC diversity has crucial implications for the development of vascular diseases. Systemic vasculitides target distinct segments and branches of the vascular tree as well as selective vascular beds. Even thrombotic or hemorrhagic conditions recognize specific vascular beds as the sites of disease occurrence. Potential implications for the pathogenesis of vascular metabolic diseases like atherogenesis are also strong. EC differences exist in the tumor vasculature at different stages, a situation which may profoundly affect the efficacy of tumor treatment.

Understanding how early, basic ECs can differentiate into a specialized assortment of organ- and tissue-associated ECs is essential for appreciating the complexity of vascular disorders and for establishing critically designed strategies of vascular diseases' treatment, through the use of glucocorticoids, immunosuppressive, immunomodulator, and anti-inflammatory drugs. Indeed, identification of vascular-bed specific molecular profiles should facilitate the development of molecular imaging for diagnosis and surveillance as well as the improvement of "intelligent" molecules targeting selected vascular districts.

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Chapter 2
Animal Models of ANCA-Associated Vasculitides

Domenico Ribatti and Franco Dammacco

Abstract Antibodies against neutrophil proteins myeloperoxidase (MPO) and proteinase-3 (PR3) are responsible for the development of anti-neutrophil cytoplasmic autoantibodies (ANCA)-associated vasculitides (AAV). Although the knowledge of these conditions is remarkably improved in the last few years, their etiology and pathogenetic mechanism(s) are still poorly understood. The establishment of experimental models has been repeatedly attempted with the aim of achieving a deeper understanding of their human counterpart. Here, we discuss the principal animal models currently used to investigate the mechanisms underlying the onset of AAV.

Keywords Animal models • Anti-neutrophil cytoplasmic autoantibodies • Vasculitis

2.1 Introduction

A number of *in vitro* and *in vivo* studies, focusing on different aspects of the neutrophil biology and function, have clearly demonstrated the potential role that neutrophils can exert in the modulation of innate and adaptive immune responses [1].

Anti-neutrophil cytoplasmic autoantibodies (ANCA) were first recognized by van der Woude et al. [2], who described circulating autoantibodies that reacted with cytoplasmic antigens of neutrophils and monocytes in patients with granulomatosis with polyangiitis (GPA). ANCA-associated vasculitides (AAV) are systemic autoimmune disorders characterized by inflammatory necrosis of small blood vessels affecting joints, lungs, kidneys, skin and other tissues [3]. Neutrophils are cardinal

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cells in the pathophysiological process underlying AAV since they are both effector cells responsible for endothelial damage and targets of autoimmunity. It should, however, be emphasized that some patients showing similar disease manifestations as those who are ANCA-positive are nonetheless ANCA-negative [4].

Four diseases are characterized by the presence of ANCA, namely GPA (formerly called Wegener's granulomatosis), microscopic polyangiitis (MPA), eosinophilic granulomatosis with polyangiitis (EGPA, formerly termed Churg-Strauss syndrome), and the necrotizing crescenting glomerulonephritis (NCGN). The etiological factors responsible for the production of vessel-damaging ANCA are unknown. Although infectious agents have been repeatedly suspected and *Staphylococcus aureus* has long been known to be associated with GPA, their precise immunologic link with AAV has not been proven.

In the 1980s, autoantibodies to cytoplasmic components of myeloid cells were detected in patients with pauci-immune necrotizing small vessel vasculitis. In AAV, the autoimmune response is directed against neutrophil and monocyte lysosomal enzymes, including myeloperoxidase (MPO) and proteinase 3 (PR3) [5]. MPO is abundantly expressed and exclusively found in azurophilic granules, and is a key component of the phagocyte oxygen-dependent intracellular microbicidal system [6]. On the other hand, PR3, also called myeloblastin, belongs to the neutrophil serine protease family and is classically localized in azurophilic granules. Following phagocytosis of pathogens, PR3 is secreted in the phagolysosome to play its crucial microbicidal function [7].

Clinical and experimental studies have provided extensive evidence for the involvement of autoantibodies to MPO and PR3 in the pathogenesis of AAV [8], thus leading to treatment strategies aimed at ANCA removal. Plasma exchange, for example, has been shown to remove plasma constituents as well as ANCA and to increase the chances of renal recovery in severe renal vasculitis [9].

The crucial factors required for animal models of vasculitis are the similarities to the clinical and pathologic phenotypes of human diseases, with the obvious assumption that their study may contribute to the pathogenetic elucidation of human vasculitis. Here, we will briefly discuss the principal animal models currently used to investigate the mechanism(s) of vascular injury in AAV.

2.2 Animal Models Involving Anti-MPO Immune Response

In spite of the large body of *in vitro* studies, unequivocal evidence that ANCA are pathogenic *in vivo* was obtained only recently [10]. The pathogenicity of ANCA has been investigated in mouse models by exploring both passive transfer and active immunization strategies in order to reproduce systemic vasculitis.

The first animal model resembling the human disease was introduced by Xian et al. [11]. They reported that injection of splenocytes, derived from MPO-deficient mice immunized with mouse MPO, into recipient mice lacking mature T and B cells (RAG2-deficient mice) caused severe necrotizing glomerulonephritis. In a second

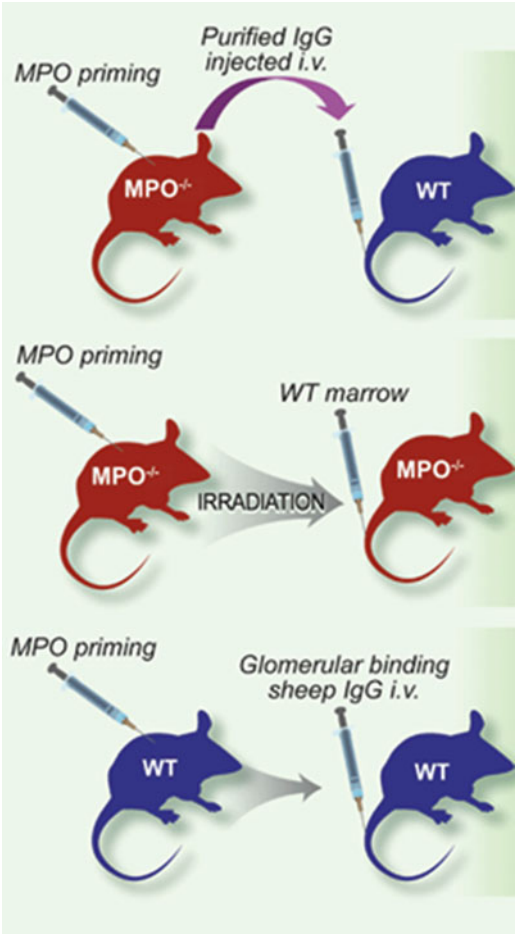

Fig. 2.1 Summary of three mouse models that have been used to study pathogenetic mechanisms in ANCA-associated vasculitis (Modified from Coughlan et al. Clin Exp Immunol. 2012; 169: 229–37)

approach, IgG were isolated from MPO-deficient mice immunized with MPO and passively transferred into wild type and RAG2−/− mice, resulting in a pauci-immune glomerulonephritis mimicking the human disease (Fig. 2.1) [11], thus confirming that neutrophil is the primary effector cell in anti-MPO-induced glomerulonephritis [12].

In an additional model, MPO-deficient mice were immunized with murine MPO; after production of anti-MPO IgG, the animals were lethally irradiated and transplanted with bone marrow from MPO-positive wild type mice (Fig. 2.1) [13]. By 8 weeks after bone marrow transplantation, the mice developed a pauci-immune glomerulonephritis with urine abnormalities. The transfer of anti-MPO lymphocytes into immune-deficient mice has also resulted in necrotizing glomerulonephritis with glomerular immune deposits [14].

A third mouse model is based on the induction of both humoral and cellular autoimmune responses to MPO (Fig. 2.1) [15]. Wild type mice were in fact

immunized with MPO and subsequently injected with a sub-nephritogenic dose of nephrotoxic serum (anti-GBM), this procedure resulting in the development of glomerulonephritis. The advantage of this model was the generation of an autoimmune response to MPO in wild type mice.

The models of anti-MPO-mediated glomerulonephritis shortly described above have proven to be useful tools for testing experimental therapies. For example, therapeutic interventions aimed at blocking the pro-inflammatory effects of tumor necrosis factor-alpha (TNFα) have been evaluated in both the MPO-ANCA mouse model [16] and the experimental autoimmune vasculitis rat model [17].

2.3 Animal Models Involving Anti-PR3 Immune Response

Following immunization with recombinant human mouse PR3, non-obese diabetic (NOD) mice develop specific anti-PR3 autoantibodies. The transfer of splenocytes from these mice into immunodeficient NOD/severe combined immunodeficiency disease (SCID) mice has been shown to result in vasculitis and severe segmental and necrotizing glomerulonephritis, leading to acute kidney failure and death [18].

Little et al. [19] have described an interesting model consisting of humanized immunodeficient NOD/SCID interleukin-2 (IL-2)- receptor knockout mice, which received human hematopoietic stem cells and developed a human-mouse chimeric immune system. These mice developed glomerulonephritis following passive transfer of PR3-ANCA IgG derived from patients with severe systemic vasculitis [19].

2.4 Concluding Remarks

Interesting animal models of anti-MPO-related vasculitis, closely resembling clinical and pathological features in humans, have been established. By inducing an abnormal immune response to MPO, these models mimic the clinical aspects of the human MPO-AAV and are contributing to elucidate how ANCA cause vasculitis.

Animal models of anti-PR3 associated disease are much less advanced, and generation of an experimental model that implies both anti-PR3-associated vasculitis and granuloma formation is a major challenge in this field. Further investigations are needed to identify the molecular mechanisms that control the complex neutrophil/endothelium interactions and to establish whether they are dysregulated in AAV [20].

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Chapter 3
Nomenclature of Vasculitides: 2012 Revised International Chapel Hill Consensus Conference

Nomenclature of Vasculitides and Beyond

J. Charles Jennette, Ronald J. Falk, and Marco A. Alba

Abstract A nomenclature system provides names and definitions for diseases, and provides the framework for establishing classification criteria for groups of patients and diagnostic criteria for individual patients. The International Chapel Hill Consensus Conference Nomenclature of Vasculitides (CHCC) provides standardized names and definitions for different classes of vasculitis, but does not provide validated criteria for classifying cohorts of patients into these classes, or for diagnosing (classifying) an individual patient. The CHCC nomenclature and definitions are useful for communication among health care providers, understanding the medical literature, guiding development of classification and diagnostic criteria, and facilitating research on cohorts of patients with vasculitis. Names and definitions evolve more slowly than classification and diagnostic criteria because the latter must change as new diagnostic technologies and clinical laboratory testing are available. For example, the discovery of anti-neutrophil cytoplasmic autoantibodies (ANCA) added a new criterion for classifying vasculitis. The most robust ongoing effort to develop classification and diagnostic criteria for vasculitis is by the Diagnostic and Classification Criteria for Vasculitis (DCVAS) study group. Once data are collected from large vasculitis patient cohorts, identifying the most clinically and biologically relevant classes, and the most accurate and precise diagnostic criteria, may require the application of supervised and unsupervised machine learning algorithms. It will be interesting to see how machine generated vasculitis classes agree (or not) with the CHCC classes that were devised by mere mortals.

Keywords Algorithms • Classification criteria • Diagnostic criteria • Nomenclature system • Systemic vasculitides

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3.1 Introduction

A nomenclature system provides names and definitions for diseases. A classification system classifies cohorts of patients into distinct classes, and provides the framework for establishing classification criteria for groups of patients and diagnostic criteria for individual patients. The International Chapel Hill Consensus Conference Nomenclature of Vasculitides (CHCC) provides standardized names and definitions for different classes of vasculitis [1, 2] (Table 3.1). The CHCC does not provide validated criteria for classifying cohorts of patients into these classes, or for diagnosing (classifying) an individual patient. The CHCC nomenclature and classification is of value for:

- Communicating among health care providers involved in the care of patients with vasculitis
- Writing and understanding medical literature pertinent to vasculitis
- Guiding the development of classification and diagnostic criteria to be validated in cohorts of vasculitis patients
- Facilitating clinical and basic research on cohorts (classes) of patients with distinct forms of vasculitis

The name and definition of a disease are specified in an accepted nomenclature system, for example the CHCC system. Effective nomenclature/classification/diagnostic systems are based on up to date clinical and pathobiological data, especially etiology and pathogenesis when known. Classification criteria are the data that are used to place groups of patients into standardized classes. Diagnostic criteria are data that demonstrate or confidently predict the presence of the defining features of a disease in a specific patient. Classification criteria and diagnostic criteria must be tested and validated by studying actual cohorts of patients, and comparing them to disease controls and healthy individuals. Classification and diagnostic criteria evolve most quickly, driven by advances in diagnostic technologies and clinical laboratory testing. For example, new biomarkers that are validated as useful clinical laboratory tests are added to existing classification and diagnostic criteria, as was the case when anti-neutrophil cytoplasmic autoantibodies (ANCA) were discovered, and the presence or absence of ANCA were added as criteria for the classification and diagnosis of small vessel vasculitis [1–3]. Effective names and definitions may persist indefinitely, such as myocardial infarction defined as focal ischemic necrosis of myocardium; whereas the diagnostic and classification criteria for myocardial infarction change over time as new imaging, electrophysiological and laboratory tests are developed.

The 1994 International Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitides (CHCC 1994) proposed names and definitions for some of the most common variants of vasculitis [1], and was widely adopted throughout the world. As expected, following publication of the CHCC 1994 article, there were many advances in the understanding of vasculitis. The CHCC 1994 purposefully was confined to proposing names and definitions for a limited number of vasculitides,

Table 3.1 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's) (GPA)
    - Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA)
  - Immune complex SVV
    - Anti-glomerular basement membrane (anti-GBM) disease
    - Cryoglobulinemic vasculitis (CV)
    - IgA vasculitis (Henoch-Schönlein) (IgAV)
    - Hypocomplementemic urticarial vasculitis (HUV) (anti-C1q vasculitis)
- **Variable vessel vasculitis (VVV)**
  - Behcet's disease (BD)
  - Cogan's 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

Modified from Jennette et al. [2]
The items highlighted in red are changes or additions compared to the 1994 International Chapel Hill Consensus Conference on the Nomenclature of Vasculitides