Chapter 2
Vascular Inflammation: From Cellular Mechanisms to Biotechnology Advances

Fernanda Cardoso da Silva and Cristina Ribas Fürstenau

Abstract Blood vessels are an interconnected network of arteries, arterioles, capillaries, veins, and venules that carry blood to all body tissues. Blood vessels are formed by (1) a single layer of endothelial cells that regulates the transit of what needs to pass between the bloodstream and the surrounding tissue; (2) more or less prominent layers of smooth muscle fibers that control the vascular tone and resistance; and (3) an external layer of a fibrous and connective tissue that connects the layers of the vascular wall with the tissues. Inflammatory vascular pathology results from both the attack of the immune cells and the response of the vascular wall, providing both regeneration and maladaptive responses. Two main stages are recognized in the inflammatory process: (1) the acute phase, characterized by increased vascular permeability, intense blood flow, and accumulation of cytokines and immune cells; and (2) the chronic phase, which relies on the action of lymphocytes and macrophages, involving the stages of neoangiogenesis and fibroplasia. Altered or nonfunctional blood vessels are present in cardiovascular diseases (CVDs) which account for more than 30% of global deaths and are a major issue of public health worldwide. Vascular inflammation involves different mechanisms, such as the activation of the renin–angiotensin–aldosterone system; the excessive production of reactive oxygen (ROS) and nitrogen (RNS) species; the thrombi formation; among others. Thus, the processes that trigger vascular inflammation and its involvement with CVDs are relevant and can be clinically useful in the diagnosis and therapy of these diseases. This chapter presents biomarkers of vascular inflammation of molecular, cellular, and chemical nature, especially in the context of CVDs, and also brings the most recent research related to biotechnological advances in diagnosis and therapies for vascular inflammation.

F. C. da Silva
Program of Post-graduation in Genetics and Biochemistry, Universidade Federal de Uberlândia, Uberlândia, MG, Brazil

C. R. Fürstenau (✉)
Laboratory of Vascular Biochemistry, Universidade Federal do ABC, Santo André, SP, Brazil
e-mail: c.furstenau@ufabc.edu.br

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2.1 Introduction

The traditional separation between noninflammatory vascular diseases and inflammatory vasculopathies is incorrect. For example, it is well known that immune cells and inflammatory pathways participate in atherogenesis in atherosclerotic vascular disease, particularly in events that lead to plaque rupture and ischemia. In this sense, it is clear that inflammation is a critical component of atherosclerosis, which places it on the same level as classic vasculitis (Hoffman et al. 2012).

The inflammatory pathology results from the attack of the immune cells and the response of the vascular wall, making the vascular tissue an active participant in inflammatory diseases, being able to provide both regeneration and maladaptive responses (Hoffman et al. 2012). The correct functioning of blood vessels is essential for the maintenance of body homeostasis. Morpho-functional changes in blood vessels can lead to the development of several diseases, including cardiovascular diseases (CVDs) (e.g., coronary heart disease, cerebrovascular disease, rheumatic heart disease, and other conditions) that are the leading cause of morbidity and mortality worldwide (Aikawa et al. 2019). Vascular inflammation is one of the most aggravating factors of CVDs (Goyal et al. 2019) and involves different mechanisms, such as the activation of the renin–angiotensin–aldosterone system, the intensification of the production of reactive oxygen (ROS) and nitrogen (RNS) species, the activation of the innate and adaptive immune system, the thrombus formation, and the formation of new blood vessels (Kvietys and Granger 2012; Petrie et al. 2018).

In this chapter, the diversity of cellular and molecular markers involved in vascular inflammation is presented. Besides, the most recent research related to biotechnological advances directed both to the identification of new markers and to therapies for vascular inflammation are also discussed.

2.2 Blood Vessels and Vascular Inflammation

Blood vessels are an interconnected network of arteries, arterioles, capillaries, veins, and venules that carry blood to all body tissues. Blood vessels are formed by (1) the tunica intima, consisting of a single layer of endothelial cells and the subendothelial space; (2) the tunica media, which may be more or less prominent depending on its function, composed of smooth muscle fibers; and (3) tunica adventitia, formed by fibrous and connective tissue cells that externally cover the vessel (Bechara and Szabó 2006) as depicted in Fig. 2.1a.

Due to its location at the interface between the bloodstream and the surrounding tissue, the vascular endothelium forms a barrier that regulates the transit of what needs to pass between these two compartments (e.g., oxygen, nutrients, proteins,

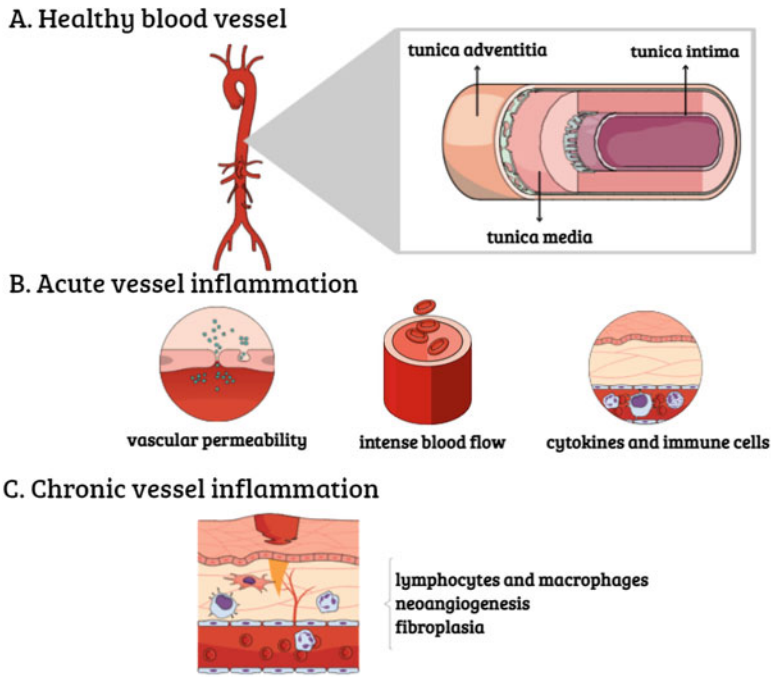

Fig. 2.1 Blood vessel structure and vascular inflammation. Panel (**a**) exhibits a healthy vascular wall consisting of the tunica intima, the tunica media, and the tunica adventitia. Panel (**b**) depicts the acute phase of vascular inflammation that is mainly characterized by increased vascular permeability, intense blood flow, and the accumulation of cytokines and immune cells. In (**c**), the chronic phase of vascular inflammation highlights the action of lymphocytes and macrophages, neoangiogenesis, and fibroplasia

molecules of different sizes, and immune cells). Among other functions, the endothelium stands out for its ability to alter its phenotype to control the inflammatory response, the anti or procoagulant function, and the vascular tone according to body needs (Geiger 2019).

Vascular smooth muscle cells determine the structure of blood vessels and their main function lies in the control of vascular tone and resistance and, consequently, in the modulation of blood pressure, through the mechanisms of vasodilation and vasoconstriction. The influx and removal of calcium from the cytosol of vascular smooth muscle cells are finely controlled by a range of biomolecules and intracellular pathways and damage to these signaling pathways can lead to vascular tone dysfunction with the consequent appearance of diseases such as hypertension and atherosclerosis (Geiger 2019).

The outermost layer of the vascular wall is formed by the tunica adventitia, which is composed of a rich-collagen layer that connects the layers of the vascular wall with the tissues. In addition to components of the extracellular matrix, adventitia also

contains fibroblasts that produce collagen in cases of injury or during healing processes (Geiger 2019).

Malfunctioning of blood vessels leads to the emergence of different pathologies, including CVDs. Some risk factors are characteristic of these diseases, such as endothelial dysfunction, inflammation and vascular remodeling, atherosclerosis, dyslipidemia, and even obesity (Petrie et al. 2018). In particular, vascular inflammation is one of the aggravating factors of these conditions and is characterized by a significant change in vascular dynamics, in addition to intensification in the process of chemotaxis and recruitment of cells from the immune system to the inflammatory site (Goyal et al. 2019).

In consensus, the researchers divide the inflammatory process into two main stages: (1) the acute phase and (2) the chronic phase. Acute phase is mainly characterized by increased vascular permeability, intensifying blood flow, and the accumulation of a variety of cytokines and immune cells at the site (Goyal et al. 2019) (Fig. 2.1b).

If the inflammation persists, it progresses to the chronic phase, which has been identified as the main cause of atherosclerosis in patients with CVDs (Goyal et al. 2019). This phase is more complex, of longer duration, and relies on the action of lymphocytes and macrophages, involving the stages of neoangiogenesis—the proliferation of new blood vessels—and fibroplasia—the proliferation of fibrous tissue (Bechara and Szabó 2006; Kreuger and Phillipson 2016) (Fig. 2.1c).

During the inflammatory process, different pathways are activated, resulting in the release of a variety of chemical and molecular mediators and cell activation (Kvietys and Granger 2012). Understanding the markers of the inflammatory process is essential in the search for new targets, both for the diagnosis and for the development of therapies for CVDs.

2.3 Cellular Markers of Vascular Inflammation

Vascular inflammation involves the activation and recruitment of *immune system cells*. Clinical studies have shown that patients affected by CVDs exhibit high counts of lymphocytes and neutrophils which are correlated with their high sensitivity to insulin that is released through inflammatory changes in adipose tissue (Moriya 2019). Leukocyte count is an easily determined marker in the blood, but the close relationship with cardiovascular risk factors and the non-specificity limits its use (Goyal et al. 2019).

In addition, it is widely accepted that the responses triggered by the innate and adaptive immune system are relevant to both the onset and progress of CVDs. In this process, besides lymphocytes and neutrophils, monocytes are also activated (Petrie et al. 2018). Neutrophils are the first cells of the immune system to migrate to the inflammatory site and promote subsequent events of inflammation through the recruitment of monocytes and the release of granules, constituting an important trap for pathogens and tissue debris. In turn, monocytes are activated and become

macrophages at the site of inflammation, especially in patients with atherosclerosis (Goyal et al. 2019).

Recent studies indicate that nonclassical monocytes act as prominent vascular rulers and are elevated in pathological states, such as chronic kidney disease, myocardial infarction, atherosclerosis, and vasculitis—a term that designates a set of rare diseases that lead to both inflammation of arteries and veins (Buscher et al. 2017). Furthermore, macrophages perform the elimination of apoptotic cells, a phenomenon called efferocytosis. In general, macrophages have regulated efferocytosis at the beginning of the inflammation, but with its intensification and other signaling pathways, they undergo cellular reprogramming, which results in unregulated action, causing post-apoptotic necrosis and chronic inflammation (Yurdagul Jr. et al. 2017).

The *erythrocyte sedimentation* is another marker of vascular inflammation, known for a long time and commonly used to verify this condition. The erythrocyte sedimentation rate (ESR) is an indication that erythrocyte aggregation occurred with the influence of blood proteins, such as fibrinogen and immunoglobulins (Bechara and Szabó 2006). This event occurs in inflammatory states and is an indicator of vascular inflammation due to CVDs (Kiyani et al. 2019). Methods for measuring ESR are fast, inexpensive, and easy to assess the inflammatory response and can contribute to determining the diagnosis and monitoring patient's condition (Tishkowski and Gupta 2020).

As previously mentioned, *endothelial cells* play an important role in vasculature. In addition to being a physical barrier that prevents the passage of pathogens from the blood to the tissues, they also produce biomolecules that modulate vascular tone, platelet aggregation, adhesion and leukocyte transmigration, and proliferation of vascular cells (Machado-Pereira et al. 2017). Therefore, changes in these cells can cause great damage and trigger vascular inflammation in a condition called endothelial dysfunction (Kvietys and Granger 2012).

Endothelial dysfunction is mainly characterized by the failure of mechanisms of endothelial repair (Yang et al. 2016) and by a reduction in nitric oxide (NO) bioavailability (Incalza et al. 2018). Consequently, there is an increase in the production of reactive oxygen species (ROS) and the onset of oxidative stress with a subsequent inflammatory process (Incalza et al. 2018).

Endothelial dysfunction is one of the causes of the main events that appear in CVDs: increased vasoconstriction, oxidative stress, alteration in the permeability of the plasma membrane, accumulation of immune system cells (Konukoglu and Uzun 2016), increased platelet aggregation, and proliferation of vascular smooth muscle cells (Yuyun et al. 2018). Thus, endothelial dysfunction can be monitored and used as a target for treatment approaches (Daiber et al. 2017).

Another important marker of vascular inflammation is the identification of many *endothelial cells in senescence*. This process is related to the development of heart failure and the progression of atherosclerotic plaques. Also, the senescence of endothelial cells is a factor inducing systemic glucose intolerance. However, since the aging process of these cells is extremely complex, there is still no known way to interfere with it (Katsuumi et al. 2018). Besides, cellular senescence concomitant

with dysregulation of innate immunity intensifies prolonged and persistent inflammation, even if the stimulus that caused the inflammation is removed or treated (Sanada et al. 2018). Cell senescence modifies the structural and functional properties of the vasculature (Maloberti et al. 2019), intensifying the inflammatory context.

In addition to playing a role in hemostasis, *platelets* are considered important agents of inflammation. For example, platelet activation leads to activation of the coagulation cascade via the intrinsic pathway, which causes thrombus formation and healing. Recent research indicates that platelets have receptors for complement system proteins and are closely related to inflammation (Mezger et al. 2019).

The increase in the volume of *perivascular adipose tissue* (PVAT) is also a marker of vascular inflammation. Due to this increase, PVAT becomes dysfunctional and starts to exhibit an inflammatory phenotype. PVAT thus produces pro-inflammatory cytokines, increases the production of oxidizing molecules, and decreases vasorelaxant and vasoprotective factors derived from adipocyte production. Together, these factors trigger subsequent inflammation processes (Nosalski and Guzik 2017).

2.4 Chemical Markers of Vascular Inflammation

Vasoactive amines (e.g., histamine and serotonin) play a role in the vascular inflammation process and are related to the acute stage of inflammation, increasing vascular permeability. These chemical markers are commonly stored in cytoplasmic granules of mast cells, basophils, and platelets and released by degranulation (Bechara and Szabó 2006). Vascular permeabilizing agents such as histamine and serotonin are involved in the angiogenesis process. Micromolar concentrations of these vasoactive amines can induce the proliferation of endothelial cells, migration, and formation of new blood vessels through the activation of TR3/Nur77 receptors (Qin et al. 2013).

Cytokines are molecules closely involved in vascular inflammation, both circulating and effector produced at the inflammation site. The central cytokines acting on the vasculature are TNF-α, interferon-γ, IL-1β, and IL-12. These cytokines contribute to vascular inflammation by influencing insulin sensitivity in peripheral tissues and modifying the release rate of this hormone (Petrie et al. 2018).

The IL-6/Th17/IL-17 activation pathway leads mainly to systemic inflammation related to cardiovascular diseases, and the IL-12/Th1/IFN-γ activation pathway is involved with inflammation of the vascular wall. This evidence is relevant to the development of new therapies (Keser et al. 2018).

Studies indicate the relevance of IL-1β in inflammation of the vasculature, making it a target for anti-inflammatory therapies. This interleukin is produced mainly by injured vascular cells and leukocytes (Libby 2017). Thus, the development of compounds such as the anti-inflammatory *Canakinumab*, a monoclonal antibody that neutralizes the action of IL-1β, is relevant because they have the

potential to significantly reduce the recurrent cardiovascular events of inflammation (Ridker et al. 2012).

C-reactive protein (CRP) is one of the most cited and researched chemical markers in the context of vascular inflammation. CRP is found mainly as a pentamer in circulation or insoluble monomers in tissues, performing different functions (Badimon et al. 2018). CRP participates in the innate humoral immune response contributing to the progression of CVDs by recognizing and binding multiple intrinsic ligands. This protein is considered a reagent in the acute phase of inflammation and is released by the liver into circulation. Some extrahepatic tissues (e.g., atherosclerotic plaques and vascular smooth muscle cells) can also synthesize CRP (Goyal et al. 2019). CRP inhibits nitric oxide production, increases the expression of cell adhesion molecules, and causes the recruitment of monocytes when binding to endothelial cells. Besides, it acts by modulating the innate immune response, activating the complement system, platelet aggregation, the coagulation cascade, tissue repair, and angiogenesis. Thus, CRP is involved in vascular inflammation through endothelial dysfunction, leukocyte recruitment, and thrombus formation (Badimon et al. 2018). Despite the recognized relevance of PCR for the diagnosis and prognosis of cardiovascular diseases, therapeutic options that target this protein are still little explored.

Another striking feature of vascular inflammation is oxidative stress that occurs due to the excessive production of *reactive oxygen* (*ROS*) and *nitrogen* (*RNS*) *species* and the reduction in the production of antioxidant molecules. Oxidative stress contributes to the activation of the five microvascular responses characteristic of inflammation: vasomotor dysfunction, recruitment of leukocytes to the site of inflammation, enhancement of vascular permeability, angiogenesis, and thrombosis (Kvietys and Granger 2012).

Both endothelial and immune cells like monocytes and macrophages can produce ROS. Particularly, the production of superoxide by NADPH oxidase 1 (NOX1) is central in the initial stages of many CVDs. Patients presenting a disease associated with the vasculature have elevated NOX1 expression compared to control patients (Gray et al. 2016). NADPH oxidase 4 (NOX4) is the most abundant oxidase, and patients with some vascular disease present a significant reduction in this enzyme. NOX4 is a generator of hydrogen peroxide (H_2O_2), which has a surprising protective effect, especially on atherosclerosis, since the deletion of the NOX4 gene in mice reduced the anti-inflammatory response and intensified the accumulation of vascular macrophages (Gray et al. 2016). NO is considered a vasoprotective biomolecule. However, when excessively generated by the activation of inducible nitric oxide synthase (iNOS) causes stress that can trigger endothelial dysfunction. This chemical molecule is one of the main RNS but the damage it can cause in the vasculature is still little known (Gliozzi et al. 2019).

Oxidized LDL (*oxLDL*) is also an important marker of inflammation in blood vessels that may also cause endothelial dysfunction. The mechanism by which oxLDL causes endothelial dysfunction is still poorly understood, but Gliozzi et al. (2019) suggested that oxLDLs negatively regulate nitric oxide endothelial synthase (eNOS) through the HMGB1-TLR4-Caveolin-1 pathway and also leads to the

activation of iNOS, causing oxidative stress in the endothelial cells (Gliozzi et al. 2019).

2.5 Molecular Markers of Vascular Inflammation

The *complement system* (*SC*) is a part of the immune system that "complements" the action of antibodies and phagocytic cells in organism defense. The *proteins and anaphylatoxins of the SC* also participate in the inflammatory process causing endothelial injury and the release of endothelial microvesicles. Anaphylatoxins C3a and C5a act by increasing vascular permeability via activation of histamine release (Fagerström et al. 2019). Anaphylatoxin C5a also acts by activating neutrophils and macrophages, causing the release of other chemical mediators (Bechara and Szabó 2006). Recent studies also point out that C3 proteins play functions in the intracellular and extracellular environments. Thus, the central roles of C3 are opsonization, the formation of the membrane attack complex, inflammation, and metabolic reprogramming (Elvington et al. 2016).

Proteins involved in the coagulation cascade contribute to the maintenance of hemostasis through the formation of clots, prevention of excessive blood loss, and initiation of the tissue repair process. The *proteins in the coagulation cascade* are involved in vascular inflammation. After cloning and knowing the coagulation factors (tissue factor, factors X, IX, V, XII, VII, VIII, and XI), it became evident that these proteins are involved both in thrombotic processes, in atherosclerotic processes, and in the response to ischemia–reperfusion injury. In these cases, as for the formation of atherosclerotic plaque, the activation of the coagulation cascade and the production of thrombin are initial events, since the coagulation factors can be produced by vascular smooth muscle cells and by cells of the immune system or recruited to the site of inflammation. Activated coagulation factors, acting as proteases, are related to a poor prognosis in patients with ischemia/reperfusion, so much so that anticoagulant drugs are used to improve patient survival. Other chemical mediators of the coagulation cascade are also involved in triggering and progressing vascular inflammation, like metabolites of arachidonic acid, lysosome granular compounds, and platelet-activating factors (Bechara and Szabó 2006).

A relevant role played by *hormones* is pointed out during the activation and resolution of inflammation at the systemic level. Thus, insulin is identified as a pro-inflammatory agent, while cortisol and glucagon have the opposite effect acting as anti-inflammatory agents (Bechara and Szabó 2006).

Fibrinogen is a protein involved in blood coagulation, being a determinant for platelet aggregation. In particular, it is worth highlighting the pro-inflammatory role of fibrinogen that has been reported in different types of inflammation, infections, cancers, and diseases that affect the cardiovascular system. According to Yakovlev and Medved (2018), products of fibrin and fibrinogen degradation present in the circulation or on the surface of endothelial cells promote leukocyte transmigration to the inflammation site, showing the signaling and chemotactic capacity of this

molecule (Yakovlev and Medved 2018). Deposits of fibrinogen are an almost universal characteristic of tissue injuries, making this molecule able to be used in early diagnosis methods and therapies (Luyendyk et al. 2019). Thus, circulating fibrinogen levels are a marker of vascular disease and there is a parallel effect of cytokines involved in the activation or inhibition of fibrinogen biosynthesis and vascular injury (Vasse et al. 1996).

The mechanism of action of the *renin–angiotensin–aldosterone system* in vascular inflammation is not yet fully understood. The type 1 (AT1R) receptor of angiotensin II (ANG II) is believed to perform most of the functions. Thus, AT1R triggers the activation of several signal transduction cascades capable of causing hypertension, vasculature remodeling, and significant damage to target organs. Among the activated signaling pathways, it is noteworthy that AT1R activation causes the regulation of vascular tone by stimulating vasoconstriction. This activation includes the release of ROS and other vasoconstrictor biomolecules and is a central event in CVDs (Forrester et al. 2018).

The *hyaluronan matrix* is altered during inflammation. Under homeostatic conditions, the vast majority of cells belonging to the immune system have a low affinity for this matrix. However, in inflamed tissue, this affinity increases significantly. During the inflammatory process, both the synthesis and the catabolism of the hyaluronan matrix are intensified and the degradation of the hyaluronan matrix generates fragments that act in chemotaxis and the spread of inflammation, recruiting mainly macrophages and dendritic cells (Grandoch et al. 2018).

Angiogenesis is the development of new blood vessels in response to hypoxia and/or ischemia, but it also contributes to the progression of CVDs and other inflammatory processes. The inflammatory environment increases the production of *pro-angiogenic factors* (bFGF, VEGF, PDGF, and TGF-β), which lead to the proliferation of endothelial cells, remodeling of the matrix, the release of growth factors, and budding of new vessels (Whiteford et al. 2016).

Non-coding RNAs, especially the long non-coding RNAs (*lncRNAs*), are emerging regulators of a variety of biological and pathophysiological processes, including CVDs. Several non-coding RNAs, for example, the CoroMarker lncRNAs (AC100865.1), MALAT1, lincRNA-Cox2, THRIL, and lincRNA-p21 present patterns of expression and involvement in regulatory pathways of inflammation and should be studied as possible targets (Haemmig et al. 2018).

Micro RNAs (*miRNAs*) are also involved in several pathological processes, including vascular complications that can be associated with other pathologies. The change in the expression of some miRNAs in patients who have diabetic cardiovascular complications is an example: miR-223, miR-320, miR-501, miR504, and miR1 have their expression increased while miR-16, miR-133, miR-492, and miR-373 have their expression reduced in these conditions, showing a relationship with vascular inflammation (Petrie et al. 2018).

Endothelial adenosine kinase (*ADK*) activity regulates intracellular endothelial adenosine levels. In the inflammatory process, ADK activity is increased, reducing adenosine levels and intensifying inflammation through signal replication in the intracellular medium, via the association of ADK with *S*-adenosylhomocysteine

(SAH) hydrolase (SAHH). Genetic knockdown of the ADK gene and the administration of exogenous adenosine attenuated the vascular inflammatory response (Xu et al. 2017).

The enzyme *α1AMPK* is also involved in vascular inflammation. α1AMPK-deleted mice have endothelial dysfunction caused by oxidative stress. Kröller-Schön et al. (2019) demonstrated that α1AMPK is responsible for reducing inflammation by limiting the recruitment of inflammatory cells and maintaining the antioxidant action of heme oxygenase 1 (Kröller-Schön et al. 2019).

Protein catabolism pathways, such as the ubiquitin-proteasome system, autophagy, and calpain, are altered during inflammation. The accumulation of certain defective proteins in blood vessel walls, which possibly triggers endothelial dysfunction, contributes to the pathogenesis of CVDs. Besides, the imbalance in protein catabolism leads to the release of pro-inflammatory and pro-angiogenic agents produced by dysfunctional endothelial cells (ROS and RNS) and the recruitment of phagocytic cells to the site, causing the progression of vascular inflammation (Miyazaki and Miyazaki 2017).

Table 2.1 Summarizes the major cellular, chemical, and molecular markers in vascular inflammation and their main features.

2.6 Biotechnology Advances in Diagnosis and Therapies for Vascular Inflammation

As seen in this chapter, the processes that trigger vascular inflammation and its involvement with CVDs are quite relevant and can be applied in the diagnosis and therapy of these diseases (Pechlivani and Ajjan 2018). Early diagnosis is a determinant for a better prognosis for patients with CVDs and consider that these new biomarkers of vascular inflammation can contribute to such progress. An example of this is the reduction of the expression of mitochondrial deacetylase Sirt3 as a marker of endothelial dysfunction since such enzyme is closely linked to the proper functioning of mitochondria (Dikalova et al. 2020).

Controlling inflammatory factors can represent a form of therapy and also of prevention of CVDs. Antioxidant therapies, for example, are used to reduce oxidative stress and inflammation. Some drugs with indirect antioxidant effects can be used for this purpose, such as angiotensin-converting enzyme (ACE) inhibitors, AT1R antagonists, and statins (Daiber et al. 2017).

Moreover, new biotechnological research and development expand the options for diagnosis and therapies (Raman et al. 2013). Monoclonal antibody therapies and gene regulation have been highlighted in the context of vascular inflammation (Guzik and Touyz 2017). For example, the neutralizing antibody to interleukin-1β, which reduces vascular inflammation and the chance of cardiovascular events (Aday and Ridker 2018). However, trials with this antibody have shown that it can cause an increase in fatal infections (Bäck et al. 2019).

Table 2.1 Cellular, chemical, and molecular markers involved in blood vessel inflammation

Markers	Characteristics/ Mechanisms
1. Cellular markers	
immune cells	high counts of lymphocytes and neutrophils that are correlated with their high sensitivity to insulin
sedimented erythrocytes	erythrocytes sedimentation rate (ESR) is an indication that erythrocyte aggregation occurred with the influence of fibrinogen and immunoglobulins
endothelial dysfunction	failure of mechanisms of endothelial repair, reduction in nitric oxide (NO) bioavailability, and increase in the production of reactive oxygen species (ROS)
vascular senescence	modification of the structural and functional properties of the vasculature, development of heart failure and the progression of atherosclerotic plaques, inductor of systemic glucose intolerance
platelets	activation of the coagulation cascade, which causes thrombus formation and healing
perivascular adipose tissue (PVAT)	increased volume of PVAT produces pro-inflammatory cytokines, increases the production of oxidizing molecules, and decreases vasorelaxant and vasoprotective factors derived from adipocytes
2. Chemical markers	
vasoactive amines (e.g., histamine, serotonin)	increase vascular permeability and are involved in angiogenesis
cytokines (TNF-α, interferon-γ, IL-1β, and IL-12)	influence insulin sensitivity in peripheral tissues
C-reactive protein (CRP)	endothelial dysfunction, leukocyte recruitment, and thrombus formation
reactive oxygen (ROS) and nitrogen (RNS) species	reduction in the production of antioxidant molecules
oxidized LDL	negatively regulates eNOS through the HMGB1-TLR4-Caveolin-1 pathway and also leads to the activation of iNOS
3. Molecular markers	
complement system proteins	increase vascular permeability, activate neutrophils and macrophages, opsonization, formation of the membrane attack complex, inflammation, and metabolic reprogramming
coagulation cascade proteins (plasma kinins)	act as proteases and are related to a poor prognosis in patients with ischemia/reperfusion
hormones	insulin is identified as a pro-inflammatory agent, while cortisol and glucagon act as anti-inflammatory agents
fibrinogen	promote leukocyte transmigration to the inflammation site
renin-angiotensin-aldosterone system	AT1R activation stimulates vasoconstriction, the release of ROS and other vasoconstrictor biomolecules
hyaluronan matrix	hyaluronan matrix fragments act in chemotaxis, recruiting mainly macrophages and dendritic cells
pro-angiogenic agents (bFGF, VEGF, PDGF and TGF-β)	proliferation of endothelial cells, remodeling of the matrix, the release of growth factors, and budding of new vessels
lncRNAs/ miRNAs	present patterns of expression and involvement in regulatory pathways of inflammation
endothelial adenosine kinase (ADK)	increased ADK activivy reduces adenosine levels and intensifies inflammation
endothelial α1AMPK	limits the recruitment of inflammatory cells and maintains the antioxidant action of heme oxygenase 1
defective protein catabolism	triggers endothelial dysfunction and recruits phagocytics cells

In addition, an anti-IL-6 receptor monoclonal antibody (MR16–1) has a protective effect against atherosclerotic lesions induced by dyslipidemia and/or inflammation (Akita et al. 2017). Other studies indicate that statins reduce the levels of CRP as well as the rates of occurrence of cardiovascular events (Aday and Ridker 2018). Similarly, studies point to a great of therapies to inhibit the action of type I interferons (IFNs), which are increased in CVDs (Chen et al. 2020).

Nanotechnology is an area of great prominence in biotechnology, making it possible to investigate the exclusive properties of nanomaterials. In this sense, there is a great potential for using nanomaterials to reduce the residual effect of certain drugs (Tu et al. 2015). For example, statins, antithrombotic, and thrombolytic agents are used for the treatment of cardiovascular diseases (Aday and Ridker 2018). In such a way, nanomaterial drug-delivery systems can be used for the treatment of vascular inflammatory diseases since vascular cells affected by inflammation have a greater tendency to incorporate nanometric materials.

The inhibition of the Toll-like receptor 9 (TLR9) is another therapeutic target for vascular inflammation, as it is known that the TLR9 activation impairs the recovery of blood flow in situations of ischemia (Nishimoto et al. 2018). Other molecular markers of vascular inflammation can be used as targets for the treatment of CVDs, as is the case for the proprotein convertase subtilisin/kexin 9 (PCSK9). Suppression of PCSK9 expression or its inhibition may be an effective way to decrease vascular inflammation in atherosclerosis (Tang et al. 2017).

Finally, current studies point to a greater need to invest in therapies aiming at the administration or activation of specialized pro-resolution mediators (SPMs), which include lipoxins, resolvins, protectins, and maresins. The administration of SPMs can take place via molecules specialized in the delivery of nanomaterials, causing a reduction in vascular inflammation, without, however, affecting the beneficial immune response (Bäck et al. 2019). Figure 2.2 illustrates the recent biotechnological advances in therapies for vascular inflammation.

2.7 Conclusion and Prospects

Cardiovascular diseases (CVDs) represent the largest cause of death worldwide. Inflammation of blood vessels is directly involved in the appearance and worsening of these pathologies. In this sense, all efforts are valid to recognize new diagnostic and therapeutic targets and curb the morbidity and mortality associated with CVDs.

The acute inflammatory process is established with increased vascular permeability, increased blood flow, and the accumulation of cytokines and immune system cells at the site of inflammation. If persistent, the inflammation reaches a chronic stage in which the action of lymphocytes and macrophages is observed, involving the formation of new blood vessels and fibroplasia. As mentioned, the identification of markers of vascular inflammation, both acute and chronic, is important in the search for new diagnostic and therapeutic targets. Thus, recent research has been

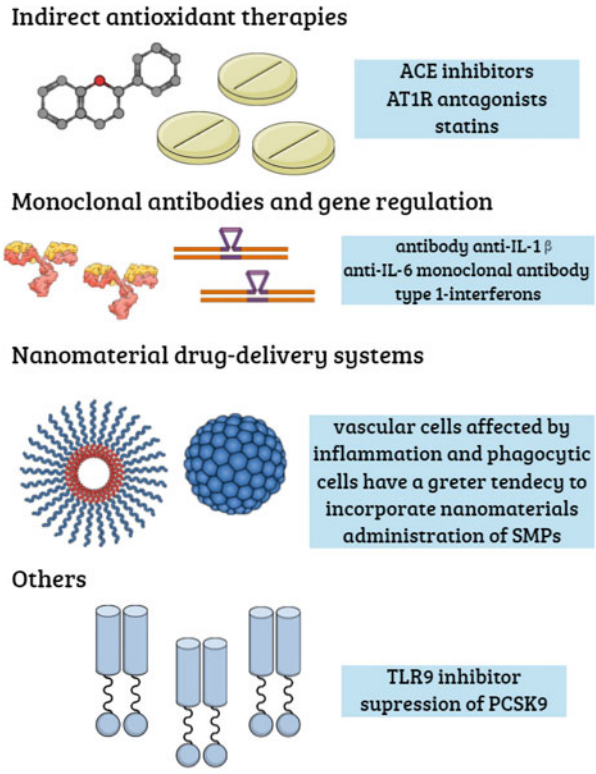

Fig. 2.2 Biotechnology advances in therapies for vascular inflammation. Indirect antioxidant therapies, antibody and gene regulation, nanomaterial drug-delivery systems, and other mechanisms (e.g., suppression or inhibition of specific enzymes and/or receptors) are effective to control the extent of blood vessels inflammation, helping to control the establishment and progression of CVDs

reporting (1) molecular; (2) cellular; and (3) chemical markers involved in the different phases of vascular inflammation.

Finally, biotechnology's contribution to the diagnosis of vascular inflammation and in the reduction of pathologies related to blood vessels is growing. Thus, therapies involving monoclonal antibodies and nanomaterial drug-delivery systems have gained prominence in this field and leveraged potentially useful targets for the clinical management of vasculature pathologies and CVDs.

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