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Review

Epigenetic Mechanisms in Vascular Inflammation: Modulation of Endothelial Adhesion Molecules and Endothelium-Leukocyte Adhesion

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Abstract

The endothelium, an essential component of the vascular system, plays a critical role in the inflammatory response. Under pro-inflammatory stimuli, endothelial cells undergo activation and dysfunction, leading to the release of inflammatory mediators and up-regulation of cell adhesion molecules. These changes facilitate the adhesion, rolling, and transmigration of leukocytes into the subendothelial space. Emerging evidence suggests that epigenetic mechanisms, including nucleic acid methylation, post-translational histone modifications, and non-coding RNA, contribute significantly to the regulation of vascular inflammation and expression of cell adhesion molecules. Understanding the epigenetic molecular signatures that govern these processes may provide new insights into the development of therapeutic strategies to combat vascular inflammation and associated diseases. This review aims to summarize the current knowledge on the epigenetic mechanisms involved in modulating the intricate processes underlying vascular inflammation, with a specific focus on the expression of endothelial adhesion molecules and endothelium-leukocyte adhesion.

Keywords: cell adhesion molecules; VCAM-1; ICAM-1; E-selectin; NF-κB; lncRNAs; miRNAs; DNA methylation; RNA methylation; histone modifications

1. Introduction

The controlled inflammatory response is a useful process, carefully regulated by a complex molecular cascade, which leads to the removal of harmful stimuli and the recovery of normal physiology. The magnitude of the inflammatory response is critical because failure to regulate acute pro-inflammatory stimulation leads to chronic inflammation, autoimmunity and excessive tissue damage [1,2]. Chronic inflammation progresses slowly, lasts longer, and can cause many diseases associated with chronic and persistent vascular inflammation, characterized by an increase in adhesion of circulating leukocytes to endothelial cells of the vascular wall and their subsequent transmigration [3]. These phenomena are largely controlled by the expression of adhesion molecules which in turn are regulated by different transcriptional and post-transcriptional mechanisms [4]. Recent evidence suggests that epigenetic changes, defined as heritable changes in gene expression that are independent of changes in DNA sequence, may be involved in chronic inflammation [4].

To preliminarily explore the role of epigenetics in the context of vascular inflammation, we conducted a literature analysis using the Clarivate Web of Science Core Collection database. We queried the database with the following terms: "epigenetics", "inflammation", and "adhesion molecules". The search yielded 39 papers, which were analyzed using the bibliometric mapping tool VOSviewer (VOSviewer version 1.6.19, Leiden University, South Holland, Netherlands) [5]. Bioinformatic analysis of the medical subject headings (MeSH) associated with the retrieved papers resulted in a total of 442 items (Fig. 1). Among these, 19 keywords met the threshold level of occurrence (minimum number of occurrences of a keyword = 3).

The keywords with greatest total link strength were selected and highlighted as bubbles (Fig. 1). There are three clusters identified with three different colours: Cluster 1, red-coloured (7 items: atherosclerosis, cardiovascular-diseases, DNA methylation, gene expression, inflammation, NF-κB, nitric-oxide synthase); Cluster 2, green-coloured (6 items: adhesion, adhesion molecules, cancer, epigenetics, expression, receptor); and Cluster 3, blue-coloured (6 items: activation, cells, inhibition, mechanisms, transcription, transcriptional regulation).

The aim of this review is to present a comprehensive and current overview of the primary types of epigenetic alterations that contribute to a dysregulated inflammatory response, with a specific focus on the expression of endothelial adhesion molecules.

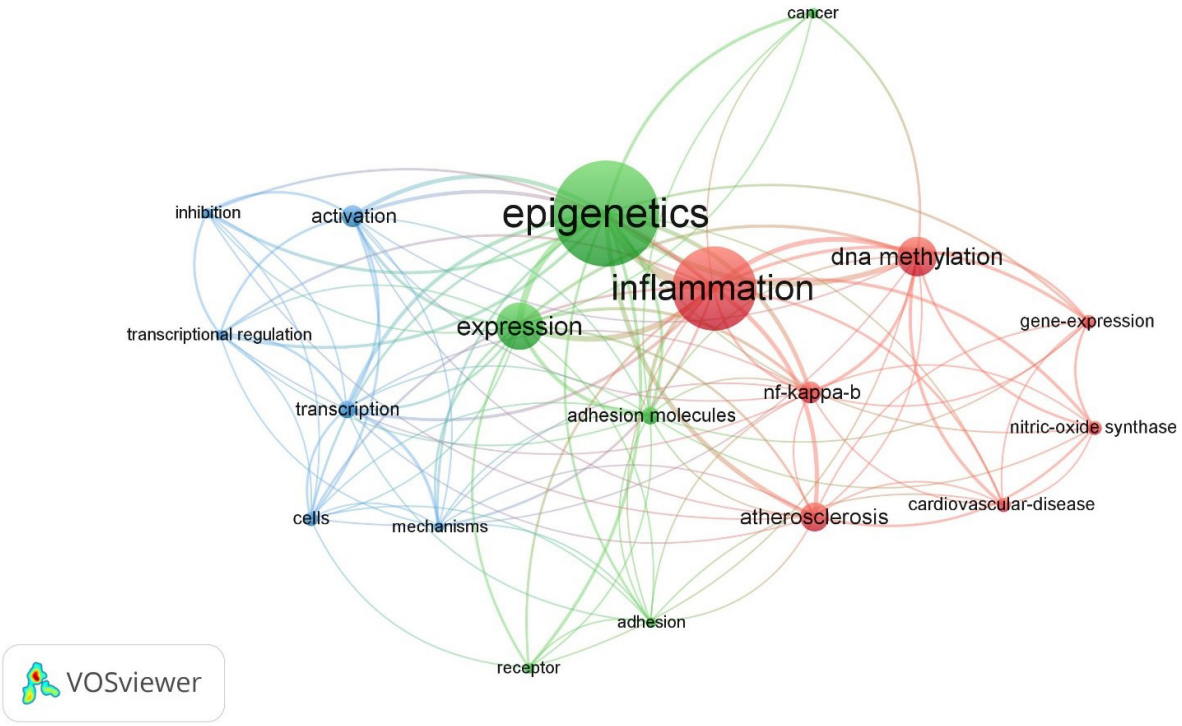

Fig. 1. The map displays the medical subject heading (MeSH) keywords selected from articles published on and retrieved from the Web of Science using the search terms "epigenetics", "inflammation", and "adhesion molecules" (all fields), resulting in 442 items. Applying a threshold of 3 keywords, 19 items met the criteria. The size of the bubbles indicates the frequency of word occurrence, while the colour of the bubbles represents their cluster affiliation. Bubbles that are closer together indicate a higher frequency of co-occurrence between the two words. The analysis was performed using the bibliometric mapping tool VOSviewer.

2. Vascular Inflammation: Role of Endothelial Adhesion Molecules

In the last few years, an increasing amount of research has recognized an active and crucial role played by the vascular wall in the inflammatory response. An essential property of the vessel wall is the ability of the inner endothelial lining to be activated in order to react to noxious stimuli or inflammatory mediators [6]. In response to proinflammatory triggers, including chemokines, cytokines, and oxidized low-density lipoproteins (ox-LDL), the endothelium is activated, and acquires new functional properties, becoming adhesive to leukocytes, due to the expression on its surface of cell adhesion molecules (CAMs) that recognize counter-receptors present on different subsets of leukocytes [4,6]. The CAM proteins which mediate endothelium-leukocyte interactions belong to four major families: selectins, selectin ligands, integrins, and members of the immunoglobulin (IgG) superfamily [7].

2.1 Selectins and Selectin Ligands

The selectin family of CAMs consists of three members (E-, P- and L-selectin), all of which mediate rolling of leukocytes along the endothelium [8]. P-selectin is stored in granules in endothelial cells and platelets and rapidly translocates to the cell surface in response to several inflammatory stimuli. E-selectin is exclusively present in endothelial cells and its expression is regulated by increased transcription after stimulation by inflammatory cytokines such as tumour necrosis factor (TNF)-α and interleukin (IL)-1β [8]. L-selectin is expressed on many subclasses of leukocytes and is rapidly shed from the surface of the leukocyte after activation [8]. The adhesive function of all selectins requires specialised counter-receptors. These ligands consist of carbohydrate moieties such as the tetrasaccharide sialyl Lewis X (sLeX), whose interaction with selectin family members is responsible for a major part of leukocyte rolling in inflammation.

2.2 Integrins and the IgG Superfamily of CAMs

Integrins are constitutively expressed on leukocytes and many other cell types. They are configured as dimers that contain one α- and one β-subunit. Integrins are rapidly activated from a low-affinity to a high-affinity state following cell activation and ligand binding [9]. They mediate adhesion of cells to matrix proteins, cellular counter-receptors and many other substrates. The interaction between integrins and IgG superfamily members is particularly important in inflammation [8]. The IgG superfamily members are large type I transmembrane proteins characterized by a series of repeating extracellular IgG-like do-

mains, a transmembrane region and a short cytoplasmic tail. They include intercellular adhesion molecules-1, 2, and 3 (ICAM-1, 2, and 3), platelet endothelial cell adhesion molecule-1 (PECAM-1), and vascular cell adhesion molecule-1 (VCAM-1). The expression of VCAM-1 and ICAM-1 increases after stimulation of the endothelium by inflammatory cytokines, while PECAM-1 is constitutively expressed on resting endothelial cells.

The main function of CAMs is to facilitate the process of leukocyte infiltration from the bloodstream into inflamed tissue, by forming bonds with ligands on circulating leukocytes, that allows for firm adhesion to the endothelium and transendothelial migration [7]. This role makes CAMs crucial in acute response to tissue damage and acute inflammation, but in chronic inflammation excessive or prolonged infiltration of leukocytes can lead to further damage.

3. Endothelial Activation and Chronic Inflammation

The main functions of CAMs become apparent during "endothelial activation", a process characterized by significant functional changes in the vascular endothelium induced by inflammatory mediators and vascular risk factors [10]. Resident immune cells, such as tissue-resident macrophages, act as "first responders" by releasing inflammatory cytokines and chemokines which activate endothelial cells and recruit leukocytes [10]. In non-inflammatory conditions, the endothelium does not support the adhesion of leukocytes. However, after activation, endothelial cells begin to express CAMs. In response to mediators like histamine, pre-synthesized CAMs (e.g., P-selectin) are rapidly transported to the cell surface within minutes. Other mediators, such as cytokines (TNF-α, IL-1β), induce a more gradual activation of endothelial cells, including gene expression and protein synthesis of various CAMs over a span of hours. These CAMs include E-selectin (within 5 hours) and ICAM-1 and VCAM-1 (within 12 hours). Furthermore, leukocytes themselves become activated and alter the expression patterns of CAMs on their surface, such as the integrins $\alpha4\beta1$ (also known as very late antigen-4 or VLA-4) and lymphocyte function-associated antigen-1 (LFA-1), which makes them more adhesive to the vascular endothelium. These changes collectively promote a multistep process of trans-endothelial migration of leukocytes. In a clear sequence of events, leukocytes initially form transient bonds with selectins on the surface of endothelial cells, which causes them to slow down and begin rolling. Conformational changes in integrins expressed on leukocytes then induce the formation of high-affinity bonds by binding to other CAMs, such as VCAM-1 and ICAM-1. In the presence of inflammatory stimuli, the activated endothelium increases the expression of endothelium-leukocyte adhesion molecules such as VCAM-1 and ICAM-1. The interaction of the IgG proteins ICAM-1 and VCAM-1 with their respective integrin counter-receptors on leukocytes allows for firm adhesion of leukocytes to the endothelium and subsequent transmigration into the sub-endothelium. After the triggering factor for inflammation is removed, the inflammatory process is typically resolved. However, this crucial step may be absent or altered in several chronic immune-mediated inflammatory diseases where CAMs play a critical role. The excessive leukocyte recruitment by CAMs can exacerbate the inflammatory process and, in many cases, worsen tissue injury [1].

Extensive studies have confirmed the implications of CAMs in (patho)physiological events in chronic inflammation on various levels [11]. Patients with several chronic diseases, including inflammatory bowel disease, hypertension, diabetes, and hyperlipidaemia, among others, have been found to have elevated plasma levels of soluble E-selectin [12]. Additionally, soluble VCAM-1 levels have been observed to be elevated in the plasma of breast cancer patients [13]. The evidence suggests that elevated levels of E-selectin and ICAM-1 can serve as molecular markers for atherosclerosis and the development of clinical coronary heart disease [14]. Lastly, it is worth noting that drugs with anti-inflammatory effects, particularly those targeting the vasculature, can reduce the levels of CAMs and inhibit leukocyte adhesion [15]. Similarly, certain natural products or nutraceuticals have demonstrated the ability to reduce the expression of CAMs on activated endothelial cells [16–20].

4. Nuclear Factor-κB and Regulation of Vascular Inflammation

The vascular endothelium functions as an important integrator and transducer in response to multiple humoral and mechanical stimuli, including the inflammatory response. As a primary inflammatory signaling factor, the transcription factor nuclear factor-κB (NF-κB) is known to significantly participate in the regulation of vascular inflammation and immune function. NF-κB is composed of homo- or hetero-dimers of RelA (p65), RelB, c-Rel, p50/p105 (NF-κB1), or p52/p100 (NF-κB2), among which the heterodimer p50/p65 is the most prominent and serves as the prototype of NF-κB [21]. These proteins carry an N-terminal Rel homology domain, which is required for dimerization, nuclear targeting, DNA binding, and interaction with the inhibitor of κB (IκB) proteins. Under physiological conditions, the NF-κB subunits are bound to IκB, which effectively sequesters NF-κB in the cytoplasm. However, when cells are stimulated by various signalling events such as stress, bacteria, viruses, or cytokines, NF-κB is rapidly activated. It undergoes a process called translocation, where it moves into the nucleus of the cell. Once in the nucleus, NF-κB binds to the κB elements of specific genes, including those involved in proinflammatory cytokines, chemokines, and endothelial adhesion molecules. This binding triggers the transcription of these genes, leading to the production of inflammatory mediators and contributing to vascular inflammation [22].

There are two distinct pathways involved in NF-κB activation, which are activated in response to different stimuli and involve distinct molecular mechanisms. In the canonical pathway, NF-κB activation is initiated by the phosphorylation and subsequent degradation of IκB proteins, which normally sequester NF-κB in the cytoplasm. Upon stimulation by specific signals such as proinflammatory cytokines or microbial products, the IKK (IκB kinase) complex is activated and phosphorylates IκB proteins. This phosphorylation targets IκB for ubiquitination and proteasome-mediated degradation, allowing NF-κB to translocate to the nucleus and activate the transcription of target genes [22]. The noncanonical pathway involves a different set of signaling events and is typically activated by specific members of the tumour necrosis factor receptor superfamily. In this pathway, the activation of NF-κB-inducing kinase (NIK) leads to the phosphorylation and processing of the NF-κB precursor protein p100. This processing generates the mature p52 subunit, which can form a complex with RelB to activate gene transcription [22].

As an important regulator of immunity and inflammation, the activation of NF-κB signalling is influenced by multiple regulatory mechanisms. Numerous post-translational modifications of p65 have been shown to have positive or negative effects on transcriptional responses of NF-κB. In addition, NF-κB signalling components have been reported to interact with chromatin-modifying enzymes, such as histone deacetylases or acetyltransferases, with other transcription factors, and with phosphatases, to fine-tune the NF-κB response [23,24]. Notably, many NF-κB target genes encode inhibitors of the NF-κB response thus resulting in a complicated network involved in the regulation of vascular inflammation [24,25].

5. Epigenetic Regulation of Vascular Inflammation

Recent evidence suggests that internal components, such as hypertension, hyperglycaemia, growth factors, oxidant stress and inflammatory factors [26], and external components, including diet, life habits, and environmental pollutants [27], may alter the epigenome, the collection of epigenetic marks on cell DNA, by modulating gene expression without altering DNA sequence [28–30]. The mechanisms determining epigenetic modifications, which are inherited and long-lasting, but also reversible, can be divided into four groups: DNA methylation, RNA methylation, histone post-translational modifications, and the broad family of epigenetic regulators made of non-coding RNAs (ncRNAs). These epigenetic mechanisms are involved in the modulation of the intricate processes underlying vascular inflammation, and will be described below with a focus on the expression of endothelial adhesion molecules and endothelium-leukocyte adhesion.

5.1 DNA Methylation

DNA methylation is the covalent attachment of a methyl group to the cytosine base of the 5′-CpG-3′ dinucleotide, known as 5-methylcytosine (5mC) by DNA methyltransferases (DNMTs), divided into maintenance (DNMT1) and de novo (DNMT3A and DNMT3B) types [31]. On the other hand, ten-eleven translocation enzymes (TET, TET1-3) can actively cause locus-specific DNA demethylation by catalysing the hydroxylation of the 5mC residue to 5-hydroxymethylcytosine [32]. Methylation of DNA in the enhancer or promoter region inhibits the binding of transcription factors, thereby decreasing gene transcription [33,34]. In contrast, DNA demethylation or hydroxylation of the methyl group within the enhancer or promoter region enhances gene activity and expression [34,35]. DNA methylation is a critical epigenetic mechanism associated with vascular inflammation and atherosclerosis development [36,37]. Aberrant genome hypomethylation has been found in leukocytes from patients with vascular disease [38] as well as in advanced and early atherosclerotic lesions [39–41]. In the atherosclerotic process, upregulated expression of enzymes that regulate DNA methylation has been observed [42]. DNMTs can promote DNA hypermethylation in the promoter region of anti-inflammatory and anti-atherosclerotic factors, leading to repression of their expression [43]. Oscillatory shear stress, a crucial factor involved in the initiation and development of atherosclerosis, has been found to upregulate DNMT1 expression in endothelial cells. Furthermore, in a mouse model, blood flow disturbed by partial carotid ligation surgery upregulates DNMT1 expression in the arterial endothelium, leading to DNA hypermethylation in the promoter of mechanosensitive transcription factors, including homeobox A5 (HoxA5) and kruppel-like factor (KLF) 3 [43].

HoxA5 is involved in the regulation of endothelial functions such as migration, inflammation and angiogenesis [43]. Inhibition of HoxA5 markedly increases the attachment of monocytes to endothelial cells, indicating the essential role of flow-mediated HoxA5 function in the regulation of endothelial inflammation [43]. Moreover, the zinc finger transcription factors KLFs play important roles in vascular biology, being involved in counteracting cytokine-induced adhesion molecule expression and immune cell adhesion [44]. In human endothelial cells, haemodynamically disturbed flow upregulates DNMT3A and inhibits KLF4 expression [45]. Moreover, ox-LDL, a major atherosclerotic risk factor, reduced the expression of KLF2 and of the cellular repressor of E1A-stimulated genes (CREG) by upregulating DNMT1 and DNMT3B, respectively [46]. DNMT1 upregulation has also been observed to modulate pro-inflammatory activation of atherosclerosis-associated macrophages and the progression of atherosclerosis [47, 48]. DNMT1 is induced in macrophages after treatment with proinflammatory cytokines, such as lipopolysaccharide (LPS) and interferon-gamma (IFN-γ). Consistently,

DNMT1 expression is elevated in atherosclerotic plaque macrophages from human and mouse samples [47]. Increased DNMT1 expression has been shown to promote macrophage activation by suppressing KLF4 expression, catalysing DNA methylation of the KLF4 promoter region [47]. Furthermore, upregulation of macrophage DNMT1 is able to suppress peroxisome proliferator nuclear receptor (PPAR)-γ-mediated anti-inflammatory effects. Indeed, PPAR-γ has been identified as a target of DNMT1-regulated DNA methylation [48]. Moreover, the DNMT inhibitor as well as antioxidant molecule N-acetylcysteine can restore aberrant hypermethylation through demethylation and significantly attenuate vascular inflammation and endothelial dysfunction [45,46].

Studies have also indicated an important role of the hydroxylation of methyl groups by TET2 in counteracting endothelial and macrophage activation in atherosclerosis [49,50]. TET2 has been found to be downregulated in atherosclerotic lesions and involved in the progression of atherosclerosis [49]. Low shear stress downregulates expression of TET2 and decreases expression of autophagy-related genes (Beclin1 and microtubule-associated protein1 light chain 3) by repressing endothelial cell autophagy [51]. By contrast, autophagy level and autophagy-related gene expression are upregulated by TET2 overexpression, which also improves endothelial function [51]. Furthermore, in ox-LDL-treated vascular endothelial cells, autophagy and autophagic flux are improved by TET2 overexpression and decreased by TET2 silencing [52]. In ApoE$^{-/-}$ mice, TET2 overexpression markedly decreases atherosclerotic lesions, by promoting autophagy and downregulating the expression of proinflammatory factors, such as monocyte chemoattractant protein 1 (MCP-1, also known as chemokine (CC-motif) ligand 2, CCL2), VCAM-1, ICAM-1, and IL-1 [52].

5.2 RNA Methylation

RNA methylation is a reversible post-transcriptional modification of RNA. It can affect the phenotype of cells by influencing transcription, splicing, stability, trans-nuclear transport, and translation of RNA [53,54]. RNA methylation can be found in both coding and non-coding RNA molecules [55], and includes the addition of either a single or a double methyl group at specific nucleotide residues in RNA, such as N6-methyladenosine (m6A) [56]. m6A methylation is the most common and abundant RNA molecular modification in eukaryotes [53]. It is mostly observed at the 5$'$ end of the terminal exon, near the stop codon; however, it may also occur at the 3$'$ untranslated region (UTR) and within long internal exons [56]. m6A methylation is regulated by three groups of proteins known as methyltransferases (writers), demethylases (erasers), and m6A binding proteins (readers) [57]. Recent evidence shows an association between m6A methylation and cardiovascular atherosclerotic risk factors and endothelial inflammation [56,58,59]. The methyltransferase-like 14 (METTL14) plays an important regulatory role in endothelial inflammation by regulating m6A modification of forkhead box O (FOXO) 1 mRNA [60]. Mechanistically, the protein METTL14 has a direct binding affinity to the mRNA of the transcription factor FOXO1. This interaction leads to an increase in the m6A modification (methylation) of FOXO1 mRNA. The m6A modification enhances the translation of FOXO1 mRNA by facilitating its recognition by the YTH N6-methyladenosine RNA binding protein (YTHDF)-1 [60]. Additionally, METTL14 has been found to interact with FOXO1 and directly act on the promoter regions of VCAM-1 and ICAM-1. This action promotes the transcription of these genes, which are involved in the inflammatory response of endothelial cells [60]. *In vivo* experiments have shown that *METTL14* gene knockout significantly reduces the development of atherosclerotic plaques and the overwhelming inflammatory response of macrophages [60,61]. Specifically, through m6A modification, METTL14 upregulates the expression of the adaptor protein myeloid differentiation primary response 88 (MyD88), which affects the transcription of IL-6 through NF-κB signalling [61]. In endothelial cells, the regulation of RNA methylation by METTL3 plays an essential role in endothelial function and angiogenesis, potentially affecting the processing of angiogenic microRNAs (let-7e and miR-17-92 clusters) [62]. METTL3 also acts during ox-LDL-induced monocyte inflammation, where, in cooperation with YTHDF-2, it modifies peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1α mRNA, mediating its degradation, and thereby enhancing the inflammatory response [63].

In addition to the methylation process, mRNA demethylation enzymes also play a significant role in inflammation and atherosclerosis. One such enzyme is FTO (fat mass and obesity-associated), which has been reported to be involved in the regulation of vascular inflammation [64]. The knockdown of FTO enhances the mRNA and protein expression of KLF2 and endothelial nitric oxide synthase (eNOS) but attenuates TNF-α-induced VCAM-1 and ICAM-1 expression, as well as the adhesion of monocytes to endothelial cells. Conversely, FTO overexpression significantly upregulates the mRNA and protein levels of VCAM-1 and ICAM-1 as well as downregulating those of KLF2 and eNOS [65].

5.3 Histone Post-Translational Modifications

In eukaryotic cells, epigenetic marks involve reversible histone modifications, including methylation and acetylation, among others, which induce conformational shifts in the protein structure allowing the docking of specific regulatory proteins [66]. Histone methylation, one of the most important post-translational modifications, is regulated by histone methyltransferases (HMTs) and histone demethylases (HDMTs). HMTs transfer methyl groups to

arginine (R) to form mono- or di-methylated residues, or to lysine (K) which can accept one, two or three methyl groups [67]. Methylation of lysine residues at the 4th site of H3 (H3K4) is associated with gene activation, and occurs mainly in regions of active transcription, such as the transcription start site, promoter, and enhancer regions. In contrast, methylation of lysine residues at the 9th and 27th sites (H3K9, and H3K27) is associated with gene silencing (Fig. 2) [67]. An interconnection between histone and DNA methylation in atherosclerosis has been demonstrated. The HMT enhancer of zeste homolog-2 (EZH2) induces the expression of the DNMT1, which, in turn, increases DNA methylation of ATP-binding cassette transporter A1 (ABCA1) promoter, inhibiting its expression and thus promoting the formation of macrophage-derived foam cells and the development of atherosclerosis [68]. When endothelial cells are exposed to elevated levels of LDL (resembling a state of hypercholesterolaemia), by inducing DNMT1, LDL recruit a transcriptional repressor complex (methyl-CpG binding protein 2, MeCP2, and EZH2) to the KLF2 promoter, which results in a shift in promoter occupancy that causes closed chromatin and repression of KLF2 expression [46]. These studies suggest that EZH2 and DNMT1 may form a positive feedback regulatory system. On one hand, they regulate foam cell formation by inhibiting ABCA1 expression; on the other, they influence endothelial dysfunction by suppressing KLF2, and jointly promoting the atherosclerotic process. Recent studies have demonstrated a link between histone methylation and high glucose-induced vascular inflammation and accelerated atherosclerosis. Transient hyperglycaemia has been shown to be able to induce upregulation of the NF-κB p65 subunit gene in endothelial cells which is associated with increased methylation of H3K4 (H3K4me1) and decreased methylation of H3K9 (H3K9me2 and H3K9me3) on the NF-κB p65 promoter [69]. At the same time, in human endothelial cells treated with high glucose, dimethylated and trimethylated H3K4 forms are enriched at the promoter of the *MCP-1* gene, and the HMTs mixed-lineage leukaemia (MLL) and Su(var)3-9, enhancer of zeste, Trithorax (SET) domain-containing protein 7 (SET7) are increased, while the histone demethylase LSD1 is decreased [70]. In human aortic cells, the HMT SET7 has also been found to mediate glucose-induced inflammation through epigenetic regulation of the transcription factor NF-κB [71]. Knockdown of SET7 reduces the H3K4me1 mark and abolishes NF-κB-dependent inflammatory signalling [71]. Concordantly, SET7 has been observed to contribute to vascular dysfunction in patients with type 2 diabetes mellitus (T2DM). In peripheral blood mononuclear cells from T2DM patients, an increase of SET7 expression and SET7-dependent monomethylation of H3K4 (H3K4me1) on the NF-κB p65 promoter is observed. This epigenetic signature is associated with upregulation of NF-κB, subsequent transcription of inflammatory genes, and increased plasma levels of ICAM-1 and MCP-1 [71]. Moreover, epigenetic changes have been implicated in the persistence of vascular inflammation induced by hyperglycemia [72]. In response to hyperglycaemia, the HMT SET7 accumulates in the nucleus of endothelial cells, promoting IL-8, ICAM-1 and CXC motif chemokine ligand 2 (CXCL2) expression in an H3K4me1-dependent manner. SET7 also inhibits heme oxygenase 1 (HMOX1) expression in an H3K4me1-independent fashion to regulate insulin sensitivity and "hyperglycemic memory" [72]. In endothelial cells, oxygen-glucose deprivation/reperfusion injury upregulates histone demethylase Jumonji domain-containing protein 3 (JMJD3) expression, leading to greater JMJD3 interactions with NF-κB and CCAAT-enhancer-binding protein at the IL-6 gene promoter, which decreases the trimethylated form of H3K27 to promote IL-6 expression and regulate the inflammatory response [73]. A similar mechanism is active in endothelial cells stimulated with LPS, where increased JMJD3 expression induces demethylation of H3K27me3 and activates the expression of target genes by interaction with NF-κB [74].

Another important post-transcriptional modification is histone acetylation, regulated by histone acetyltransferases (HATs) and histone deacetylases (HDACs). Histone modifications through acetylation are fundamental for remodelling chromatin and consequently activating gene expression. The imbalance between acetylation and deacetylation activity causes transcriptional dysregulation associated with several disorders. HATs consist of two types: type A, mainly localised at the nucleus, acetylates nucleosomal histones by transferring an acetyl group from acetyl-CoA, and include p300/cyclic AMP response element-binding protein (CBP) families; type B, located in the cytosol, acetylates free histones or non-histone proteins [75]. Acetylation of nucleosomal histones is generally associated with the activation of transcription, since the addition of an acetyl group to lysine neutralizes the positive charge of lysine residues, resulting in decreased histone-DNA interactions, with decondensation of chromatin and increased accessibility of DNA to transcription factors (Fig. 2). HDACs remove acetyl groups from acetylated proteins, consequently repressing gene expression by condensing nucleosomes. They are classified into four categories: class I (HDAC1,2,3, and 8), class II (2a: HDAC4,5,7, and 9; 2b: HDAC6, and 10), class III (sirtuin, SIRT1-7), and class IV (HDAC11) [76]. Alterations in the expression level of HDACs have been related to inflammatory diseases such as atherosclerosis. Indeed, HDAC2 may be downregulated by ox-LDL, resulting in increased oxidative stress [77]. HDAC3 seems to have a protective role for endothelial integrity, and HDAC3 deletion has been linked to reduced endothelial cell survival and increased atherosclerosis [78]. In human advanced plaques, increased HDAC9 is associated with the expression of proinflammatory markers in macrophages [79]. Macrophages from

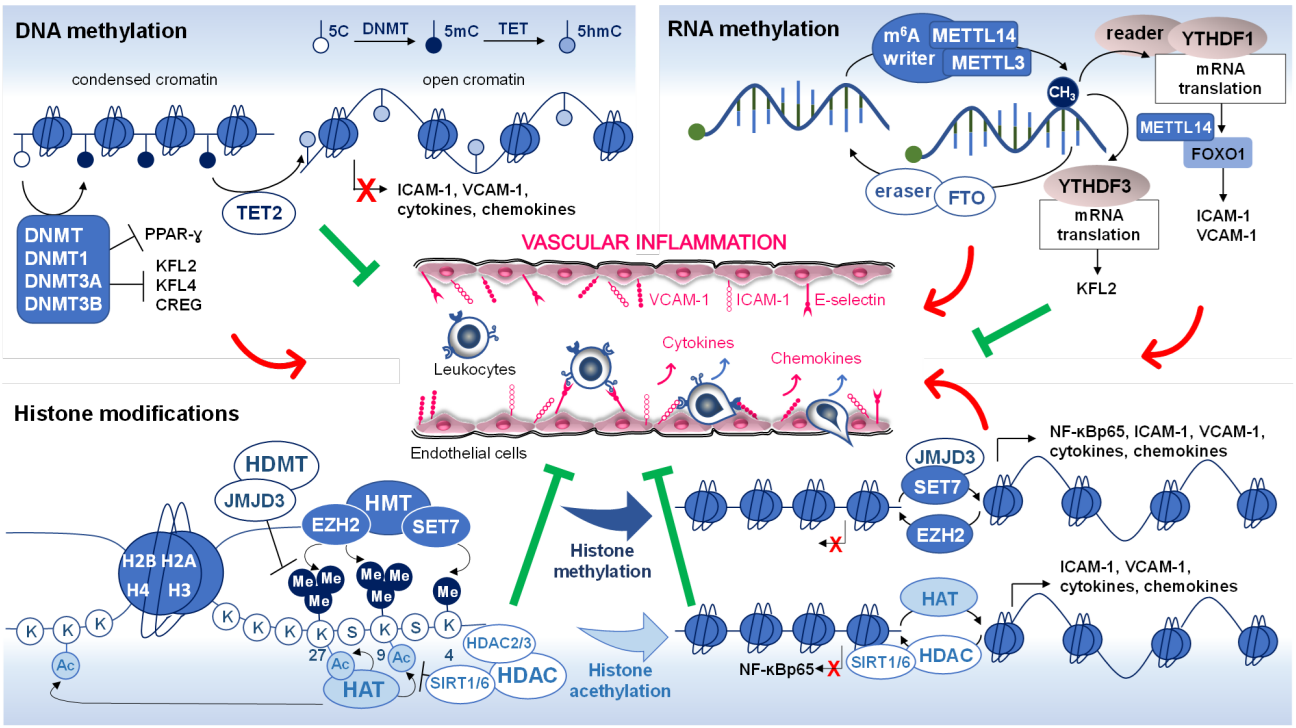

Fig. 2. Epigenetic modifications in vascular inflammation. DNA methylation, RNA methylation, and histone modifications (methylation and acetylation) are common epigenetic alterations that have been associated with changes in gene expression affecting vascular inflammation. The red arrow indicates increased levels of expression and the green lines (block sign) indicates reduced levels of expression. DNMT, DNA methyltransferase; TET, ten-eleven translocation; 5C, 5-cytosine; 5mC, 5-methylcytosine 5hmC, 5-hydroxymethylcytosine; KLF2 and 4, kruppel-like factor 2 and 4; CREG, cellular repressor of E1A-stimulated genes; PPAR-γ, peroxisome proliferator nuclear receptor-γ; ICAM-1, intercellular adhesion molecules-1; VCAM-1, vascular cell adhesion molecule-1; MELLT3 and 14, methyltransferase like 3 and 14; YTHDF1 and 3, YTH N6-methyladenosine RNA binding protein 1 and 3; FTO, demethylase fat mass- and obesity-associated protein; FOXO1, forkhead box O1, and O3; HMT, histone methyltransferase; EZH2, enhancer of zeste homolog-2; SET7, Su(var)3-9, enhancer of zeste, Trithorax (SET) domain-containing protein 7; HDMT, histone demethylases; JMJD3, Jumonji domain-containing protein-3; HAT, histone acetyltransferase; HDAC, histone deacetylase; SIRT1 and 6, sirtuin 1 and 6; NF-κB p65, nuclear factor-κB p65 subunit; Ac, acetylation; Me, methylation.

HDAC9-deficient mice are less responsive to LPS stimulation in release of proinflammatory cytokines. In addition, HDAC9 deficiency upregulates histone H3 and H4 acetylation and increases levels of ABCA1 and PPARγ, preventing the efflux of cholesterol [80]. Thus, HDAC9 deficiency results in macrophages that are polarized towards promoting inflammation resolution and reverse cholesterol transport, which can brake atherosclerosis progression and promote lesion regression [80]. Sirtuins, now known as class III KDACS (lysine deacetylases), are nicotinamide adenine dinucleotide $(NAD)^+$-dependent HDACs and play pivotal roles in the regulation of metabolism, stress responses, and ageing processes [81]. The major function of sirtuins includes deacetylation of histones as well as some non-histone proteins like NF-κB, FOXOs, PPAR-γ, PGC1-α, enzymes, and structural proteins. SIRT1 and SIRT6 protect against atherosclerosis by preventing endothelial dysfunction through pleiotropic effects on oxidative stress and inflammation. SIRT1 reduces inflammation by direct deacetylation of the NF-κB p65 subunit, whereas SIRT6 reduces inflammation by deacetylating H3K9 at NF-κB target gene promoters [81]. Histone acetylation mediates the expression and secretion of inflammatory mediators in various infectious diseases. During the infection process, monocytes increase secretion of IL-8 through hyperacetylation of histone H3 and H4 at the promoter of IL-8 in addition to NF-κB-activated transcription [82]. In this context, endothelial cells increase the expression of inflammatory genes, including IL-6, IL-8, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), and IFN-γ, regulated by Rho-GTPase-related acetylation of histone H3 and H4, leading to the development of chronic vascular lesions [83]. In endothelial cells, HDAC inhibitors are reported to markedly reduce TNF-α-stimulated VCAM-1 expression [84,85], as well as, the LPS-induced expression and secretion of proinflammatory genes, such as MCP-1, IL-6, and IL-1β, by enhancing histone H3 acetylation and associated up-

regulation of oxidative stress protective genes, including catalase, superoxide dismutase 2 (SOD2), FOXO3A, and PGC-1α expression [86]. In many chronic diseases, histone acetylation plays a critical role in endothelial dysfunction associated with inflammation. In addition to inducing DNA hypomethylation, in endothelial cells LDL promote the acetylation of histone H3K9 and H3K14 in the promoter of p66shc, a major mediator of oxidative stress-induced vascular dysfunction, thereby increasing endothelial p66shc expression [87]. Furthermore, ox-LDL induces inflammatory activation of human endothelial cells via the lectin-like oxidized LDL receptor-1 (LOX-1) and extracellular regulated kinases (ERK1/2) signalling pathway, leading to acetylation of histone H3 and H4 on the promoters of IL-8 and MCP-1 [88]. Histone acetylation promotes the recruitment of NF-κB p65/RelA and RNA polymerase II to the promoters of IL-8 and MCP-1, increasing their expression. Pre-treatment with anti-inflammatory agents such as statins prevents ox-LDL-induced histone acetylation on the IL-8 and MCP-1 promoters, decreasing the expression of the two inflammatory cytokines [88]. Moreover, the proatherogenic lipid lysophosphatidylcholine induces mitochondrial ROS-dependent H3K14 acetylation, increasing the binding of the proinflammatory transcription factor activator protein 1 (AP-1) in the promoter of ICAM-1 and inducing ICAM-1 transcription in endothelial cells [89]. Upon long-term inflammation, high amounts of proinflammatory cytokines affect endothelial function by downregulating RNase1, a circulating extracellular endonuclease, regulating vascular homeostasis of extracellular RNA and acting as a vessel- and tissue-protective enzyme [90]. TNF-α- or IL-1β-challenged endothelial cells reduce RNase1 expression by inducing hypoacetylation of histone H3K27 and histone H4 through HDAC2 accumulation to the RNase1 promoter, while class I HDAC specific inhibition abolishes the changes [91]. In pulmonary artery endothelial cells, lipoxin A4 (LXA4), an endogenous lipoxygenase-derived eicosanoid mediator, exerts potent dual anti-inflammatory and pro-resolving effects by increasing formyl peptide receptor 2 (recently renamed ALX/FPR2) mRNA and protein levels through the HAT p300 which restores chromatin accessibility [92]. It is noteworthy that, small molecules of plant origin, including flavones, are nutraceutical bioactive compounds known to interfere with HDAC class I enzymes and to enhance acetylation, restoring cell homeostasis. This occurs because flavones, i.e., apigenin and luteolin, can interact as ligands with HDAC1 and 2 at the active site binding pocket [93]. Regulation of HDAC activity by dietary flavones could have important implications in developing epigenetic therapy to regulate the cell gene expression. Furthermore, it has been shown that the natural polyphenol resveratrol can bind SIRT1 by enhancing its interaction with RelA/p65, leading to reduced activity of NF-κB [94]. In endothelial cells, resveratrol can inhibit the inflammatory response by regulating the transcriptional and translational levels of SIRT2, SIRT5, and SIRT7 [94].

Overall, current knowledge underlines an important role of nucleic acids and histone modifications in regulating vascular inflammation and atherosclerosis and suggests them as potential targets in the treatment of inflammatory diseases, such as atherosclerosis.

5.4 Non-Coding RNAs

Advanced genome- and transcriptome-wide analyses have revealed that only less than 2% of the human genome contains protein-coding transcripts, while more than 75% is transcribed into ncRNAs with no protein-coding potential [95]. Based on their sizes, ncRNAs can be divided into two groups: the long non-coding RNAs (lncRNAs), that are more than 200 nucleotides long, and the short ncRNAs that are less than 200 nucleotides in length, including microRNAs (miRNAs). Generally, ncRNAs can be categorized into housekeeping ncRNAs and regulatory ncRNAs. The former, profusely expressed in all cell types, including ribosomal, transfer, small nuclear, and telomerase RNAs, are necessary for cells to survive; the latter, including lncRNAs and miRNAs, usually participate in regulation of gene expression, acting at epigenetic, transcriptional, and post-transcriptional levels [95]. In this section, an update of ncRNAs' contribution to inflammation and immunity is given.

5.4.1 Long Non-Coding RNAs

LncRNAs constitute the major portion of the non-coding component of the human genome. A growing body of data suggests that lncRNAs may regulate genes either *in cis* (on neighbouring genes) or *in trans* (on distant genes) through specific interactions with proteins, DNA, and other types of RNA [96]. Numerous lncRNAs are functionally correlated with endothelial dysfunction, vascular inflammation, and associated cardiovascular diseases [97]. It is worth noting that several lncRNAs play a crucial role in NF-κB signalling during inflammatory responses (Fig. 3) [24,98]. One of the first known lncRNAs in humans was lncRNA H19, a key mediator of endothelial cell function, which is down-regulated by proinflammatory cytokines, such as IL-1β and TNF-α [99]. More recently, Hofmann *et al.* [100] found that H19 is expressed in the adult endothelium and its depletion results in premature endothelial senescence. Furthermore, H19 loss-of-function activates the inflammatory signalling pathway and impairs endothelial cell function. Correspondingly, the overexpression of H19 ameliorates endothelial function in aged aortas [100]. These results show a central role of H19 in reducing endothelial cell dysfunction in ageing by controlling endothelial cell senescence, proliferation, and inflammatory activation. However, recent evidence also points out a contradictory role for H19, since its overexpression leads to an increase of p38 mitogen-activated protein kinase (MAPK) activity and p65 nuclear translocation/expression in human endothelial cells, with activation of the NF-κB

pathway [101,102]. Endothelial functions are also affected by the lncRNA named metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) [103,104]. In LPS-treated human lung microvascular endothelial cells, MALAT1 upregulates ICAM-1 expression by competitively binding to the microRNA miR-150-5p, whereas MALAT1 silencing or miR-150-5p overexpression decreases the expression of pro-inflammatory mediators, including IL-6, IL-1β, TNF-α, and E-selectin, thus alleviating vascular injury [105]. Furthermore, Zhao *et al.* [106] showed that MALAT1 regulates the LPS-induced inflammatory response through its interaction with NF-κB (Fig. 3). Mechanistically, MALAT1 interacts with NF-κB subunits p65 (RelA) and p50 to inhibit NF-κB DNA binding activity and production of the proinflammatory cytokines TNFα and IL-6 in macrophages. These findings suggest that MALAT1 may function as an auto-negative feedback regulator of NF-κB to help fine-tune innate immune responses. The lncRNA Lethe (named after the mythological river of forgetfulness for its role in negative feedback) was one of the first lncRNAs demonstrated to be involved in modulating NF-κB signalling [107]. Lethe, a chromatin-associated lncRNA, is selectively induced by proinflammatory cytokines via NF-κB. Specifically, Lethe physically associates with RelA (p65) to block the DNA binding activity of NF-κB. Therefore, Lethe, which is induced in a p65-dependent fashion, appears to act as a negative feedback regulator of NF-κB [108]. Lethe levels decrease with ageing, a physiological state associated with increased NF-κB activity. Lethe is expressed in mouse embryonic fibroblasts upon exposure to TNF-α and, IL-1β, but is not responsive to toll-like receptor agonists, indicating that it may have a function in inflammation, but not in innate immunity [107]. Another important lncRNA in inflammation is Antisense Non-coding RNA in the INK4 Locus (ANRIL) [109]. In human vascular endothelial cells, ANRIL is remarkably induced in response to pro-inflammatory factors in an NF-κB-dependent manner. Elevated ANRIL affects the expression of a large portion of inflammatory genes downstream of NF-κB, such as IL-6 and IL-8 [110]. Mechanistic studies indicate that ANRIL forms a functional complex with the transcriptional factor Yin Yang 1 to exert transcriptional regulation on NF-κB-dependent inflammatory genes. Together, these reports suggest that lncRNAs both positively and negatively regulate NF-κB-dependent gene expression, contributing to the fine regulation of NF-κB-responsive genes.

5.4.2 MicroRNAs

miRNAs, a class of ncRNAs with important roles in regulating gene expression, have emerged as key players in vascular inflammation and chronic inflammatory diseases [111]. Usually, miRNAs are transcribed from DNA sequences into primary miRNAs (pri-miRNAs) and processed into precursor miRNAs (pre-miRNAs) and mature miRNAs. In most cases, miRNAs interact with the 3′ UTR of target mRNAs to suppress expression [112]. Mechanistically, miRNAs function by post-transcriptionally regulating protein accumulation and by regulating the transcription of other miRNAs [113]. Within a given cell type, a single miRNA can target hundreds of mRNAs, and a single mRNA is often the target of multiple miRNAs [112]. miRNAs can either silence the expression of the positive signalling proteins or the inhibitors of the same pathway [112].

Several studies have pointed out miRNAs as regulators of the main proinflammatory cytokines. The regulatory relationship between cytokines and miRNAs seems to be reciprocal: not only do miRNAs target cytokine mRNA and thereby regulate cytokine expression, but also the cytokine signalling likewise has an impact on miRNA expression [114]. It has been observed that hyperglycaemia strongly induces miR-155, which in turn can directly raise TNF-α [115]. *In vivo* studies have confirmed that mice overexpressing miR-155 produce more TNF-α when challenged with LPS [116]. Furthermore, miR-155, as a central regulator of the immune system, regulates the expression of MyD88 adaptor protein by translational repression leading to the suppression of IL signalling (Table 1, Ref. [108,116–138] and Fig. 4) [117]. As occurs with other cytokines, the expression of IL-6, a hallmark of chronic inflammatory states, is also regulated by miRNAs [139]. Chen *et al.* [140] demonstrated that IL-6 down-regulates miR-223 expression, leading secondarily to an increase in STAT3, which then drives the expression of IL-6 and IL-1β in a positive regulatory loop. Up-regulation of miR-146a/b, another important regulator of IL-6 metabolism, provides negative feedback in the inflammatory response [118,141]. In primary human fibroblasts, the overexpression of miR-146a/b suppresses IL-6 and IL-8 secretion down-regulating interleukin-1 receptor-associated kinase (IRAK)-1, a crucial component of the IL-1 receptor signal transduction pathway, thus restraining the excessive secretion of inflammatory cytokines, and limiting inflammation [118]. Furthermore, in response to pro-inflammatory cytokines, miR-146a/b is strongly induced in endothelial cells and inhibits expression of endothelial adhesion molecules and endothelial activation [142]. Notably, miR-146a/b induction is delayed and sustained compared to the expression of leukocyte adhesion molecules, and in fact coincides with the down-regulation of inflammatory gene expression [142].

Overall, various miRNAs are involved in the regulation of immune responses and inflammatory processes and might play a role in controlling the switch from an early proinflammatory response to the resolution phase of the inflammatory process [143,144]. The role of miRNAs in vascular inflammation is based not only on regulating the inflammatory stimulus but also on the response of the vascular endothelium to inflammatory triggers. In the following sections, the regulatory function of miRNAs in the expression of the endothelial adhesion molecules is described.

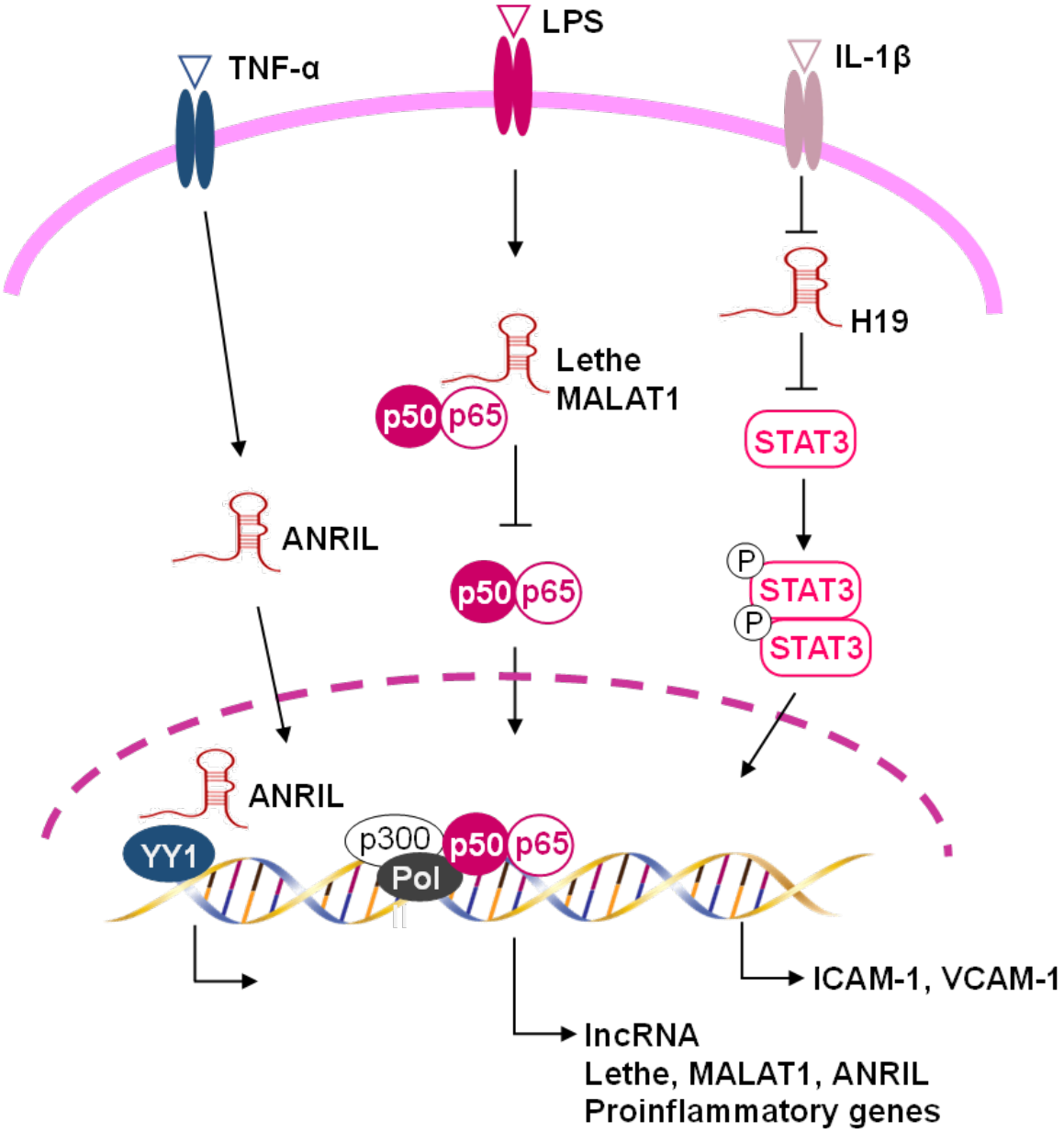

Fig. 3. Functional lncRNAs involved in the regulation of vascular inflammation. LncRNAs regulate, either positively or negatively, the expression of genes involved in vascular inflammation. LncRNA Lethe and MALAT1 (metastasis associated lung adenocarcinoma transcript 1) suppress the NF-κB signalling pathway. LncRNA H19 inhibits the phosphorylation of signal transducer and activator of transcription 3 (STAT3) and reduces vascular cell adhesion molecule 1 expression. LncRNA ANRIL (Antisense Non-coding RNA in the INK4 Locus) interacts with the transcription factor yin yang 1 (YY1) to form a functional complex that regulates proinflammatory gene expression.

5.4.3 Expression of Endothelial Adhesion Molecules: Role of miRNAs

Recent evidence supports the role of miRNAs in regulating vascular inflammation and particularly the expression of endothelial cell adhesion molecules including E-selectin, ICAM-1, and VCAM-1 [111,145]. Various miRNAs can target the expression of endothelial adhesion molecules both directly and indirectly through modulation of the NF-κB pathway (Table 1 and Fig. 4) [145]. One of the most highly expressed miRNAs in endothelial cells is miR-126 (also referred to as miR-126-3p), which has been associated with vascular inflammation (Table 1 and

Table 1. Pro-inflammatory and anti-inflammatory miRNAs and their targets and functions involved in vascular inflammation.

Pro-inflammatory miRNAs			
miRNAs	Target (s)	Functions	References
miR-155	MyD88, κB-RAS1, NF-κB p65	miR-155 regulates the immune response and vascular inflammation	[116,117]
miR-92a	KLF2, KLF4	miR-92a enhances the expression of endothelial adhesion molecules and endothelium-leukocyte adhesion	[136]
miR-34a	SIRT1	miR-34a regulates flow dependent endothelial inflammation	[138]
miR-132	SIRT1, p300	miR-132 is a pleiotropic miRNA that both counteracts and promotes endothelial inflammation	[136,137]
Anti-inflammatory miRNAs			
miRNAs	Target (s)	Functions	References
miR-126	VCAM-1	miR-126 blocks the adhesion and infiltration of leukocytes into vascular wall	[119–122]
miR-221, miR-222, miRNA-141, miRNA-17-3p	ICAM-1	miR-221, miR-222, miRNA-141, and miRNA-17-3p reduce leukocyte-endothelial cell adhesion	[108,123–125]
miR-31	E-selectin	miR-31 inhibits leukocyte adhesion and rolling on the endothelium	[126,127]
miR-146a/b	IRAK1, TRAF6, CARD10	miR-146a/b inhibits endothelial adhesion molecule expression and endothelial activation	[118]
miR-100	mTOR	miR-100 regulates vascular inflammation and preserves endothelial functions	[135]
miR-181b	Importin-α3, CARD10	miR-181b inhibits vascular inflammation	[132–134]
miR-125a/b	TRAF6	miR125a/b decreases the accumulation of macrophages and neutrophils in the myocardium	[128,129]
miR-10a	TAK1 and β-TRC	miR-10a regulates endothelial athero-susceptibility/protection by targeting key regulators of IκB-α degradation	[130]
miR-23b	IKKβ, NF-κB	miR-23b regulates inflammatory cytokine pathways	[131]

MyD88, myeloid differentiation primary response 88; κB-RAS1, NF-κB p65 subunit, nuclear factor-κB p65 subunit; KLF2 and 4, kruppel-like factor 2 and 4; SIT1, sirtuin 1; VCAM-1, vascular cell adhesion molecule-1; ICAM-1, intercellular adhesion molecules-1; IRAK1, interleukin-1 receptor-associated kinase 1/2; TRAF6, TNF receptor-associated factor 6; CARD10, caspase recruitment domain family member 10; mTOR, mammalian target of rapamycin; TAK1, transforming growth factor-β activated kinase 1; β-TRC, β-transducin repeat-containing gene; IKKβ, IκB kinase β.

Fig. 4) [119]. This miRNA can bind to the 3′ UTR VCAM-1 transcript, inhibiting mRNA translation and protein synthesis, thereby blocking adhesion and infiltration of leukocytes into the vascular wall. Transfection of endothelial cells with an antisense construct targeting endogenous miR-126 allows an increase in TNF-α-stimulated VCAM-1 expression [119]. The expression of miR-126 is regulated by factors as varied as oestrogens and endotoxins. The oestrogen E_2 increases miR-126, which decreases VCAM-1 and monocyte adhesion [120]. Endotoxin LPS downregulates miR-126 at the transcriptional level leading to depression of VCAM-1, while the overexpression of miR-126 attenuates LPS-induced vascular injury [121]. In mice, mimic-miR-126 inhibits vascular inflammation by targeting VCAM-1 [122]. The expression of ICAM-1 is also regulated by multiple miRNAs such as miR-221 and, miR-222 [123], which are complementary to the ICAM-1 3′ UTR region and modulate ICAM-1 expression at the post-transcriptional level leading to a significant reduction in leukocyte-endothelium adhesion [108]. A similar effect has been shown for miR-141and miR-17-3p (a passenger miRNA of miR-17), other miRNAs targeting ICAM-1 [124,125]. Moreover, miR-31 directly downregulates E-selectin expression, induced by the pro-inflammatory cytokines IL-1β and TNF-α, impairing leukocyte adhesion and rolling on the endothelium [126,127].

Several miRNAs are indirectly involved in the regulation of endothelial cell adhesion molecules, affecting NF-κB signalling (Table 1 and Fig. 4) [145]. miR-146a has been found to be transcriptionally induced by NF-κB in response to the activation of innate immune signalling in monocytes [146]. miR-146a targets the adaptor proteins tumour necrosis factor receptor-associated factor 6 (TRAF6) and IRAK1/2 and can inhibit activation of the NF-κB pathway, suggesting that miR-146a participates in a negative feedback loop to control NF-κB signalling [147,148]. In

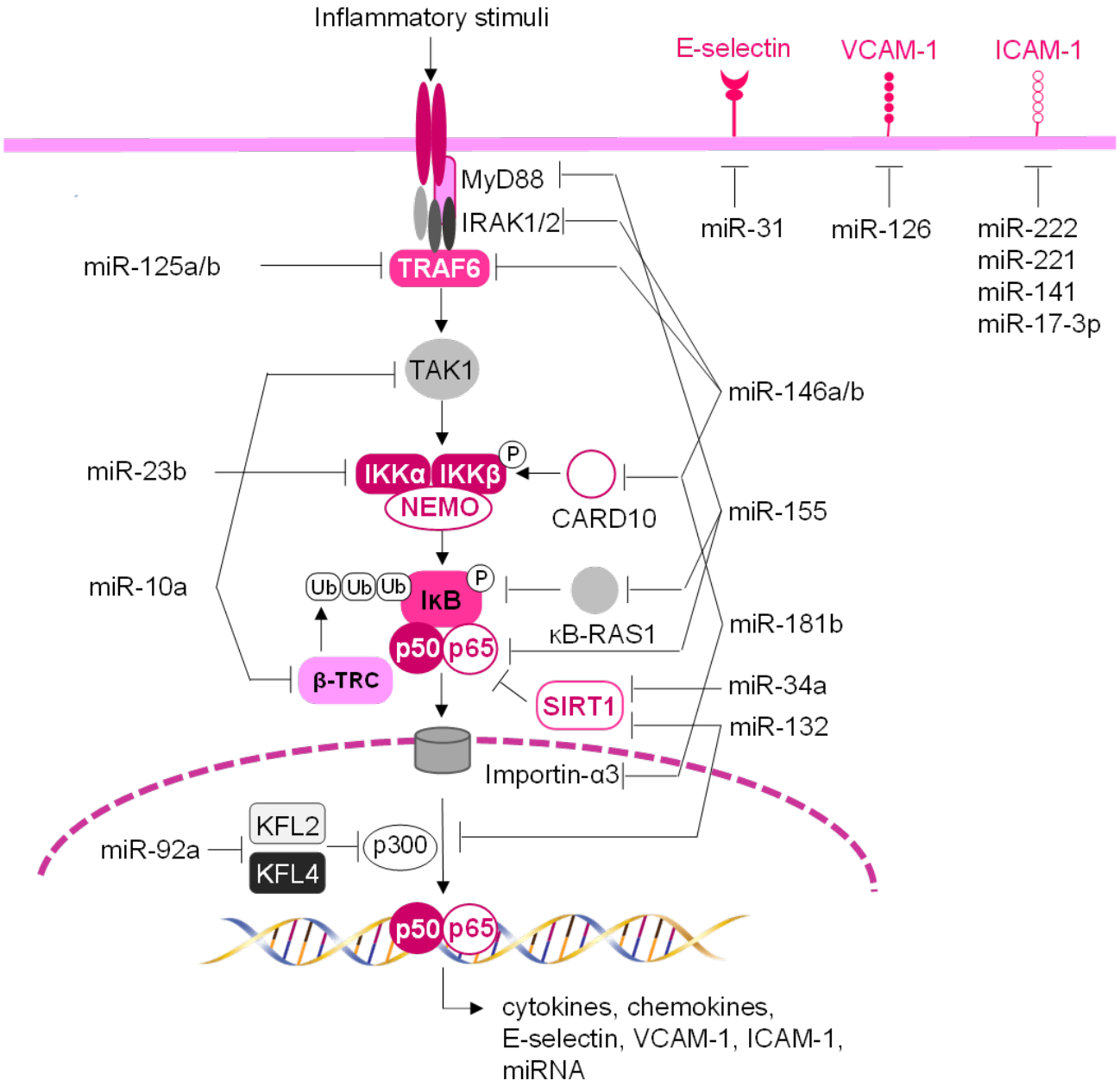

Fig. 4. Schematic network of miRNAs regulating vascular inflammation and adhesion molecule expression. miRNAs can regulate the endothelial inflammatory response and leukocyte-endothelium adhesion, by directly targeting endothelial adhesion molecule transcripts and/or by modulating NF-κB signaling pathway and subsequent transcription of pro-inflammatory genes. In unstimulated cells, NF-κB subunits (e.g., p65/p50) are sequestered in the cytoplasm through their interaction with inhibitor-κB (IκB). In response to inflammatory stimuli, the IκB kinase (IKK) complex phosphorylates IκB, which is then ubiquitylated by β-transducin repeat-containing gene (β-TRC), leading to its degradation. Then NF-κB can translocate to the nucleus, where it can bind to its transcriptional targets, which include leukocyte adhesion molecules, chemokines, and cytokines. miRNAs can modulate the NF-κB signaling pathway to various levels thus by dampening its activation.

addition to pro-inflammatory agents, dysmetabolic stimuli may also regulate endothelial adhesion molecules by affecting miRNA activities. Ox-LDL can 'de-repress' NF-κB activity by reducing miR-125a, counteracting the effects of ox-LDL on inflammation, namely the expression of ICAM-1 and VCAM-1 and leukocyte adhesion [128].

Moreover, transfection of miR-125b into the heart significantly suppresses the expression of ICAM-1 and VCAM-1, decreases the accumulation of macrophages and neutrophils in the myocardium, and reduces serum levels of TNF-α and IL-1β in mice, by targeting TRAF6-mediated NF-κB activation [129]. Furthermore, in human aortic endothelial cells, miR-10a impairs NF-κB-mediated expression of E-selectin, VCAM-1, MCP-1, IL-6, and IL-8 by targeting key regulators of IκB-α degradation [130]. Numerous other miRNAs, such as miR-23b and miR-181b, are also down-regulated by inflammatory stimuli to derepress NF-κB activity, promoting endothelial activation [131,132]. In addition, miR-181b also targets importin-α3, an importer protein required for the nuclear translocation of NF-κB, so diminishing the downstream expression of inflammatory genes, such as VCAM-1 and E-selectin [133]. Following research also showed that systemic delivery of miRNA-181b inhibits NF-κB activation, vascular inflammation, and atherosclerosis in ApoE$^{-/-}$mice [134]. This study reveals the endothelial-specific mechanisms by which miR-181b exerts its protective effect in the vascular endothelium and provides the rationale for the potential clinical use of miR-181b mimetics to treat chronic vascular inflammatory diseases such as atherosclerosis [134]. A recent study by Pankratz *et al.* [135] has identified miR-100 as a potent suppressor of endothelial adhesion molecule expression, by attenuation of NF-κB signalling, resulting in decreased leukocyte-endothelium interaction *in vitro* and *in vivo*. These findings add miR-100 to the regulatory network of anti-inflammatory miRNAs, suggesting a critical role in the restraint of vascular inflammation and the maintenance of an endothelial equilibrium. Furthermore, recent evidence reports that miR-17-3p exhibits anti-inflammatory effects in endothelial cells by inhibition of the NF-κB signalling pathway and the expression of pro-inflammatory genes. Indeed, in addition to directly targeting ICAM-1 mRNA, miR-17-3p suppresses the LPS-induced phosphorylation of IκBα and the NF-κB p65 subunit [125].

Some miRNAs, induced by proinflammatory cytokines, exert a multifunctional role. They can target and repress several genes with complex effects on cell physiology. miR-132 is a pleiotropic miRNA that both counteracts and promotes endothelial inflammation. As an inflammation promoter, miR-132 increases NF-κB signalling by targeting SIRT1 to promote inflammatory processes including ICAM-1 expression [136]. As an inflammation inhibitor, miR-132 targets the transcriptional coactivator of NF-κB p300, which in turn modulates the transcription of miR-132. This feedback loop may contribute to the transient expression of miR-132 [137]. Furthermore, in human aortic endothelial cells, miR-92a boosts NF-κB activity by targeting the endothelial transcription factors KLF2 and KLF4, that inhibit NF-κB activity by competing for access to the transcriptional coactivator p300/CBP. miR-92a thus enhances the expression of inflammatory molecules including E-selectin and, VCAM-1 and contributes to leukocyte adhesion [149]. Some miRNAs are associated with shear stress conditions [150]. Several investigations have revealed that atheroprone flow (oscillatory flow) inhibits whereas atheroprotective pulsatile blood flow increases various miRNAs including miR-30 and miR-10a. The transcription of miR-30 is mediated by KLF2 and activated in response to pulsatile blood flow. Then, miR-30 inhibits the activation of endothelial cells and the expression of E-selectin, ICAM-1, and VCAM-1 [151]. miR-10a is crucial for endothelial response to different flow patterns by regulating the expression of its direct target GATA-binding factor 6 (GATA6) and downstream expression of VCAM-1 [152]. In contrast, miR-34a is reduced by pulsatile blood flow and increased by oscillatory blood flow [138]. miR-34a affects the NF-κB-mediated expression of ICAM-1 and VCAM-1, de-repressing the NF-κB activity through direct regulation of SIRT1, thus regulating the flow-dependent endothelial inflammation [138]. miR-663, another miRNA induced by oscillatory blood flow, is necessary for the efficient transcription of E-selectin and VCAM-1 [153]. Oscillatory blood flow also induces the c-Jun/AP-1-mediated transcription of miR-21, which targets PPAR-α, an inhibitor of the transcription factor AP-1. This feedforward loop enables the sustained induction of miR-21, contributing to the proinflammatory responses of the vascular endothelium, including the expression of VCAM-1 and MCP-1, and the consequential adhesion of monocytes *in vitro* [154].

5.4.4 Circulating miRNAs and Vascular Inflammation

Recent studies have reported significant levels of miRNAs in serum and other body fluids, raising the possibility that circulating miRNAs could serve as useful clinical biomarkers and modulators of vascular inflammation [155]. Although the traditional idea suggests that RNA molecules cannot be stable in extracellular environments due to ubiquitous ribonucleases, miRNA has now been shown to circulate in a stable form in various body fluids, mainly associated in extracellular vesicles (exosomes or microvesicles, also known as microparticles) [156,157]. In a cohort cross-sectional study, positive correlations between circulating miR-1185 and the expression of E-selectin and VCAM-1 have been observed [158]. Mechanistic analysis has confirmed that miR-1185 induces a significant increase in the VCAM-1 and E-selectin levels in human cultured endothelial cells, suggesting a crucial role in endothelial activation and atherosclerosis development [158]. Another study that measured levels of miR-122 in blood samples after ischaemic stroke showed a correlation between reduced levels of miR-122 and increased expression of target genes such as VCAM-1 and ICAM-1 in the brain [159]. A clinical trial has revealed that circulating levels of miR-126, miR-92a, and miR-155 are significantly reduced in patients with coronary artery disease compared with healthy subjects [160]. A recent clinical study has also shown that cir-

culating miR-505 is elevated in patients with hypertension [161]. In an animal model of hypertension, miR-505 modulates the levels of endothelial activation markers, VCAM-1, and E-selectin, as well as monocyte-endothelium adhesion [162]. These findings linking miR-505 to endothelial dysfunction and inflammation under hypertensive conditions support the translational value of miR-505 as a biomarker of hypertension-associated endothelial impairment and inflammatory injuries [162].

In addition to their potential as diagnostic biomarkers, circulating miRNAs can be delivered to endothelial cells and regulate inflammatory responses [156,157]. In the vascular system, microvesicles are the major form of miRNA delivery, and the endothelium is one of the primary targets of circulating microvesicles [156,157]. Lipoxin LXA_4 stimulates endothelial miR-126-5p expression and its transfer via microvesicles, thus enhancing endothelial repair functions [163]. Jansen *et al*. [164] demonstrated that miR-222 is transported into recipient endothelial cells by endothelial microparticles and functionally regulates expression of its target protein ICAM-1 *in vitro* and *in vivo*. After simulating diabetic conditions, endothelial microparticles derived from glucose-treated endothelial cells contain significantly lower amounts of miR-222 and show reduced anti-inflammatory capacity *in vitro* and *in vivo* [164]. Finally, a lowered circulating miR-222 level has also been confirmed in patients with coronary artery disease compared to healthy subjects [164]. Moreover, Li *et al*. [165] found that thrombin-activated platelet-derived exosomes inhibit endothelial cell expression of ICAM-1 via miR-223, through regulation of NF-κB and MAPK pathways, during the thrombosis-inflammation response [165]. It has been observed that high-density lipoprotein (HDL) particles, purified from plasma, can transfer functional miRNAs, such as miR-223, suppressing the expression of ICAM-1 [166].

Overall, miRNAs are emerging as new markers and potential targets and therapeutic tools for the treatment of diseases associated with vascular inflammation. Further studies are needed to fully understand the interrelationships between the different epigenetic mechanisms and the miRNA network involved in the regulation of vascular inflammation.

6. Conclusions

The vascular inflammatory response is a complex process influenced by internal and external factors that can lead to epigenetic changes such as DNA and RNA methylation, histone modification, and ncRNA changes. Epigenetic signatures can modulate gene expression by regulating the different phases of the inflammatory process through an intricate network of interactions. Multiple epigenetic mechanisms finely regulate the expression of endothelial adhesion molecules, influencing leukocyte-endothelium adhesion and extravasation leading to chronic vascular inflammation. Endothelial adhesion molecules can be targeted both directly by epigenetic regulators and indirectly through modulation of the NF-κB pathway, the major player in inflammation. Although epigenetics has shed light on the intricate mechanisms underlying vascular inflammation, the continuous exploration in this area may lead to a better understanding of the molecular basis that regulates the chronic inflammatory process and the identification of targeted strategies for the prevention and treatment of diseases related to vascular inflammation.

Unlike genetic modifications, epigenetic states of genes are reversible and can be altered by certain intrinsic and extrinsic factors. Accumulated evidence shows that dietary phytochemicals with chemopreventive effects are also potent epigenetic regulators. They can reverse altered epigenetic regulation by changing DNA methylation and, histone modification, and modulating miRNA expression or directly interacting with enzymes. Thus, pharmanutritional strategies could be exploited as epigenetic agents aimed to prevent pathological vascular inflammation and related diseases.

Availability of Data and Materials

All raw data can be provided upon request.

Author Contributions

NC and MAC contributed to the study conception and design. NC, MM, and MAC made substantial contributions to the acquisition, analysis, and interpretation of data for the work. ES, CC, TV contributed the analysis and interpretation of data. The first draft of the manuscript was written by NC and MAC. All authors (NC, MM, ES, CC, TV and MAC) edited the draft and revised the manuscript for important intellectual content. All authors contributed to editorial changes in the manuscript. All authors have read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

Given their roles as Guest Editors, Nadia Calabriso and Maria Annunziata Carluccio, had no involvement in the peer-review of this article and have no access to information regarding its peer-review. The authors declare no conflict of interest.

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