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REVIEW ARTICLE

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Visfatin: An emerging adipocytokine bridging the gap in the evolution of cardiovascular diseases

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Abstract

Visfatin/nicotinamide phosphoribosyltransferase (NAMPT) is an adipokine expressed predominately in visceral fat tissues. High circulating levels of visfatin/NAMPT have been implicated in vascular remodeling, vascular inflammation, and atherosclerosis, all of which pose increased risks of cardiovascular events. In this context, increased levels of visfatin have been correlated with several upregulated pro-inflammatory mediators, such as IL-1, IL-1Ra, IL-6, IL-8, and TNF-α. Furthermore, visfatin is associated with leukocyte recruitment by endothelial cells and the production of adhesion molecules such as vascular cell adhesion molecule 1, intercellular cell adhesion molecule 1, and E-selectin, which are well known to mediate the progression of atherosclerosis. Moreover, diverse angiogenic factors have been found to mediate visfatin-induced angiogenesis. These include matrix metalloproteinases, vascular endothelial growth factor, monocyte chemoattractant protein 1, and fibroblast growth factor 2. This review aims to provide a

comprehensive overview of the pro-inflammatory and angiogenic actions of visfatin, with a focus on the pertinent signaling pathways whose dysregulation contributes to the pathogenesis of atherosclerosis. Most importantly, some hypotheses regarding the integration of the aforementioned factors with the plausible atherogenic effect of visfatin are put forth for consideration in future studies. The pharmacotherapeutic potential of modulating visfatin's roles could be important in the management of cardiovascular disease, which continues to be the leading cause of death worldwide.

KEYWORDS
adipocytokine, atherosclerosis, cardiovascular disease, inflammation, NF-κB, visfatin

1 | INTRODUCTION

Cardiovascular disease (CVD) remains the predominant cause of death worldwide (Virani et al., 2020). Many factors are implicated in the pathogenesis of this disease. Some of these factors are produced by adipose tissues whose exact role has been reinvestigated in the past decade (Oikonomou & Antoniades, 2019). The role of adipose tissue evolved from just being the main reservoir of energy in the form of triglycerides to become an endocrine gland and essentially a part of the endocrine system (AlZaim et al., 2020). This is due to the fact that adipose tissues secrete hormone-like substances known as adipokines or adipocytokine (Murphy & Bloom, 2006). Adipokines comprise many inflammatory mediators such as complement factors B, C3, and D, haptoglobin, hepatocyte growth factor, adiponectin, interleukin (IL)−1ß, IL-6, IL-8, IL-10, leukemia inhibitory factor, macrophage migration inhibitory factor, tumor necrosis factor alpha (TNF-α), and many more (Hassan et al., 2012). The concentration of these adipokines may be altered or dysregulated in some metabolic disorders, such as obesity (Fain et al., 2004; W. J. Lee et al., 2009) and type 2 diabetes (W. J. Lee et al., 2009), sepsis (S. H. Jia et al., 2004), and cardiovascular disorders, such as hypertension and atherosclerosis (Belo et al., 2013; Dahl et al., 2007; Dogru et al., 2006; Fardoun et al., 2020; Gunes et al., 2012), suggestive of a potential role of adipokines in the pathogenesis of these cardiovascular disorders.

Visfatin/nicotinamide phosphoribosyltransferase (NAMPT) is an adipocytokine that is abundantly produced in visceral adipose tissue (Dakroub et al., 2020; Fukuhara et al., 2005). It is also expressed in the bone marrow, liver, muscles, heart, placenta, lung, and kidney (Samal et al., 1994). Visfatin exists in intracellular (iNAMPT) and extracellular (eNAMPT) forms. Whereas the former plays a regulatory role in NAD^+ biosynthesis, the latter is associated with many hormone-like signaling pathways and intracellular signaling cascades (Revollo et al., 2007; Verdin, 2015).

The gene encoding visfatin is located on the long arm of chromosome 7 between 7q22.1 and 7q31.33 (S. H. Jia et al., 2004). The structure of visfatin has been studied in terms of other phosphoribosyltransferases including nicotinic acid phosphoribosyltransferase (NAPRTase) and quinolic acid phosphoribosyl transferase (QAPRTase) (T. Wang et al., 2006). Despite differences in the topology of the residues in the active sites, visfatin is considered a structural homolog of NAPRTase from *Thermoplasma acidophilum* and has some limited structural similarities to *Myobacterium tuberculosis* QAPRTase and yeast NAPRTase (T. Wang et al., 2006).

Visfatin is a homodimeric protein that belongs to the dimeric class of type II phosphoribosyltransferases (T. Wang et al., 2006). Visfatin consists of two 491-residue monomers (Figure 1), with each comprising 19 β-strands and 13 α-helices that are arranged into two structural domains (M.-K. Kim et al., 2006; Figure 2). The interaction among seven-stranded antiparallel β-sheet, two antiparallel β-strands, and an α-helix bundle constitutes the first structural domain (M.-K. Kim et al., 2006). Alternative folding of the classical (β/α) 8-barrel constitutes the second structural domain (M.-K. Kim et al., 2006). Visfatin has two active sites aligned at the dimer interface where two NMN molecules bind (T. Wang et al., 2006). This suggests a rather vital role for dimerization in modulating the catalytic activity. The dimer formed has an extensive intermolecular interface that spans a total surface area of 8,077$Å^2$ (T. Wang et al., 2006). The

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1    MNPAAEAEFN ILLATDSYKV THYKQYPPNT SKVYSYFECR EKKTENSKLR
51   KVKYEETVFY GLQYILNKYL KGKVVTKEKI QEAKDVYKEH FQDDVFNEKG
101  WNYILEKYDG HLPIEIKAVP EGFVIPRGNV LFTVENTDPE CYWLTNWIET
151  ILVQSWYPIT VATNSREQKK ILAKYLLETS GNLDGLEYKL HDFGYRGVSS
201  QETAGIGASA HLVNFKGTDT VAGLALIKKY YGTKDPVPGY SVPAAEHSTI
251  TAWGKDHEKD AFEHIVTQFS SVPVSVVSDS YDIYNACEKI WGEDLRHLIV
301  SRSTQAPLII RPDSGNPLDT VLKVLEILGK KFPVTENSKG YKLLPPYLRV
351  IQGDGVDINT LQEIVEGMKQ KMWSIENIAF GSGGGLLQKL TRDLLNCSFK
401  CSYVVTNGLG INVFKDPVAD PNKRSKKGRL SLHRTPAGNF VTLEEGKGDL
451  EEYGQDLLHT VFKNGKVTKS YSFDEIRKNA QLNIELEAAH H
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FIGURE 1 Primary structure of visfatin. Amino acid sequence of *Homo sapiens*'s visfatin

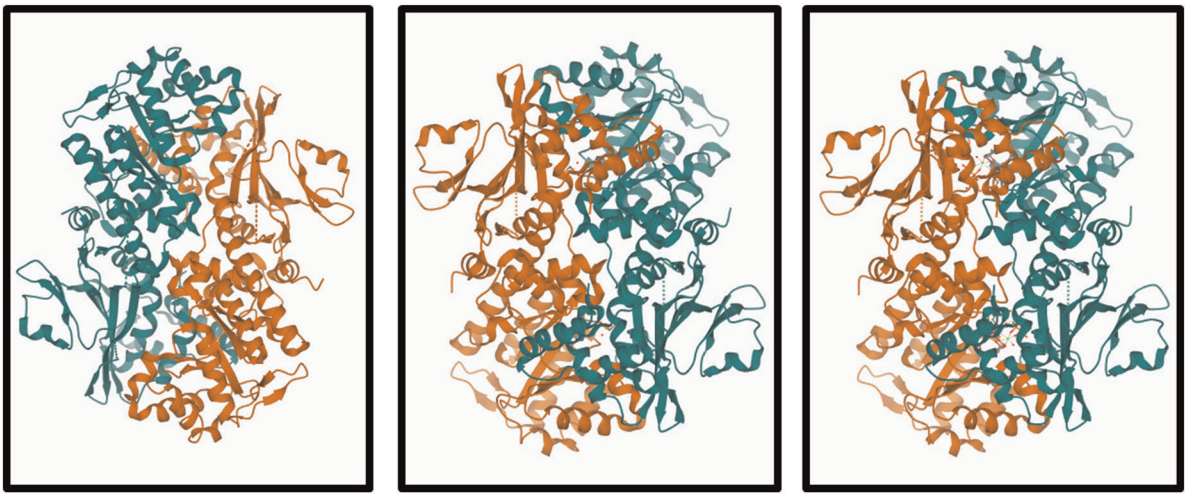

FIGURE 2 Crystal structure of visfatin. Crystal structure of visfatin of *Rattus norvegicus* (left) (M.-K. Kim et al., 2006), or *Homo sapiens* complexed with either ADP (middle) or nicotinamide mononucleotide and pyrophosphate (right) (Burgos et al., 2009)

interface includes a total of 89 polar and hydrophobic residues that are almost evenly distributed (M.-K. Kim et al., 2006). The intramolecular interactions are mediated by 42 hydrogens bonds (M.-K. Kim et al., 2006). The residues located within the active site were found to be highly conserved among 13 aligned sequences of visfatin homologs (M.-K. Kim et al., 2006; Figure 2). This includes residues essential for binding to the nicotinamide ring and others contributing to the ribose binding site (M.-K. Kim et al., 2006). Visfatin structure might provide some insight into the missing link between its effects and NAD^+ biosynthesis.

When originally discovered, visfatin was shown to act as an immune modulating cytokine (Samal et al., 1994) stimulating the release of many inflammatory mediators (W. J. Lee et al., 2009; Moschen et al., 2007). Moreover, it appears to induce MCP-1 production (Adya et al., 2009) and matrix metalloproteinases (MMPs) expression (Adya et al., 2008). Visfatin elicits the activation of many inflammatory signaling pathways, including NF-κB (W. J. Lee et al., 2009), mitogen-activated protein kinase (MAPK), and phosphatidylinositol 3 kinase (PI3K) (S.-R. Kim et al., 2008). Based on the multifaceted intracellularly activated signaling pathways, it is only reasonable to investigate a putative role of visfatin in CVD. This review aims at illustrating how these pathways contribute to various pathophysiological aspects of vascular remodeling known to be associated with increased risks of cardiovascular events (Brown et al., 2018).

2 | VISFATIN IN ATHEROSCLEROSIS

Atherosclerosis is the most common cause or mediator of CVD (Gisterå & Hansson, 2017; Nasser et al., 2021). It is a chronic inflammatory process that affects the structure and architecture of the vasculature and involves remodeling of arterial extracellular matrix (ECM) (Badran et al., 2020; Galis et al., 1994; Ross, 1999). It progresses slowly and involves the deposition of fatty and fibrous lesions that lead to plaque (atheroma) formation in the walls of medium- and large-sized arteries (Ross, 1999). Atherogenesis, the process that leads to atherosclerosis, has been linked in most of its stages to inflammatory responses (Libby, 2012; Ross, 1999), which are believed to be regulated by several immune cells including T lymphocytes, macrophages, and monocytes as well as the products they secrete like TNF-α, IL-1, IL-6, and interferon-ɣ (IFN-ɣ) (Ross, 1999). One of the key transcription factors that mediate inflammatory and innate or adaptive immune responses is nuclear factor kappa B (NF-κB) (Winther et al., 2005).

NF-κB is a vital regulator of several genes. It regulates cytokines (IL-2, IL-6, IL-12, and TNF-α), adhesion molecules (VCAM-1, ICAM-1, and E-selectin), and chemokines (IL-7, macrophage inflammatory protein [MIP]−1α, and MCP1) (Baldwin, 2001; Ghosh & Karin, 2002; Ghosh et al., 1998; Hayden & Ghosh, 2004; Q. Li & Verma, 2002; Silverman & Maniatis, 2001; Yamamoto & Gaynor, 2001, 2004). In addition, it is an important regulator of genes required for the regulation of cell cycle (B-cell lymphocyte/leukemia-2 [Bcl-2], cyclin) (Karin & Lin, 2002; Winther et al., 2005) or apoptosis (Fas, blc-2, c-FLIP, caspase, c-IAPs, BFL-1, TNF-receptor associated factor [TRAF], and c-MYC) (Karin & Lin, 2002; Yamamoto & Gaynor, 2004). It also activates inducible enzymes, such as cyclooxygenase (COX-2) and nitric oxide synthase (iNOS) (Yamamoto & Gaynor, 2004). NF-κB regulates the synthesis of major receptors in immune recognition, such as major histocompatibility complex (MHC), and cytokines necessary to elicit immune reactions, proliferation, and differentiation of lymphocytes (Yamamoto & Gaynor, 2004). Moreover, NF-κB is a key regulator of cell adhesion, migration, invasion, metastasis, angiogenesis, and many other processes (Xia et al., 2014). Therefore, dysregulation of the NF-κB signaling cascade can alter the regulation of these processes and thus likely affect a wide number of genes, leading to alterations of several inflammatory molecules. Indeed, the NF-κB signaling cascade is implicated in several steps involved in the

initiation and progression of atherosclerosis (Winther et al., 2005). Interestingly, several studies unveiled possible relations between NF-κB and visfatin in the inflammation and adhesion stages of atherosclerosis vasculo-pathology (S.-R. Kim et al., 2008; W. J. Lee et al., 2009; Moschen et al., 2007). More importantly, recent evidence shows that visfatin exacerbates inflammation and promotes atherosclerosis in apoE knockout mice (Kong et al., 2019).

2.1 | Role of visfatin in inflammation

Visfatin expression and secretion is increased in many inflammatory diseases including rheumatic diseases like rheumatoid arthritis and osteoarthritis (Gómez et al., 2011), inflammatory bowel disease (IBD; Crohn's disease and ulcerative colitis) (Moschen et al., 2007), and acute lung injury (Ye et al., 2005). This suggests a possible role for visfatin in mediating inflammation. Indeed, many studies demonstrated that visfatin/NAMPT upregulates the production of pro- and anti-inflammatory cytokines, such as IL-1, IL-1Ra, IL-6, IL-8, IL-10, and TNF-α in human monocytes (Brentano et al., 2007; Dahl et al., 2007; W. J. Lee et al., 2009; Moschen et al., 2007; Tilg & Moschen, 2008). Visfatin has also been reported to act as a chemotactic factor for $CD14^+$ monocytes and $CD19^+$ B cells (Moschen et al., 2007) and to promote the production of costimulatory molecules, such as CD80, CD54, and CD40 (Moschen et al., 2007; Tilg & Moschen, 2008), which are linked to pro-inflammatory signaling pathways (Barbé-Tuana et al., 2006; Borcherding et al., 2010; Nolan et al., 2009; Parker, 2018). In addition, visfatin upregulates mannose receptor (CD206)-mediated phagocytosis in monocytes (Moschen et al., 2007).

Visfatin's upregulation of inflammatory mediators within endothelial cells appears to be mediated by the NF-κB p65 pathway (W. J. Lee et al., 2009). In addition, the p38 and MEK1 pathways have been found to be implicated in visfatin-mediated production of pro-inflammatory cytokines and human leukocyte activation (Moschen et al., 2007) (Figure 3). In line with this study, expression of visfatin upregulated in activated neutrophils during inflammatory responses (S. H. Jia et al., 2004). More importantly, visfatin inhibits the apoptosis of neutrophils and prolongs their survival during inflammatory responses such as sepsis (S. H. Jia et al., 2004). Recent evidence further argues that the inflammatory effects of visfatin are due to its ability to increase expression of lipoxygenase in human endothelial cells (Han et al., 2020). This is consistent with another recent report showing that visfatin induces endothelial dysfunction via NLRP3-inflammasome and paracrine IL-1β signaling (Romacho et al., 2020). Other mechanisms for visfatin's role in endothelial dysfunction have also been suggested (Pereira et al., 2019; Yin et al., 2019).

Visfatin is associated with different mediators known to underlie a multitude of inflammatory diseases. In this regard, visfatin is associated with the pro-inflammatory markers, IL-6 and C-reactive protein (CRP) in chronic kidney disease (CKD) (Axelsson et al., 2007). It enhances the expression of IL-6 (J.-Y. Kim et al., 2009), a key player in defective angiogenesis and several vascular diseases (Yongfeng Fan et al., 2008; Gopinathan et al., 2015; Kayakabe et al., 2012; Wani

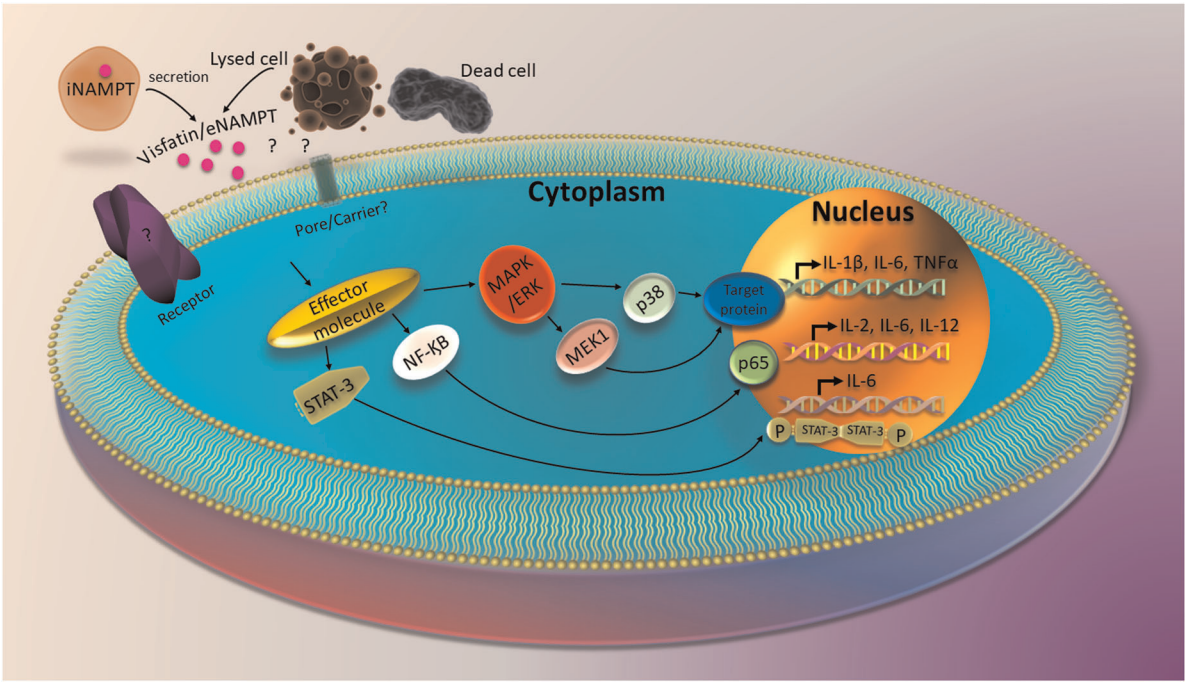

FIGURE 3 Major signaling pathways that mediate visfatin-induced inflammation. Visfatin induces the production of several inflammatory mediators including IL-1 beta, IL-6, TNF-alpha via the MAPK/ERK signaling pathway. Visfatin induced production of IL-2, IL-6, and IL-12 involve NF-κB activation and p65. Visfatin may induce IL-6 production via the STAT-3 signaling cascade. IL, interleukin; MAPK/ERK, mitogen-activated protein kinase/extracellular signal-regulated kinases; NF-κB, nuclear factor kappa B; TNF-α, tumor necrosis factor alpha

et al., 2011; Wei et al., 2003). Remarkably, many of IL-6-elicited effects are mediated by vascular endothelial growth factor- (VEGF) and STAT-3-dependent mechanisms (Cohen et al., 1996; Gopinathan et al., 2015; Kayakabe et al., 2012; Wani et al., 2011; Wei et al., 2003). In addition, visfatin-associated IL-6 leads to CRP production, clearly suggestive of a role for visfatin in priming an inflammatory milieu (Oki et al., 2007). Interestingly, visfatin levels are positively correlated with IL-6 only in women, suggesting gender differences in visfatin regulation (Seo et al., 2008).

Visfatin may perpetuate inflammation via exerting broad-spectrum effects in immune cells. In this context, visfatin promotes the survival of macrophages via an IL-6/STAT3-dependent pathway (Y. Li et al., 2008). It also promotes B cell precursor maturation and inhibits neutrophil apoptosis (S. H. Jia et al., 2004). In addition, it activates macrophages, dendritic cells, and monocytes (Moschen et al., 2007). Given that macrophage-mediated inflammation critically contributes to obesity-induced insulin resistance and atherosclerosis (Wellen & Hotamisligil, 2005) and that visfatin levels are upregulated in such cardiovasculo-metabolic disorders (Berndt et al., 2005; Chen et al., 2006; Dahl et al., 2007; Haider et al., 2006; Jurdana et al., 2013; Kaminska et al., 2010; López-Bermejo et al., 2006; Nourbakhsh et al., 2015; Pitoulias et al., 2017; Sandeep et al., 2007), elevated circulating visfatin levels might thus contribute to the pathophysiology of these disorders by altering immune cell physiology. Therefore, monitoring circulating eNAMPT/visfatin levels would be an essential intervention in the therapeutic management of these disorders. Indeed, the multimodal immune-modulatory effects of visfatin in different inflammatory diseases suggest a possible underlying role in mediating inflammation.

2.2 | Role of visfatin in adhesion

It is well established that the initial step in many vascular pathologies, including atherogenesis, involves the expression of adhesion molecules on endothelial cell surfaces (Takahashi et al., 1996). This facilitates the adhesion of leukocytes to endothelial cells, which is an initial and rather critical step in vascular inflammation and remodeling (Takahashi et al., 1996). Interestingly, visfatin has been shown to increase the expression of adhesion proteins such as soluble ICAM-1 (sICAM-1)/CD54, sVCAM-1 (CD106), and sE-selectin (CD62E) (W. J. Lee et al., 2009; Moschen et al., 2007). In this regard, visfatin appears to be associated with serum level of s-VCAM-1 in CKD patients (Axelsson et al., 2007). In addition, visfatin has been found to upregulate CD40 in human monocytes CD40 (Moschen et al., 2007; Tilg & Moschen, 2008), a protein known to promote adhesion (Elgueta et al., 2009; Karmann et al., 1995).

Increased levels of adhesion molecules have been linked to several cardiovasculo-metabolic disorders. For instance, circulating sICAM-1 has been linked to β-cell destruction in type 1 diabetes (Toivonen et al., 2001). In addition, high levels of sICAM-1 and sVCAM-1 are associated with coronary heart disease (CHD) (Hwang et al., 1997; Luc et al., 2003; Malik et al., 2001) and myocardial infarction (Ridker et al., 1998), and indeed have been used as prognostic markers (Blankenberg et al., 2001; Mulvihill et al., 2001). Similarly, ICAM-1 and VCAM-1 are expressed on endothelial cells of human atherosclerotic lesions (Poston et al., 1992; Printseva et al., 1992; Takahashi et al., 1996). Interestingly, the increased risk of CHD associated with sICAM-1 appears to be highly dependent on the presence of high levels of sVCAM-1 as well (Shai et al., 2006). Visfatin seems to maintain the dependency on these adhesion molecules by upregulating both s-ICAM-1 and s-VCAM-1, thus serving as a significant risk factor for CHD and possibly other metabolic disorders (Shai et al., 2006). Obviously, the cellular processes and signaling pathways involved in the visfatin-induced upregulation of the adhesion molecules might serve as attractive therapeutic targets in the future.

Mechanistically, visfatin has been shown to enhance the expression of ICAM-1 and VCAM-1 through the NF-κB signaling pathway (W. J. Lee et al., 2009; Yin et al., 2019). Alongside, it has been shown that visfatin upregulates these two adhesion molecules via a ROS-dependent NF-κB pathway (S.-R. Kim et al., 2008). This upregulation occurs via p38/PI3K/Akt signaling pathway (Lin et al., 2019) (Figure 4). Interestingly, visfatin can also upregulate ICAM-1 via a p38-mediated suppression of miR-320a (Law et al., 2020).

3 | SIGNALING PATHWAYS IN VISFATIN-INDUCED VASCULAR REMODELING

The vascular system is basically formed by two main processes, vasculogenesis and angiogenesis (Beck & D'Amore, 1997; Drake et al., 2000; Hoeben et al., 2004; Muller et al., 1997). Vasculogenesis is the de novo synthesis of early vessel tubes from angioblasts (endothelial cell precursors) and it occurs mostly during early development. Angiogenesis is the formation of small blood vessels by budding from larger vessels (L Beck & D'Amore, 1997). These two processes are central mechanisms for vascular remodeling. Contextually, vascular remodeling involves the appearance of new vessels and the disappearance of others. Moreover, vascular remodeling entails any changes in diameter, size, lumen, thickness, stiffness, or others in response to stimuli (L Beck & D'Amore, 1997). Of note, angiogenesis has a central role in atherosclerosis and many other vascular diseases (Camaré et al., 2017).

The progression of many vascular diseases, including atherosclerosis, is heavily dependent on vascular remodeling. This remodeling often involves many key signaling molecules such as VEGF, MMPs, and others. Interestingly, visfatin is expressed in atherosclerotic plaques within lipid-loaded macrophages and is especially upregulated in unstable carotid plaques and coronary atherosclerosis (Auguet et al., 2016; Dahl et al., 2007). Being a cytokine itself, it is not surprising that visfatin regulates the expression of critical regulators of vascular remodeling such as VEGF (Adya et al., 2007), fibroblast growth factor 2 (FGF-2) (Bae et al., 2009), and MMPs (Adya et al., 2007). Indeed, recent evidence shows that visfatin promotes angiogenesis of endothelial progenitor cells via a

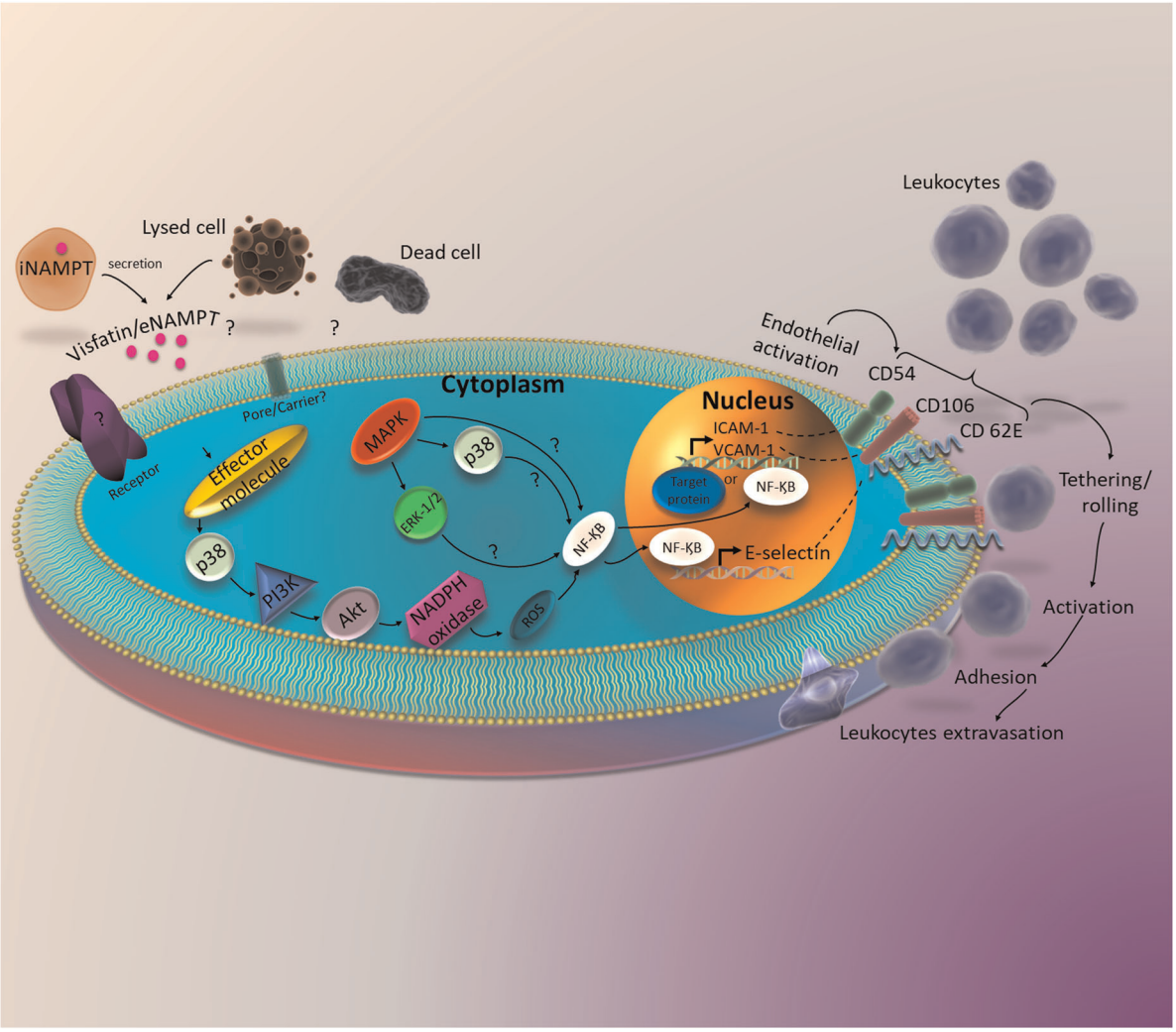

FIGURE 4 Major signaling pathways involved in visfatin-induced adhesion during inflammatory diseases. Visfatin induces NF-κB activation via p38-PI3K-Akt-ROS dependent pathway. Visfatin also utilizes MAPK/ERK signaling cascade to activate NF-κB. Visfatin induced NF-κB activation upregulates adhesion molecules ICAM-1 (CD54), VCAM-1(CD106), and E-selectin (CD62E). These adhesion molecules facilitate leukocyte binding and extravasation and thereby mediate inflammation. MAPK/ERK, mitogen-activated protein kinase/extracellular signal-regulated kinases; NF-κB, nuclear factor kappa B

VEGF-dependent mechanism (Tsai et al., 2020). Moreover, a direct role for visfatin in arterial remodeling has recently been reported (X. Sun et al., 2020). As such, a missing link between visfatin and cardiovascular disorders, especially atherosclerosis, becomes appealing to dissect. However, this remains to be established.

3.1 | Visfatin and MCP-1

MCP-1, a family member of the C-C motif chemokines, is encoded by a single gene that is conserved in several primates (Yoshimura, Robinson, et al., 1989). It can exert a chemotactic effect on various cell types, including T-lymphocytes ($CD4^+$ and $CD8^+$ cells), monocytes, basophils, and even natural killer cells (Carr et al., 1994; Kuna et al., 1992; Loetscher et al., 1994; Matsushima et al., 1989; Taub et al., 1995; Yoshimura, Yuhki, et al., 1989). Moreover, it can also exert chemotactic activity on human endothelial cells, which expresses C-C chemokine receptor type 2 (CCR2) (Salcedo et al., 2000). Together with this CCR2, MCP-1 mediates angiogenesis (Salcedo et al., 2000), suggesting a possible role for these two proteins in vascular diseases. Indeed, MCP-1 is now considered a major player in early atherosclerotic lesions, monocyte recruitment, vasculogenesis, thrombosis, and many other vascular processes (Charo & Taubman, 2004).

The interplay between MCP-1 and visfatin has been investigated, where indeed a correlation between these proteins was shown to play a role in cardiovascular pathologies particularly by virtue of being proangiogenic (Adya et al., 2009). In this regard, visfatin has been found to induce MCP-1 expression and secretion from endothelial cells (Adya et al., 2009; Han et al., 2020), via PI3K and NF-κB, but not MEK (Adya et al., 2009). In addition, it has been suggested that visfatin stimulates MCP-1 production via the insulin

receptor or through an autocrine/paracrine signaling involving CCR2 (Adya et al., 2009; Liu et al., 2009). Given that MCP-1 promotes vascular remodeling (Singh et al., 2017; Y. Sun et al., 2016), visfatin's contribution to arterial structural changes becomes evident and critical. Indeed, very recent evidence shows that visfatin potentiates the expression of osteopontin, matrix metalloproteinases and collagen, all of which are key contributors to remodeling (Ezzati-Mobaser et al., 2020).

3.2 | Visfatin and VEGF

VEGF, a homodimeric glycoprotein, is a growth factor that regulates vasculogenesis and angiogenesis (Beck & D'Amore, 1997; Drake et al., 2000; Hoeben et al., 2004; Muller et al., 1997). Following endothelial injury, VEGF exerts a vasculoprotective action by promoting endothelial regeneration and reducing neointimal formation (Baumgartner & Isner, 2001). On the other hand, several studies have demonstrated pro-inflammatory and arteriosclerotic effects of VEGF. In this regard, it has been shown that VEGF promotes the migration and activation of monocytes (Barleon et al., 1996; Marumo et al., 1999) and boosts neointimal formation by stimulating intraplaque angiogenesis (Moulton et al., 1999).

Literature shows that visfatin augments gene expression and protein production of VEGF (Adya et al., 2007; Astern et al., 2013; Dambala et al., 2017; Park et al., 2011). This visfatin-induced VEGF expression has also been documented in other types of cells (B. C. Lee et al., 2018). The mechanism for this induced upregulation of VEGF appears to be mediated by the MAPK and PI3K/Akt pathways (Adya et al., 2007). Taken together, these findings suggest a role for visfatin in angiogenesis and vascular remodeling, which is likely potentiated via VEGF production (Figure 5).

3.3 | Visfatin and fibroblast growth factor-2

Fibroblast growth factor-2 (FGF-2) is a potent angiogenic factor that interferes with various cellular processes including cell division, differentiation, migration, as well as other vascular processes, such as vascularization and tissue repair (Nugent & Iozzo, 2000; Presta et al., 2005; Yun et al., 2010; Zittermann & Issekutz, 2006). Interestingly, FGF-2 is also implicated in the development of atherosclerotic lesions by triggering vascular smooth muscle cell proliferation and migration to the intima (Barillari et al., 2010). In addition, its role in angiogenesis is well-established (T. Jia et al., 2020; Pallotta & Nickel, 2020).

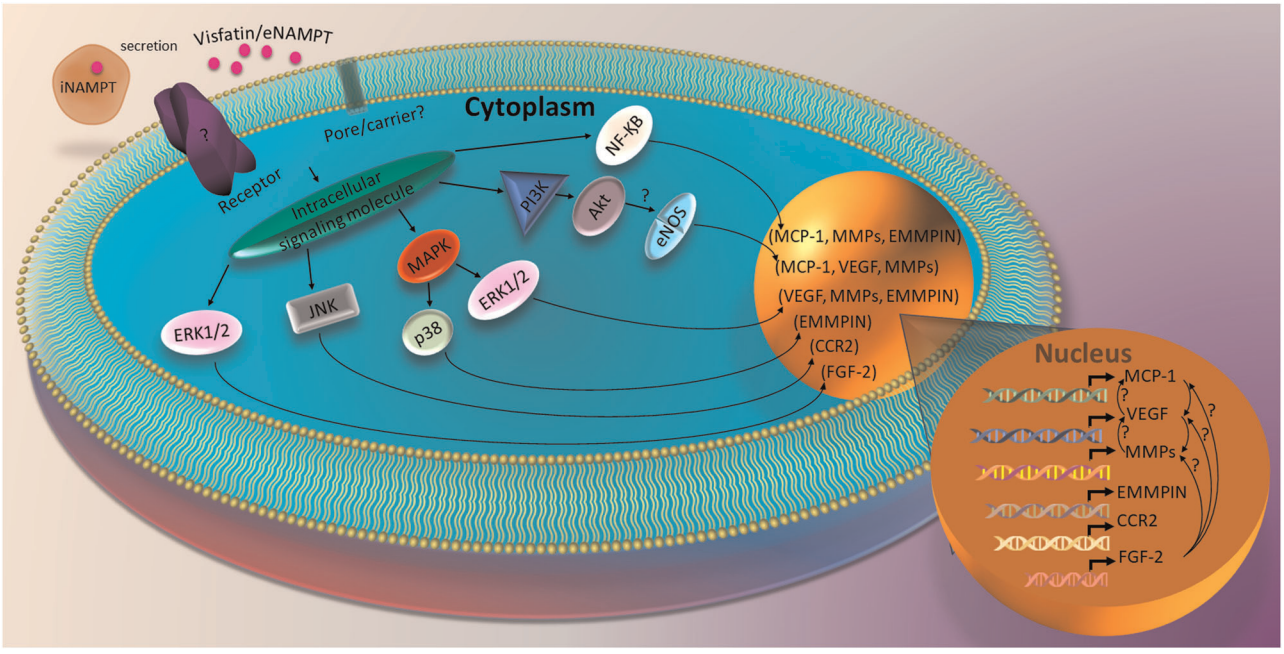

FIGURE 5 Various signaling pathways involved in visfatin-induced vascular remodeling. Visfatin/NAMPT upregulates monocyte chemoattractant protein 1 (MCP-1), vascular endothelial growth factor (VEGF), matrix metalloproteinases (MMPs), extracellular MMP inducer (EMMPIN), C-C *chemokine* receptor type 2 (CCR2), and fibroblast growth factor 2 (FGF-2) which are key players in vascular remodeling. Visfatin induced NF-κB activation upregulates MCP-1, MMPs, and EMMPIN. Visfatin also activates endothelial nitric oxide synthase (eNOS) via PI3K/Akt dependent pathway to upregulate VEGF expression. Visfatin was shown to upregulate VEGF and MMPs via MAPK/ERK signaling pathway. Visfatin can induce EMMPIN through MAPK (p38, ERK1/2)-NF-κB signaling pathway. ERK 1/2 and JNK were found to be involved in visfatin induced FGF-2 and CCR2 respectively. The relation between visfatin, MCP-1, VEGF, MMPs seem to be a bidirectional relation. MCP-1 can upregulate VEGF which can upregulate MMPs expression. Conversely, VEGF can induce MCP-1 expression. In addition, EMMPIN is also an inducer for MMPs. A relation between FGF-2 and several angiogenic factors also exists

Whether visfatin and FGF-2 interact to regulate angiogenesis is only beginning to be understood. In this context, visfatin has been shown to increase the levels of FGF-2 mRNA and protein, eventually leading to endothelial angiogenesis (Bae et al., 2009, 2010; Yuan et al., 2010). The involvement of visfatin and FGF-2 in angiogenesis has been suggested to be a two-step mechanism, with extracellular signal-regulated kinases (ERK)1/2 being a key mediator (Bae et al., 2009) (Figure 5). Taken together, by upregulating FGF-2, one can speculate on the role of visfatin in promoting angiogenesis and other aspects of CVD.

3.4 | Visfatin and MMPs

Vascular remodeling involves degradation and reorganization of the extracellular matrix (ECM) and the proteins therein. Several proteases are involved in these processes. Interestingly, visfatin increases the production of many of these enzymes such as MMP-2, 9,1, and 13 (Adya et al., 2007; Cheleschi et al., 2019; Moses, 1997). Importantly, these MMPs regulate cell proliferation, differentiation, migration, and even cell death (Sternlicht & Werb, 2001). They can also modify epithelial tissue architecture owing to their ability to degrade intercellular junctions and basement membrane (Sternlicht & Werb, 2001). In view of this, MMPs are major contributors to many long-term physiological and pathological remodeling processes underlying inflammation, embryogenesis, growth, cancer metastasis, fibrosis, and body responses to injury (Egeblad & Werb, 2002; Galis et al., 1994; Matrisian, 1992; Mun-Bryce & Rosenberg, 1998; Page-McCaw et al., 2007; Trojanek et al., 2019; W. Wang et al., 2002; Woessner, 1991). Moreover, MMPs have been implicated in coronary artery diseases (Galis et al., 1994), hypertension (Trojanek et al., 2019), dilated cardiomyopathy, and myocardial infarction (Creemers Esther et al., 2001). The increase of a particular species of MMPs, known as gelatinases (MMP-2 and MMP-9), has been also observed in patients with acute coronary syndromes (Kai et al., 1998). Furthermore, overexpression of activated MMPs in atherosclerotic plaques contributes to the destabilization of human atheroma, which may ultimately lead to stroke or myocardial infarction (Galis et al., 1994).

A role for visfatin in modulating MMP levels and activities is emerging. Indeed, visfatin induces MMP-9 in many cells including monocytes and peripheral blood mononuclear cells (PBMCs) (Dahl et al., 2007; Dambala et al., 2017). The ability of visfatin to induce several MMPs have also been reported by many other studies (Adya et al., 2007, 2008; Brentano et al., 2007; Dahl et al., 2007; Y. Fan et al., 2011; B. Li et al., 2016; Nokhbehsaim et al., 2013; G. Wang et al., 2016). Mechanistically, the PI3K/Akt (Adya et al., 2007) and the NF-κB (Adya et al., 2008) pathways appear to mediate visfatin's role in increasing the expression and gelatinolytic activity of MMP-2/9. Given that visfatin promotes angiogenesis via increasing eNOS, a downstream effector of the PI3K/Akt signaling (Lovren et al., 2009), it becomes tempting to propose eNOS as the missing molecular link between PI3K/Akt signaling and its target genes (Figure 5).

Recently, it was shown that visfatin is associated with earlier onset and higher incidence of major adverse cardiovascular events (Zheng et al., 2020). Interestingly, the pro-inflammatory effect of visfatin in atheroma has been attributed to its ability to increase levels and enzymatic activity of MMP-9 and extracellular MMP inducer (EMMPIN) through p38-, ERK1/2- or NF-κB -dependent pathways (Y. Fan et al., 2011). Furthermore, the NF-κB signaling is implicated in the atherogenic effects of visfatin, which upregulates several MMPs (MMP-1,−2,−8, and −9) in macrophages, promotes collagen degradation, and destabilizes plaques (B. Li et al., 2016) (Figure 5). Given that NF-κB is dependent on PI3K/Akt and MAPK pathways (Madrid et al., 2001; Sizemore et al., 1999), it is tempting to speculate that visfatin plays a central role in the initiation, progression and even complications of atherosclerosis by activating NF-κB, a downstream effector of the MAPK and/or PI3K/Akt pathways. However, this remains to be established.

Upregulation of MMP-2 and MMP-9 by visfatin is associated with a concomitant decrease in tissue inhibitors of MMPs (TIMPs), namely TIMP-1 and TIMP-2 (Adya et al., 2007). Hence, visfatin can activate the activators while also repressing the repressors of MMPs. Collectively, these findings suggest that visfatin-induced dysregulation of MMPs may significantly affect ECM metabolism and subsequently evoke events typical of CVD (Figure 5).

3.5 | The intersection of the angiogenic signaling pathways

Several lines of evidence indicate that visfatin-orchestrated vascular remodeling is a multi-operated process involving several intersecting angiogenic signaling pathways (Figure 5). To promote angiogenesis, VEGF requires MMP processing to effectively deliver its signal (Bergers et al., 2000). Although VEGF and its receptor, VEGFR, are constitutively expressed, VEGF levels are limited and not enough for effective signaling (Bergers et al., 2000). MMP-9 processing is required to mobilize VEGF to its receptor, where it can bind and initiate angiogenesis (Bergers et al., 2000). Reciprocally, MMPs are upregulated by VEGF in vascular smooth muscle cells (H. Wang & Keiser, 1998) and human umbilical vein endothelial cells (Adya et al., 2007). Given that VEGF and MMP-2/−9 are implicated as key players in vascular pathology underlying dysfunctional angiogenesis (Deryugina & Quigley, 2015; Ferrara & Davis-Smyth, 1997; Moses, 1997), it is not surprising that their crosstalk partly constitutes their molecular mechanisms underlying vascular remodeling (Figure 5).

The relationship between the trio, visfatin, MMP, and VEGF has been documented in one study. Indeed, visfatin increased the expression of MMP-2, MMP-9, and VEGF in micro- and macro-vascular endothelial cells via the MAPK, PI3K/Akt, and VEGF/VEGF type 2 receptor (VEGFR2) signaling pathway (Adya et al., 2007). Likewise, MCP-1 induces angiogenesis in a two-step mechanism, where MCP-1 induces gene expression of VEGF, which then induces angiogenesis (Hong et al., 2005). Interestingly, the MCP-1-driven upregulation of VEGF contributes to visfatin-induced endothelial angiogenesis, since blockade of MCP-1 attenuated visfatin-evoked production of VEGF (Adya et al., 2009) (Figure 5). Conversely, it has been shown that in retinal microvascular endothelial cells, VEGF induces the expression

of MCP-1, which may promote monocyte migration, neovascularization, and vascular injury (Marumo et al., 1999). Clearly, these findings suggest bidirectional crosstalk between VEGF and MCP-1. However, whether VEGF-induced upregulation of MCP-1 underlies the angiogenic or atherogenic effect of visfatin remains to be elucidated.

On the other hand, unidirectional crosstalk between FGF-2 and different angiogenic factors has been defined. In this context, FGF-2 has been found to induce several MMPs (Im et al., 2007; Lungu et al., 2008; Pickering et al., 1997; Pintucci et al., 2003). Likewise, it has been reported that FGF-2–induced angiogenesis is partly dependent on the stimulation of VEGF expression in endothelial cells and stromal cells (Claffey et al., 2001; Seghezzi et al., 1998). The FGF-2 upregulation of the MCP-1 in the angiogenic process has been also shown in endothelial (Wempe et al., 1997) and vascular smooth muscle cells (Fujii et al., 2006) (Figure 5). Thus, the contribution of these interactions to visfatin-induced angiogenesis and/or atherogenesis is not unlikely and warrants future investigation.

3.6 | Visfatin: A friend or a foe?

Visfatin has been linked to many aspects of diseases affecting the vasculature, including atherosclerotic plaque stability. Whereas some studies reported that visfatin induces plaque destabilization (Dahl et al., 2007; B. Li et al., 2016), others showed that visfatin promotes collagen synthesis (Yu et al., 2010), enhances vascular smooth muscle cell proliferation (Yu et al., 2010) and activates endothelial nitric oxide synthase (eNOS) thus improving endothelial cell function (Lovren et al., 2009). Notably, these actions are known to stabilize the atherosclerotic lesion and to decrease the risk of plaque rupture. Moreover, high levels of visfatin might mitigate inflammation by promoting the production of anti-inflammatory cytokines, such as IL-10 and IL-1Ra (Tilg & Moschen, 2008). Therefore, the exact role of visfatin and its precise effect on the atherosclerotic plaque is still unclear. VEGF and MMP provide some insights to partly explain these mechanisms. For example, MMP may explain visfatin-induced cancer cell migration as well as visfatin-induced plaque destabilization. Similarly, VEGF may explicate the final steps that lead to visfatin-induced angiogenesis. However, the exact and precise mechanisms underlying visfatin's biological effects require further investigation.

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