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Human neutrophil peptides: a novel potential mediator of inflammatory cardiovascular diseases

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¹The Keenan Research Centre in the Li Ka Shing Knowledge Institute of Saint Michael's Hospital; and ²Departments of Anaesthesia and Physiology, ³Cardiovascular Sciences Collaborative Program, ⁴Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, Ontario, Canada

Quinn K, Henriques M, Parker T, Slutsky AS, Zhang H. Human neutrophil peptides: a novel potential mediator of inflammatory cardiovascular diseases. *Am J Physiol Heart Circ Physiol* 295: H1817–H1824, 2008. First published September 19, 2008; doi:10.1152/ajpheart.00472.2008.—The traditional view of atherosclerosis has recently been expanded from a predominantly lipid retentive disease to a coupling of inflammatory mechanisms and dyslipidemia. Studies have suggested a novel role for polymorphonuclear neutrophil (PMN)-dominant inflammation in the development of atherosclerosis. Human neutrophil peptides (HNPs), also known as α -defensins, are secreted and released from PMN granules upon activation and are conventionally involved in microbial killing. Current evidence suggests an important immunomodulative role for these peptides. HNP levels are markedly increased in inflammatory diseases including sepsis and acute coronary syndromes. They have been found within the intima of human atherosclerotic arteries, and their deposition in the skin correlates with the severity of coronary artery diseases. HNPs form complexes with LDL in solution and increase LDL binding to the endothelial surface. HNPs have also been shown to contribute to endothelial dysfunction, lipid metabolism disorder, and the inhibition of fibrinolysis. Given the emerging relationship between PMN-dominant inflammation and atherosclerosis, HNPs may serve as a link between them and as a biological marker and potential therapeutic target in cardiovascular diseases including coronary artery diseases and acute coronary syndromes.

α -defensins; inflammation; cytokine

THE TRADITIONAL VIEW OF ATHEROSCLEROSIS as a predominantly lipid retentive disease has recently been redefined as a coupling of inflammatory mechanisms and dyslipidemia (71), resulting in the formation of pathological lesions in the vasculature. Atherosclerosis is associated with the accumulation of cholesterol deposits in subendothelial macrophage-derived foam cells, adherence and entry of leukocytes into the arterial wall, migration of smooth muscle cells into the intima, activation and aggregation of platelets, activation of T cells, endothelial dysfunction, and the production of inflammatory cytokines (39, 77, 118).

Although the role of monocytes, macrophages, T cells, and platelets is well recognized in the context of atherosclerosis, only recently have emerging studies provided compelling evidence that polymorphonuclear neutrophils (PMNs) have been overlooked in the pathogenesis of cardiovascular diseases (CVDs), including their presence in atherosclerotic plaques (26, 101, 105, 130, 140). Kougias et al. (64) discussed the potential role of human neutrophil peptides (HNPs) in atherosclerosis in a review article in 2005. The present article will expand the discussion to include some novel findings in recent clinical and experimental studies. In particular, we highlight the mechanisms of inflammation with a focus on recent re-

search on PMNs and their contribution to the development of atherosclerosis. Finally, we propose a role for HNPs as a biomarker and potential target molecule for novel therapeutic approaches.

Inflammation and Atherosclerosis

Leukocyte adhesion and transmigration to the vascular wall. The development of atherosclerosis involves leukocyte adhesion and subsequent migration through the vascular endothelium (2). This process includes several interrelated procedures: tethering (capture and rolling), triggering (integrin activation), adhesion, and motility (migration). Adhesion molecules such as P- and E-selectin, β_2 -integrins (CD18/CD11a, CD11b, and CD11c), and vascular and intercellular adhesion molecule-1 (VCAM-1 and ICAM-1, respectively) are involved in mediating this adherence and transmigration (2, 22, 41).

Recent studies (82) have demonstrated that PMN chemotaxis and adhesion to endothelial cells are critical events during inflammation. Moreover, PMNs, platelets, and monocytes adhere to activated endothelial cells and interact with each other through the formation of heterotypic aggregates, resulting in enhanced leukocyte adhesion to the endothelium (139).

PMN counts have been shown to be an independent risk factor and prognostic indicator of future cardiovascular outcomes, regardless of disease status (80). A recent study in over 350,000 patients with atherosclerosis confirms higher relative and absolute acute and chronic mortality rates in patients with

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high versus low PMN counts (21). The presence of activated circulating PMNs in acute coronary syndromes (ACSs) has been documented (84). In patients with acute myocardial infarction, atherectomy specimens with plaque rupture or erosion showed distinct PMN infiltration, and the number of PMNs and neutral endopeptidase-positive PMNs within the pathological lesion was significantly higher in patients with unstable angina pectoris than those with stable angina pectoris (88). Moreover, the PMN count is associated with coronary artery disease (CAD) complexity in patients with ACSs (6) and major adverse cardiovascular events (47).

In patients with chronic stable angina, the PMN count is an independent predictor of the presence of multiple complex stenoses irrespective of the extent of CADs (8, 60). Although both C-reactive protein (CRP) levels and PMN count are higher in angina patients with coronary stenoses compared with those without, the PMN count, but not CRP levels, correlates with angiographic stenosis complexity (8). Furthermore, PMN infiltration of lesions with release of elastase and myeloperoxidase has been implicated in the pathogenesis of atherosclerosis (88).

T cells and costimulatory molecules. In addition to PMNs, T-cell infiltrates are frequently found in atherosclerotic lesions (46). Upon an encounter, T cells upregulate their adhesion receptors and costimulatory molecules including CD40, CD11a/CD18 (lymphocyte function-associated antigen-1), CD28, and CD152/cytotoxic T-lymphocyte-associated antigen-4, which bind their cognate ligands CD80 (B7-1) and CD86 (B7-2) on dendritic and endothelial cells (15, 49). CD4⁺ lymphocytes dominate the infiltrate and are thought to be involved in a T-cell-dependent, autoimmune response to oxidized (ox)LDL (117). CD8⁺ and natural killer T cells have been shown to be present in lesions, and their activation accelerates the atherosclerotic process in mice deficient for apolipoprotein E (*ApoE*^{-/-}) (76, 129), the mouse model most used in genetic and physiological studies of atherosclerosis (124). Taken together, the activation of T cells via atherosclerotic antigen can lead to the production of many downstream inflammatory cascades (117).

Macrophage migration and foam cell formation. A hallmark of atherosclerosis involves monocyte adhesion and subsequent migration through the endothelial wall into tissue (37, 113). Monocytes are initially attracted to lesion-prone sites by inflammatory molecules including monocyte chemoattractant protein-1 (MCP-1); migratory inflammatory protein-1; regulated on activation, normal T cells expressed and secreted; macrophage colony-stimulating factor; granulocyte/macrophage colony-stimulating factor; tumor necrosis factor- α (TNF- α); transforming growth factor- β ; endothelin-1 (ET-1); and others (23, 78, 111, 116, 123, 127, 135, 141). The deficiency of MCP-1 or its receptor chemokine (C-C motif) receptor-2 in *ApoE*^{-/-} mice results in significantly reduced lesions (13, 43).

After migration, monocytes proliferate and differentiate into macrophages (69), accompanied by an increased expression of scavenger receptors A and BI, CD36 and CD68, and scavenger receptors for phosphatidylserine and oxidized lipoprotein (14, 28, 29, 73, 77, 120). The expression of scavenger receptors by macrophages has been shown in specimens of human atherosclerotic arteries (53, 85, 86, 123). These receptors can bind and internalize polyanionic ligands including oxLDL (31, 58, 112, 137), leading to the formation of large (30–60 μ m

diameter) foam cells characterized by a lipid-engorged cytoplasm (24, 37, 73). Increasing numbers of macrophages and foam cells are found in the necrotic core and in adjacent areas shouldering the plaque (77, 118). These foam cells function to secrete cytokines, chemokines, growth factors, metalloproteinases, and other hydrolytic enzymes upon antigen encounter (72, 97) and facilitate plaque destabilization and rupture (118, 123).

Reactive oxygen species. Many cell types including PMN, monocytes, and endothelial cells can generate a range of reactive oxygen species (ROS) in response to activation (45, 91). An overproduction of reducing equivalents such as NAD(P)H may result in increased redox cycling of substances that can undergo repetitive rounds of oxidation/reduction, ultimately leading to the increased generation of superoxide anion radical (O_2^-). Superoxide then spontaneously dismutates to hydrogen peroxide (H_2O_2) (30). ROS have been implicated in promoting inflammation (118) and vascular smooth muscle cell proliferation leading to enhanced atherosclerotic lesion development.

ROS are responsible for oxidation of LDL, contributing to the development of atherosclerosis (5). oxLDL in turn activates endothelial cells, resulting in the production of adhesion molecules and chemokines (68, 112, 118), which along with oxLDL itself, can chemoattract monocytes and T cells (83, 96).

Coagulation. Plasma fibrinogen levels in humans have been shown to be an independent risk factor for myocardial infarction associated with enhanced thrombosis and fibrin deposition in atherosclerotic lesions (12, 108, 136). Intravascular clearance of fibrin is predominantly mediated by plasmin, which is formed through the cleavage of its inactive precursor plasminogen by endogenous activators such as tissue type plasminogen activator (tPA).

Plasminogen activator inhibitor-1, an inhibitor of tPA, has been identified as a risk factor for myocardial infarction in humans (136) and is abundantly expressed in the tissue of patients with atherosclerosis (114). However, some studies suggest that plasminogen activator inhibitor-1 can be present in a latent or inactive form such that fibrinolysis may still occur (104).

Human Neutrophil Peptides

Role in innate and acquired immunity. HNPs are a family of small cationic antimicrobial peptides, containing six cysteines that form three intramolecular disulfide bonds (34, 36). HNP-1, -2, -3, and -4, also known as α -defensins, are stored in PMN azurophilic granules and comprise up to 50% of the protein content in primary granules and 5% of the total protein content in PMNs (36, 109). HNPs play an important role in innate immunity for host defense. HNPs can be released into the extracellular milieu following PMN activation as a consequence of degranulation, leakage, cell death, and lysis during inflammation (35).

It is noteworthy that although HNPs were long considered to be stored in only PMNs, it has been recently reported that monocytes, macrophages, natural killer cells, B cells, T cells, and immature dendritic cells also express HNPs (62, 63, 79, 99). Thus HNPs could also be released during inflammatory responses acting as a host component in acquired immunity (62, 63, 79, 99).

HNP levels in inflammatory diseases. Normal plasma levels of HNPs range from undetectable to 50–100 ng/ml. At the onset of bacterial infection and during nonbacterial infection, mean HNP levels are 2–4-fold greater than in healthy volunteers (57). HNP levels in the plasma of patients with sepsis range 900–170,000 ng/ml compared with a mean of 42 ± 53 ng/ml in the plasma of healthy controls (94). An excellent correlation was found between the concentration of HNP and the number of PMNs in the blood of patients with inflammatory diseases (57). The elevated levels of HNPs in inflammatory diseases suggest that HNPs play a critical role in the leukocyte-dominant proinflammatory responses that may contribute to cardiovascular disorders (9, 51, 65, 89, 94).

Localization of HNPs in atherosclerotic lesions. HNPs released from activated PMNs in the circulation may reflect the acute inflammatory phase, whereas tissue deposition of HNPs as a biomarker may indicate its accumulative inflammatory contribution to atherosclerosis as a “footprint” of PMNs.

Indeed, it has been shown that HNPs are abundant in and around intimal and medial smooth muscle cells within human atherosclerotic carotid and coronary arteries (9, 51). HNPs were found in lesions in which intimal thickening was minimal, suggesting that HNP deposition occurs early in the disease process (9, 51). Furthermore, a significant correlation was revealed between HNP skin deposition and the severity of CADs as evaluated by the number of blood vessels associated with focal lesions and stenosis (89).

Most recently, Zerneck et al. (140) demonstrated PMN infiltration in chronically inflamed arteries, and the crucial role of PMN contributing to atherogenesis was evidenced by a reduced atherosclerotic burden when PMNs were depleted in *ApoE*^{−/−} mice.

Interestingly, murine PMNs lack HNPs (27), which raises the question regarding the importance of HNPs in the atherosclerotic pathology observed in *ApoE*^{−/−} mice (143). The model of *ApoE*^{−/−} mice is an important tool to study the mechanisms by which LDL, as a sole mediator, induces atherosclerosis. However, the overall inflammatory feature seen in clinical conditions was missing in the *ApoE*^{−/−} mice. We believe that both the inflammatory responses mediated by HNPs and the direct effects of LDL in the pathogenesis of CVDs are equally important.

HNPs induce adhesion and expression of costimulatory molecules. An increase in surface expression of CD80, CD86, and ICAM-1 on human primary small airway epithelial cells and alveolar type II-like A549 cells and the corresponding major ligands (CD28, CD152, and CD11a/CD18) on CD4⁺ lymphocytes has been demonstrated in response to the stimulation with HNPs (134). Consequently, HNPs increase lymphocyte adhesion to the epithelial cells (134). These findings observed in acute lung injury have yet to be demonstrated in the settings of atherosclerosis, although the general inflammatory responses appear to be similar in the two pathophysiological conditions.

Importantly, human pulmonary artery endothelial cells and human umbilical vein endothelial cells (HUVECs) stimulated with HNPs show a significant increase in adhesion to either primary human PMNs or the monocytic cell line U-937 (unpublished data), suggesting that similar mechanisms of cell interaction as observed in epithelial cells may be applied to endothelial cells.

HNP chemoattract immune cells. HNPs are directly chemotactic for mast cells, macrophages, immature dendritic cells, and T cells (42, 138). HNP-1 and -2 chemoattract CD3⁺ T cells (20) and monocytes (128). Grigat et al. (42) found that HNP-1 and -3 recruit human monocyte- and murine bone marrow-derived macrophages. We observed that the incubation of mouse lung explants with HNPs results in the production of the CC chemokine MCP-1 (142), also known as chemokine (C-C motif) ligand-2, a potent chemoattractant for monocytes, memory T cells, and basophils (17).

IL-8 is a pivotal inflammatory chemokine that functions as an immune cell chemoattractant and activating factor (59). High concentrations of HNPs are associated with increased levels of IL-8 in the plasma of patients with a variety of inflammatory diseases (1, 4, 57). The stimulation of human lung alveolar epithelium, primary bronchial epithelial cells, and monocytes with HNPs results in the production of IL-8 (16, 61, 103, 121, 132–134), which is associated with an upregulation of IL-8 mRNA (132). Furthermore, we have recently demonstrated the ability of HNPs to induce the production of ET-1 in HUVECs (122). Since ET-1 can induce IL-8 and MCP-1 production from endothelial cells (19, 54), HNPs may be indirectly chemoattracting leukocytes through this mechanism.

HNPs promote oxidative stress. HNPs have been shown to induce endothelial dysfunction by reducing endothelium-dependent relaxation and increasing endothelial production of O₂[−] levels in porcine coronary arteries (65). In addition, our laboratory has demonstrated that HNP stimulation results in an increased release of H₂O₂ in murine lung explants (95) and nitrotyrosine in HUVECs (122), a by-product of nitrosative stress.

HNPs inhibit fibrinolysis. HNPs bind fibrin and plasminogen and promote the binding of plasminogen to fibrin and endothelial cells in ex vivo culture conditions (50, 64). HNPs also inhibit tPA- and plasminogen-mediated fibrinolysis in a dose-dependent manner (50), perhaps through the direct interaction between HNPs and tPA (64). The inhibition of fibrinolysis, and hence increased fibrin deposition, mediates the formation of thrombi within the lumen and the development of atherosclerotic lesions (98).

HNPs block angiogenesis. HNPs prevent capillary tube formation and angiogenesis (18, 64). The inhibition of angiogenesis by HNPs may extend to several pathophysiological processes including the impaired development of a functional vasa vasorum, a defect that is associated with the development of CADs (9, 64).

HNPs as an adjuvant. Tani et al. (125) demonstrated the ability of HNPs to recruit antigen-presenting dendritic and T cells and to upregulate antigen-specific Ig production in vivo. This suggests a role for HNPs as an adjuvant through the induction of antigen-specific cellular and humoral immune responses.

HNPs exhibit cytotoxic effects. High concentrations of HNPs have been shown to exhibit significant in vitro cytotoxic damage in different cell types including HUVECs, epithelial cells, and cancer cells (92, 131). HNP-mediated cytotoxicity is concentration dependent and requires prolonged incubation times of at least 10–12 h.

HNPs and Cardiovascular Diseases

Inflammation and HNPs in CVDs. It is intriguing that following resuscitation, patients with cardiac arrest acquire a "sepsis-like" syndrome associated with leukocyte-driven immunologic disorders (3). Sepsis-like syndrome is characterized by elevated levels of soluble ICAM-1, VCAM-1, P- and E-selectin (32, 33), and circulating cytokines including TNF- α and IL-8 (66). Furthermore, myocardial infarction secondary to ACSs leads to inflammatory activation, which amplifies the cardiogenic shock syndrome by releasing several cytokines including IL-6, IL-8, and TNF- α , among others (40). High concentrations of IL-6 in patients with cardiogenic shock are an independent predictor of mortality (40).

Although there is no data regarding HNP levels in the circulation of patients with resuscitated cardiac arrest, we recently observed that patients with ACSs, similar to those with sepsis (94), had a dramatic increase in the plasma concentration of HNPs compared with healthy controls (unpublished data). A larger sample size is required to confirm these findings.

Possible mechanisms of action by HNPs in relation to cardiovascular diseases. HNPs form stable, multivalent complexes with LDL (10, 52) both in solution and on cell surfaces (51, 52) and stimulate the binding of 125 I-labeled LDL to HUVECs, smooth muscle cells, and fibroblasts in a dose-dependent and saturable manner (52). It has been proposed that HNP-LDL complexes bind to heparin sulfate-containing proteoglycans (HSPG) (52).

The LDL receptor-related protein (LRP)/ α -2 macroglobulin receptor is a membrane protein of the LDL receptor (LDLR) superfamily (106) that is involved in atherogenesis (11, 55, 67, 70, 87, 119). An increased expression of LRP has been demonstrated in vascular smooth muscle cells isolated from human atherosclerotic lesions (74). LRP1 gene expression is also increased in blood mononuclear cells from patients with myocardial infarction (74, 107). Nassar et al. (90) demonstrated that HNPs directly bind LRP both in solution and on the surface of smooth muscle cells. The overall structure of HNPs, with a hydrophobic and cationic face, generally resembles many apolipoproteins that bind to LDLR family members and proteoglycans (52). Hence, the ability of HNPs to modulate the catabolism of LDL may occur through similar mechanisms (52). However, since many molecules (i.e., ApoE, thrombospondin, protein C, tPA, thrombin, and others) are also ligands of LRP, the biological consequences of HNP and LRP bindings remain to be investigated in the pathogenesis of atherosclerosis (100, 106).

Purinergic P₂ receptors, including the P2X and P2Y families, are functional ligands of extracellular nucleotides that mediate intracellular signal transduction. We have demonstrated that the pyrimidinergic receptor P2Y₆, a seven-transmembrane G protein-coupled UDP receptor, mediates HNP-induced inflammation through the production of IL-8 (61). Recently, it has been suggested that the P2Y receptor family may mediate the development of atherosclerosis (25, 48, 110), thus the functional significance of HNP and the P2Y family in the context of atherosclerosis remain to be investigated (Fig. 1).

LDL retention by HNPs. Because the HNP-LDL complex binds to HSPG (52), the diversion of LDL binding away from the LDLR pathway to the HSPG pathway by HNPs may slow

Fig. 1. Proposed mechanisms of action of human neutrophil peptides (HNPs) in atherosclerosis. Proposed (dashed line) or published (solid line) action of HNP interaction with cells: 1) purinergic P2Y (P2Y₆; Ref. 61); 2) LDL receptor-related protein (LRP; Ref. 90); 3) Zhang et al. (unpublished); and 4) LDL receptor (LDL-R; Ref. 52). ROS, reactive oxygen species; RNS, reactive nitrogen species.

the degradation of the lipoprotein (52) and subject it to oxidation and other modifications (52, 64). Correspondingly, there is an inverse relationship between circulating HNP levels and total and LDL-cholesterol (75), suggesting an increased deposition of LDL within the vasculature as a consequence of interactions with HNPs (75).

HNP was also found to bind Lp(a) lipoprotein [Lp(a)] (10, 51) and cause an increase in the amount of Lp(a) internalized by endothelial and smooth muscle cells but did not result in Lp(a) degradation (51). This mechanism results in a marked increase in the total amount of cell-associated lipoprotein (51), which predisposes atherosclerosis.

Taken together, these studies suggest that HNPs may alter LDL metabolism that modulates the course of atherosclerosis.

Neutralization of HNPs. A failure of serum levels of α_1 -antitrypsin (α_1 -AT) to rise during the acute phase of myocardial infarction is associated with a poor clinical outcome including cardiogenic shock and mortality (38). Thus α_1 -AT deficiency is considered to be an important pathogenic factor responsible for the development of atherosclerosis (115). Importantly, α_1 -AT can neutralize HNPs as an endogenous inhibitor (56, 90). Excessive levels of HNPs may devastate a biological balance between α_1 -ATs, resulting in uncontrolled inflammation, promoting the proteolytic activity of serine proteases (93) and contributing to plaque rupture. The effect of HNP neutralization by the administration of exogenous α_1 -AT remains to be examined in cardiovascular diseases including atherosclerosis.

Significance. There is an emerging role for PMNs in the pathogenesis of atherosclerosis (6, 8, 21, 26, 44, 47, 60, 80, 81, 84, 88, 101, 102, 126, 130, 140). It is evident that HNPs released from PMNs modulate inflammatory responses and LDL metabolism and, as such, could serve as a viable biomarker for the development of atherosclerosis. HNP, as a potential risk factor or precipitator of CVDs, has yet to be confirmed. A proposed therapeutic testing includes the blocking of HNP ligands and the neutralization of HNPs. These novel therapeutic strategies would require further investigation in vivo before being introduced into clinical trials.

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