Minireview

Secretory leukocyte protease inhibitor promising protective roles in obesity-associated atherosclerosis

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Abstract

Secretory leukocyte protease inhibitor (SLPI), a serine protease inhibitor, which was most commonly examined in mucosal fluids such as saliva, is a versatile molecule and plays non-redundant roles. In addition to its anti-protease activity, SLPI has been shown to express anti-bacterial, anti-viral, anti-fungal, and anti-inflammatory properties as well as participating in innate and adaptive immune responses, most of which has been well documented. Recently, it is reported that SLPI is expressed in adipocytes and adipose tissue where it could play an important feedback role in the resolution of inflammation. Furthermore, circulating SLPI has been shown to correlate with progressive metabolic dysfunction. Moreover, adenoviral gene delivery of elafin and SLPI attenuates nuclear factor-κB-dependent inflammatory responses of human endothelial cells and macrophages to atherogenic stimuli. This review contributes to unraveling the protective role of SLPI in obesity-related atherosclerosis development, and the potential role in preventing arterial plaque rupture.

Keywords: Secretory leukocyte protease inhibitor, obesity, atherosclerosis, inflammation, adipokine, adipose tissue inflammation

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Introduction

Secretory leukocyte protease inhibitor (SLPI), comprised of 107 amino acids with a low molecular weight (11.7 kDa), is a non-glycosylated, cationic protein due to its abundant arginine and lysine residues. As to its molecule structure, SLPI is composed of two different whey acid protein domains, and the anti-protease activity is situated in a single amino acid—leucine 72 within the C-terminal domain. SLPI is a serine protease inhibitor, serving to control the excess release of host-secreted proteases according to injurious effects. The protease inhibitors can be divided into two groups: 'systemic' inhibitors and 'alarm' inhibitors. 'Systemic' inhibitors are synthesized principally in the liver and include α1-proteinase inhibitor and antichymotrypsin. In contrast, the 'alarm' inhibitors include the two low-molecular-mass proteinase inhibitors of the anti-leukoprotease family—SLPI and elafin[1]—which were synthesized and secreted locally at the site of injury and are produced in response to primary cytokines such as interleukin (IL)-1β and tumor necrosis factor (TNF).

SLPI was first found to be an inhibitor of a large number of serine proteases mainly including trypsin, chymotrypsin, elastase, and cathepsin G. Later, researchers also found that SLPI is a pleiotropic molecule. Sallenave[1] discovered that SLPI could be synthesized *in vitro* by tracheal, bronchial, bronchiolar and type II alveolar cells, and by monocytes, alveolar macrophages and neutrophils, where its anti-bacterial and anti-inflammatory properties have been well proposed. In acetaminophen-induced acute liver failure (AALF), the concentration of SLPI was found to be elevated in liver tissue and plasma. Immunohistochemistry revealed SLPI expression in areas of necrosis in biliary epithelial cells and hepatic macrophages (H-mψ), in which SLPI participates in regulating the anti-inflammatory phenotype and functional characteristics of H-mψ and circulating monocytes.[2] In addition, a report clarified that SLPI was expressed in myelocytes, acting as a new-candidate myelopoiesis regulatory factor, where SLPI plays an important role in promoting the proliferation, differentiation, and cell cycle of myeloid cells by regulating intracellular signaling.[3] Additionally, it has been noted that SLPI is strongly

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upregulated in response to cerebral ischemia and that SLPI has a neuroprotective function that is likely related to its inflammation-suppressing ability.[4] Moreover, a recent study reported that SLPI is also expressed in adipose tissue and may play an anti-inflammatory role in adipocytes.[5] Immunohistochemical studies on autopsy samples of human coronary arteries revealed elevated expression of elafin in SMCs, endothelium cells and extracellular matrix (ECM) in atherosclerotic coronary arteries, which may correlate to the stability of atherosclerotic plaques.[6] Moreover, adenoviral gene delivery of elafin and SLPI attenuates nuclear factor-κB (NF-κB)-dependent inflammatory responses of human endothelial cells and macrophages in response to atherogenic stimuli.

As is known, atherosclerosis is a chronic inflammatory disease characterized by lipid-containing inflammatory lesions of large and medium-sized arteries, which is a progressive process starting with accumulation of lipids, lipoproteins, and immune cells in the arterial wall.[7] The properties of lipids play a critical role in the progression of atherosclerosis. Meanwhile, mechanisms of inflammation and the innate immune response are involved in the early stage development of atherosclerotic lesions.[7] TNF-α, secreted by certain immune cells and tissue cells, is one of the most important pro-inflammatory cytokines involved in the formation and progression of atherosclerosis. Researchers have clarified that SLPI can reduce the systemic and local expression of inflammatory cytokines, including TNF-α. Furthermore, growing evidence suggests that there is a negative correlation between SLPI and risk factors of atherosclerosis, such as obesity and inflammation.[5,7–10] Thus, because SLPI plays a significant role in the pathological mechanism from obesity to atherosclerosis, we discuss what is currently known about SLPI, focusing on its anti-inflammation role, antioxidative properties, and the potential role in preventing arterial plaque rupture.

Anti-inflammatory role of SLPI in obesity-associated atherosclerosis

Obesity-induced systemic and adipose tissue inflammation leading to atherosclerosis

Obesity is a well-known risk factor for atherosclerosis, which accelerates atherosclerosis disease progression through a variety of mechanisms including abnormal lipid profiles, systemic inflammation, and increased blood pressure and blood glucose levels.[8] In 1993, Hotamisligil and colleagues first described elevated local and systemic levels of the cytokine TNF-α following diet-induced obesity in rodents, which was recognized as a chronic low grade inflammatory condition. Since then, obesity has been linked with elevations in numerous other inflammatory molecules such as C-reactive protein, plasminogen activator inhibitor-1, serum amyloid A, migration inhibitory factor, resistin, inducible nitric oxide synthase (iNOS), IL-6, colony stimulating factor 1 (CSF1), and monocyte chemoattractant protein-1 (MCP-1).[11–13]

Obesity-induced chronic low-grade inflammation primarily originating from adipose tissue has been shown to play a crucial role in the development of obesity-related diseases.[12,14] In particular, excessive visceral adipose tissue accumulation is responsible for adipocyte dysfunction and associated metabolic disorders.[15] The key role of obesity in the development of coronary artery disease (CAD) and metabolic syndrome (MS) might be partly attributed to the overproduction of pro-inflammatory molecules (adipokines) within perivascular adipose tissue (PVAT).[15] White adipose tissue is distributed in both subcutaneous and internal organs, the latter is at a higher risk of obesity-related metabolic diseases, which can in turn increase adipose tissue mass in the abdominal region.[16]

Historically, the major function of adipose tissue was often thought to be surplus energy storage; however, adipose tissue is now widely recognized as an independent and active endocrine organ capable of releasing pro- or anti-inflammatory bioactive molecules named adipokines. Adipokines, such as leptin, TNF-α, resistin, and adiponectin, significantly affect obesity-related metabolic diseases by controlling fat metabolism, energy homeostasis, and insulin sensitivity.[17] TNF-α is over-expressed in obese animal and humans subjects as compared to their respective lean counterparts. TNF-α expression is correlated with waist-to-hip size ratio rather than with body mass index (BMI), suggesting a role of abdominal adipose tissue in the expression of this adipocytokine. The contribution of TNF-α to endothelial dysfunction has been highlighted in obese and T2DM mice.[18] Moreau *et al*. also documented that TNF-α contributes to impaired endothelial-dependent vasodilation and arterial stiffening in estrogen-deficient postmenopausal women, which increased the risk of developing atherosclerosis.[19] TNF-α-mediated endothelial dysfunction may also be associated with Nox4-dependent oxidative stress and inflammation.[20] Moreover, there is evidence that TNF-α can directly stimulate the transformation of reduced low-density lipoprotein (LDL) to oxidized LDL (ox-LDL). Release of pro-inflammatory cytokines led to increased uptake and accumulation of oxLDL and minimally modified LDL in aortic macrophages. Macrophages then present atherogenic antigens against oxLDL or apolipoprotein (apo) B to CD4+ T cells, which in turn results in chemo-attraction of leukocytes, T-cell proliferation, and production of TNF-α and interferon-γ (IFN-γ).[21] Another effect of TNF-α is an increase in monocyte activation and cytokine release.[22] Meanwhile, Chandrasekharan *et al*. clarified that both receptors of TNF-α (TNFR1 and TNFR2) seem to mediate synthesis of adhesion molecules, yet TNFR2 appears to have a greater role in production of E-selectin and intercellular adhesion molecule-1 (ICAM-1).[23] It was demonstrated that: (1) hypertrophic adipocytes could secrete low levels of TNF-α; (2) TNF-α stimulated pre-adipocytes and endothelial cells to produce MCP-1; (3) MCP-1 was in turn responsible for attracting macrophages to the adipose tissue, thus favoring a state of chronic low-grade inflammation.[24] Another report verified that the adhesion molecules and MCP-1 mediated inflammatory cell recruitment into the sub-endothelial space, favoring the progression of atherosclerosis plaques.[25] Furthermore, Maria Giovanna Scioli *et al*. demonstrate that the specific inhibition of Nox4 prevents oxidative stress-induced ICAM-1 and vascular cell adhesion molecule-1 (VCAM-1) expression as well as

MCP-1 and IL-8 secretion in response to serum deprivation and TNF-α stimulation.[20] Various adipokines have been reported to directly modulate the atherogenic environment of the blood vessel wall by regulating the function of endothelial, arterial smooth muscle, and macrophage cells.[26] The novel role of adipokines in the link between obesity and atherosclerosis is well-documented in Yoo and Choi's review.[8]

Digestion of lipids results in the production of free fatty acids (FFA), which can then either be oxidized or stored in adipocytes as energy-rich molecules in the form of triglycerides.[27] When FFA or triglycerides are produced in excess, they are converted into fatty acid intermediates, which can then activate pro-inflammatory serine-kinases such as protein kinase C (PKC), IkappaB kinase (IKK), and c-Jun N-terminal kinase (JNK), inhibiting insulin receptor signaling by serine phosphorylation of insulin receptor substrates.[24] Moreover, there is evidence that the high-fat diet response was similar to the low-dose lipopolysaccharide (LPS) infusion response. Saturated fatty acids are reported to be capable of binding and activating toll-like receptor 4 (TLR4)–NF-κB pathway in pre-adipocyte cell line and human adipocytes.[28] In contrast, loss of function mutations in TLR4 attenuate circulating inflammatory cytokines in high fat fed animals.[29] NF-κB not only plays a central role in the development of inflammation via regulating the expression of the genes encoding pro-inflammatory cytokines such as active NF-κB,[30] but also induces transcription of cell adhesion molecules such as ICAM-1, VCAM-1, and E-selectin, as well as several chemokines and cytokines including MCP-1, macrophage-CSF (M-CSF), granulocyte-macrophage-CSF (GM-CSF), IL-1β, IL-6, IL-8, and TNF-α.[31]

SLPI, anti-inflammation effects in the bridge between obesity and atherosclerosis

Obesity as a chronic inflammatory state may be associated with SLPI. Abel López-Bermejo *et al*.[32] find that circulating SLPI increases with progressive metabolic dysfunction, which is a chronic low-grade inflammatory status. In these studied subjects, circulating SLPI was significantly correlated with age, BMI, pulse pressure, high-density lipoprotein-cholesterol, triacylglycerol, HbA1c, neutrophil and monocyte counts, and soluble tumor necrosis factor receptor-2. In contrast, SLPI was unrelated to inflammatory markers in subjects without metabolic dysfunction, who do not exhibit the aforementioned chronic low-grade inflammation state. There is evidence that sustained activation of the anti-inflammatory response is thought to be mounted as an attempt to counterbalance the pro-inflammatory state.[33] In MS, an interpretation could be that SLPI is upregulated to counterbalance the increase in inflammatory factors that characterizes this condition.[32]

Adapala *et al*.[5] demonstrated—for the first time—that SLPI is upregulated in adipose tissue in obesity. Higher expression of SLPI was observed in epididymal and mesenteric depots compared to the subcutaneous depot, and in the stromal vascular faction compared to adipocytes. Meanwhile, high fat feeding increased TNF-α mRNA in adipose tissue of mice. Higher expression of TNF-α was observed in epididymal and mesenteric depots compared to the subcutaneous depot, and in the stromal vascular faction compared to adipocytes. The increase in SLPI expression in adipose tissue in diet-induced obesity suggests that SLPI may play a role to antagonize inflammation in adipose tissue. The higher expression of SLPI in the stromal vascular fraction correlates well with the elevated expression of TNF-α. This suggests that SLPI expression is induced in proportion to the degree of inflammation and agrees with a role for SLPI in dampening the inflammatory state. It also indicates that immune cells such as macrophages, which make up the bulk of the stromal vascular fraction, may be the major source of adipose tissue SLPI. The endogenous mechanisms that trigger adipose tissue inflammation are less well studied, but there is evidence that innate pattern recognition receptors such as TLR2 and TLR4 may be involved in this process.[34,35]

Moreover, in macrophages as well as in adipocytes the activated TLR2 and TLR4 could elevate the expression of SLPI. TLR2 and TLR4 are activated in adipose tissue in obesity;[34,35] the induction of SLPI in adipose tissue during obesity may be influenced by the activated state of the TLRs. Likewise, the anti-inflammatory action of SLPI may involve stabilization of IKBα abundance. It was demonstrated that obesity accompanied by increased expression of SLPI in adipose tissue may act to suppress local inflammation.[5] Nigel Hoggard *et al*.[36] demonstrated that SLPI are expressed much higher in omental adipose tissue relative to subcutaneous adipose tissue in both mRNA and protein level. As previous mentioned, the adipose tissue mass in the abdominal region is at a higher risk of obesity-related metabolic diseases.[16] This is in agreeance with numerous studies that show a correlation between obesity and a chronic, mild inflammatory response, reflecting an increase in the circulating levels of several inflammatory markers such as IL-6 and TNF-α in the obese state.[12] Sustained inflammation leading to endothelial dysfunction represents an early step of the atherogenetic process.[37,38] Given its anti-inflammatory role, the elevated SLPI in omental adipose tissue may keep up with the anti-inflammatory demands of the body in situations characterized by chronic stress such as MS.[32] Mayu Fujiwara *et al*. indicated that lung injury and oxidative stress could be attenuated by a reduction in SLPI-dependent and LPS-induced pro-inflammatory expression of TNF-α, MIP-2, and iNOS expression, in addition to reduced 8-OHdG immunostaining in the lung tissue and bronchoalveolar lavage fluid (BALF).[39] Meanwhile, SLPI was reported to increase the expression of IκBα, which could inhibit NF-κB.[9] Considering the pro-inflammatory gene targets of NF-κB, many up-stream signaling elements leading to NF-κB activation have been identified to be atherogenic.[31]

Accordingly, it is demonstrated that SLPI may play an indirect, yet critical role in suppressing inflammation in obesity. The inflammatory suppression role of SLPI works either through counteracting the effect of inflammatory factors such as TNF-α, or by preventing activation of the inflammatory transcription factor NF-κB, which may

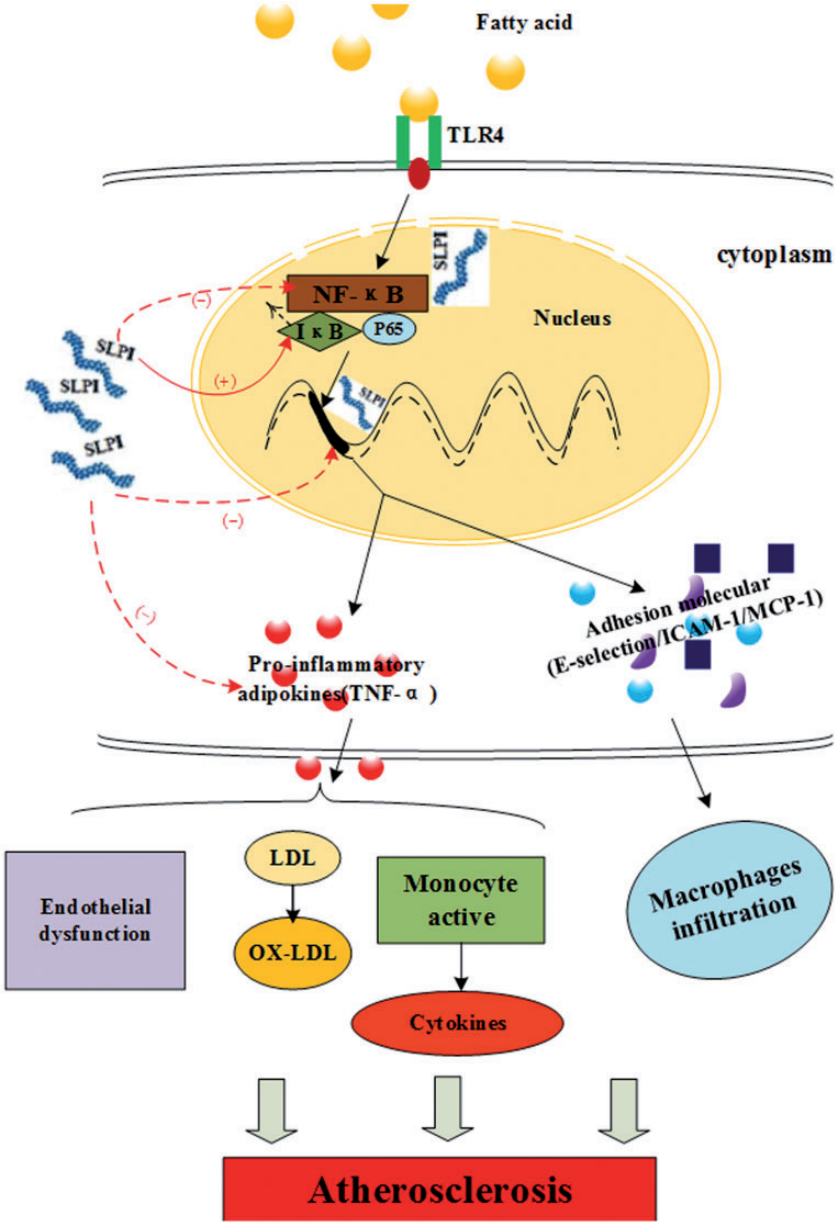

Figure 1 Schematic view of the anti-inflammatory roles of SLPI in obesity-related atherosclerosis pathway. In obesity-related chronic low-grade inflammatory status, SLPI may act as an anti-inflammation factor through several aspects: (1) inhibit the activation of NF- κB; (2) prevent endogenous IκBα degradation; (3) bind to the DNA of NF-κB regions within the IL-8 and TNF-α promoters, and prevent p65 interaction with the NF-κB consensus region; (4) may be interference with parallel pro-inflammatory signaling pathways to inhibit cytokine production. All of those consequently lower the production of pro-inflammatory adipokines and the expression of adhesion molecules, which are conformed to lead to atherosclerosis through varies pathways. (–): inhibit; (+): promote. (A color version of this figure is available in the online journal.)

protect an organism against atherosclerosis. The possible mechanism involved in this process is summarized in Figure 1.

However, it cannot be excluded that elevated expression of SLPI in omental adipose tissue compared to subcutaneous adipose tissue may play a role in mediating the pro-inflammatory response associated with obesity.[5,40] Though most findings suggest that SLPI can be identified as a 'tolerogenic' immunomodulatory molecule, some data suggest an immune-stimulatory role for SLPI. Specifically, SLPI may act as a secreted pattern recognition receptor that results in phagocytosis of mycobacteria when stimulated.[41] Thus it seems that the pro- or anti-inflammatory properties of SLPI are dependent on the type of pathogen and the progress of the inflammatory response.[42] SLPI-mediated suppression of transforming growth factor-β (TGF-β) (a well-known anti-inflammatory cytokine) expression[43] and SLPI's inhibition on the induction of regulatory T-cell differentiation[44] provide corroborating evidence that SLPI has prominent pro-inflammatory properties. Additionally, André Michael Muller et al.'s research suggests that in experimental autoimmune encephalomyelitis (EAE), the accepted disease model of multiple sclerosis and the pro-inflammatory functions of SLPI are likely associated with

down-regulation of TGF-β and may have a greater impact than SLPI's anti-inflammatory effects.[45]

SLPI, anti-inflammation in atherosclerosis

In Nobuhiko Harada et al.'s research, the deletion of the Nrf2 gene, which encodes a master regulator of the oxidative stress response in mammals, reportedly attenuates atherosclerosis formation.[10] Recently, some reports have also shown that Nrf2 overexpression *in vivo* induces SLPI.[46] Moreover, expression of SLPI was significantly decreased in the lesions of the A0N0 mice (Nrf2 and ApoE double-knockout) compared to the A0N2 mice (ApoE knockout) after 12 weeks of the high-fat cholesterol diet. Therefore SLPI as a target gene of Nrf2, may play a vital role in regulating the inflammatory state of macrophages in atheroma plaques.[10]

Furthermore, Peter Henriksen *et al*.[9] use adenoviral gene delivery of Elafin and SLPI to clarify that Elafin and SLPI are potential gene therapy targets for treatment of atheroma. Their studies show for the first time that: (1) overexpression of elafin protects human endothelial cells from human neutrophil elastase (HNE)-induced damage and (2) both elafin and mouse secretory leukocyte protease inhibitor (mSLPI) have broad-ranging anti-inflammatory activity, capable of reducing endothelial cell IL-8 production in response to TNF-α, LPS, and oxidized LDL and TNF-α production by human macrophages in response to LPS. Inflammatory factors such as TNF have an established role in plaque inflammation.[47] SLPI is well demonstrated to reduce the serum levels of TNF-α and the CXC chemokine macrophage inflammatory protein (MIP)-2.[48]

Additionally, the anti-inflammatory actions of elafin and mSLPI were exemplified to be associated with dampening the transcription factor NF-κB and concomitantly reducing IκBα degradation. In general, the activity of NF-κB in unstimulated cells was very low. In human umbilical vein endothelial cells (HUVECs) stimulated with LPS, oxidized LDL, and/or TNF-α (100 pg/mL) led to an increase in NF-κB activity. In contrast, cell stimulation with Ad-elafin and Ad-mSLPI significantly reduced NF-κB activity. Meanwhile, they found that Ad-mSLPI and Ad-elafin significantly protected HUVECs and macrophages from TNF-α and LPS-induced IκBα degradation, respectively. Ad-IκBα produced overexpression of mutated IκBα (as evidenced by its higher m.w.), but in accordance with other studies Ad-IκBα did not completely prevent endogenous IκBα degradation. Ad-elafin and Ad-mSLPI also reduced LPS-induced macrophage NF-κB activation in accordance with their inhibitory action on production of the NF-κB-regulated pro-inflammatory cytokine TNF-α. That do not exclude elafin and mSLPI interference with parallel pro-inflammatory signaling pathways activated by TNF-α, LPS, and oxidized LDL, because inhibition of cytokine production was more striking than suppression of NF-κB activation (particularly for TNF-α.) supporting this possibility.

Moreover, Clifford Taggart *et al*.[49] present evidence to show that upon incubation with peripheral blood monocytes (PBMs), SLPI enters the cells and is rapidly localized to the cytoplasm and nucleus, where it affects NF-κB activation by binding directly to NF-κB binding sites in a site-specific manner. SLPI can also prevent p65 interaction with the NF-κB consensus region at concentrations proportional to physiological nuclear levels of SLPI and p65. It was demonstrated that SLPI can bind DNA. They use chromatin immunoprecipitation (ChIP) to show that SLPI can bind to NF-κB regions within the IL-8 and TNF-α promoters but not the IL-10 promoter region, as it does not contain a NF-κB binding site. They also use ChIP to show that p65 binding to the NF-κB regions within IL-8 and TNF-α promoters can be inhibited in the presence of SLPI, which may help explain the immunomodulatory/anti-inflammatory role of SLPI in suppressing NF-κB induced responses in monocytes. Furthermore, it was found that inhibition of the MAPK pathway (especially p38 inhibition) led to decreased expression of SLPI, which strongly indicates that p38 is a regulator of SLPI expression.[50]

SLPI overexpression not only inhibits TNF-α induction, but also reduces E-selectin gene induction in response to infiltrating tumor cells in the liver.[51] E-selectin plays a pivotal role in atherosclerotic plaque formation.[52] At the molecular level, endothelial cells demonstrate increased expression of adhesion molecules and chemokines during atherosclerotic plaque growth. Active NF-κB induces transcription of cell adhesion molecules, and macrophages are the predominant cells in the mononuclear cell filtrate.[9] It has not yet been reported whether or not SLPI can inhibit the expression of adhesion molecules in endothelial cells.

SLPI, antioxidative properties

Oxidative stress has been linked to the pathogenesis of atherosclerosis and incidence of CAD. However, SLPI may have antioxidative properties. In studies by Gillissen *et al*.,[53] recombinant SLPI (rSLPI) (100 mg/L) was aerosolized to sheep, and levels of SLPI, glutathione (GSH), anti-NE capacity, and anti-H_2O_2 capacity were evaluated in respiratory epithelial lining fluid (ELF) over a 30-h period. As expected, aerosolization of rSLPI increased ELF SLPI levels and anti-NE capacity. Strikingly, post-aerosol levels of GSH in ELF increased (5-fold 24 h after aerosol) concomitantly with ELF anti-H_2O_2 capacity; i.e. rSLPI augmented the antioxidant screen of ELF. This suggests that SLPI indirectly raises the antioxidant capacity of ELF by raising ELF GSH levels. Consequently, SLPI has antioxidative properties that may play a role in conditions where oxidants are high, such as atherosclerosis. Studying the antioxidative properties of SLPI could prove to be very rewarding, since little information is currently known in this area.

SLPI/Elafin in atherosclerosis plaque stability

Work by Dollery *et al*.[54] has implicated that HNE plays a critical role in atherosclerosis plaque development. HNE is a serine elastase present at high concentration in neutrophil azurophilic granules. The role of HNE in ECM degradation and tissue injury has been demonstrated in neutrophil elastase knockout mice.[55] Cellular localization of HNE mRNA into macrophage and endothelial cells was identified using *in-situ* hybridization within human atheroma;[54] localization

of HNE mRNA was particularly abundant within macrophages located at the shoulders of atherosclerotic plaques. It is well documented in Peter Henriksen' review how HNE contributes to matrix degradation and weakening of vessel walls associated with complications of aneurysm formation and atherosclerotic plaque rupture.

Elafin and SLPI are members of the four-disulfide core family with anti-HNE activity that exhibit up-regulation in response to inflammatory stimuli. In 1997, Yahong Zhang *et al*. demonstrated that SLPI could block matrix metalloproteinase (MMP) production through inhibition of PGE2 due to the suppression of prostaglandin-endoperoxide synthase-2. The ability of SLPI to block of MMP production suggests that SLPI may have a significant role in suppressing the destruction of connective tissue by blocking the signal transduction pathway leading to the production of MMPs by monocytes. This effect appears to be independent of the protease inhibitory properties of SLPI. It is known that the MMP family can degrade all ECM components, which is related to atherosclerosis and plaque rupture.[56] Thus, SLPI may be involved in preventing plaque erosion independently of its anti-protease property. Furthermore, Henry *et al*.[57] demonstrate that SLPI and elafin are resistant to proteolytic inactivation by MMP-8, a property that may enhance their use in NE-mediated plaque rupture therapeutic applications.

Elafin has a unique repeating sequence in its prosegment that is rich in glutamyl and lysine residues, and its moiety is readily cross-linked to the ECM protein by the enzyme tissue transglutaminase (tTG). tTG plays an important role in the targeting of elafin to the site of action. Immunohistochemical studies on autopsy samples of human coronary arteries revealed that the expression of tTG and elafin in SMCs, endothelium, and ECM was enhanced in atherosclerotic coronary arteries. In contrast, tTG expression was hardly detectable in accumulating macrophages or at the lipid core. Yoshihiko Sumi *et al*.[6] speculated that the decreased expression of tTG contributes to the instability of atherosclerotic plaques and leads to plaque destruction and erosion. Moreover, overexpression of elafin protects human endothelial cells from HNE-induced damage.[9] These findings implicate that elafin may have the ability to stabilize atheroma plaques. Despite there being no direct evidence that SLPI correlates with plaque stability, SLPI is worthy of further investigation as it is one of the natural regulators of neutrophil elastase.

Conclusions

It is becoming increasingly clear that SLPI is far more than just a protease inhibitor, as exemplified by the studies that have been discussed in this review. SLPI has been shown to play a critical role in obesity-associated inflammation and be atheroma-protective via its anti-inflammatory capacity. However, there is still not enough direct evidence that SLPI can shield atherosclerosis formation and plaque rupture. With respect to SLPI in obesity-related atherosclerosis, relatively little is known about the molecular mechanisms involved. Uncovering these mechanisms will lead to a better understanding. Given that these effects have only been identified in recent years, it is likely that many more discoveries will arise. Likewise, further exploration of SLPI's role in the atheroma development and plaque erosion will lead to new advances in the treatment of atherosclerosis and its complications.

Additionally, previous studies show that the presence of MS is associated with a higher degree of inflammation.[58] Rana *et al*.[58] suggest that in people with MS an increased level of physical fitness might exert its beneficial effect via attenuating inflammation. Moreover, circulating SLPI increased with progressive metabolic dysfunction is related to metabolic and inflammatory parameters in men.[32] In overweight patients with CAD, exercise training and weight loss are associated with a decrease in platelet reactivity that may predict an improved prognosis.[59] These data show that SLPI may be involved in the response to physical fitness or physical activity through controlling inflammation in MS or obesity. The further research may find new mechanism and advances in the relationship between SLPI and MS or obesity.

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DECLARATION OF CONFLICTING INTERESTS

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