Antioxidative defense mechanisms can balance the formation of reactive oxygen species in a healthy endothelium. These antioxidative processes include scavenging (e.g. by vitamins C and E) or enzymatic degradation (e.g. by superoxide dismutases, catalase, and glutathione peroxidase). If this redox-sensitive equilibrium is altered by increased reactive oxygen species or by reduced antioxidative capacity, augmented oxidative stress is formed. Vascular oxidative stress can reduce the nitric oxide (NO) availability and increase the oxidative modification of low-density lipoprotein, thus promoting cardiovascular diseases (1).

Nicotine adenine dinucleotide phosphate (NADPH) oxidase is a major source of endothelial oxidative stress (2, 3). The classical NAD(P)H oxidase complex involves four essential subunits, membrane-bound subunits gp91phox and p22phox and initially cytosolic subunits p47phox and p67phox. After phosphorylation of p47phox, they translocate from the cytosol to the membrane and form an active NAD(P)H oxidase complex. In addition, small G proteins are involved.

Increased superoxide generation by NAD(P)H oxidase has been associated with endothelial dysfunction and clinical risk factors of atherosclerosis (4). Furthermore, NAD(P)H oxidase subunit expression has been associated with the severity of atherosclerosis (5). Growing evidence supports a link between angiotensin II, inflammation, oxidative stress, and cardiovascular diseases. Angiotensin II increases the superoxide anion formation in vascular smooth muscle (6) and endothelial cells (7, 8) and might contribute to the development of endothelial dysfunction and atherosclerosis (9). A link between inflammation and oxidative stress is supported by the activation of NAD(P)H oxidase in response to TNF-α, whereby TNF-α induces p47phox phosphorylation, followed by p47phox-TNF-α receptor-associated factor (TRAF4) association and membrane translocation that leads to increased superoxide anion formation (10). Inhibitors of the NAD(P)H oxidase and oxidative stress have been considered as novel therapeutic targets in the treatment of cardiovascular diseases (11).

In this issue of Thrombosis and Haemostasis, Nascimento-Silva, Arruda et al. (see article beginning on page 88) identify an Aspirin™-triggered lipoxin A₄ analog (ATL-1) as a novel inhibitor of NAD(P)H oxidase-mediated endothelial oxidative stress. ATL-1 can block the angiotensin II-, thrombin- and TNF-α-induced reactive oxygen formation in endothelial cells. This antioxidative action of ATL-1 is mediated by its G protein-coupled receptor ALX. ATL-1 prevents the activation of NAD(P)H oxidase by inhibiting agonist-induced p47phox phosphorylation and subsequent translocation from the cytosol to the membrane. As a consequence, ATL-1 inhibits angiotensin II-mediated activation of nuclear factor kappa B (NFκB). These data support a novel antioxidative mechanism of aspirin-triggered lipoxin A₄ analog ATL-1 by inhibiting NAD(P)H oxidase activity in endothelial cells. However, it is still unknown whether this molecule affects additional sources of reactive oxygen species in the vessel wall. Ongoing experimental and clinical studies will shed further light in this direction.

Lipoxins are generated from arachidonic acid, and acetylsalicylic acid-triggered 15-epi-lipoxin can be synthesized through an additional pathway (13). These aspirin-triggered lipoxins can exceed the potency of native lipoxins and might contribute to the pleiotropic beneficial effects of aspirin, including anti-inflammatory actions (14). Aspirin directly affects neutrophils and platelets in a dose-dependent manner (15), thus protecting the endothelium from oxidative stress and reducing endothelial dysfunction. It has antioxidant activity, enhances fibrinolysis, and suppresses plasma coagulation and platelet-dependent inhibition of thrombin formation (16). Aspirin reduced oxidized low-density lipoprotein (oxLDL)-mediated lectin-like oxLDL receptor LOX-1 expression and superoxide anion generation in human coronary artery endothelial cells. It has also been shown to prevent hydrogen peroxide-induced caspase and NFκB activation in a dose-dependent manner through inhibition of phosphorylation and degradation of IκB (17). These findings further support a link between increased oxidative stress and the coagulation cascade.

Safe and efficient inhibition of vascular oxidative stress is an important issue of ongoing research. Especially in the light of the still contradictory use of dietary antioxidants such as vitamins C and E for the prevention of cardiovascular diseases in randomized clinical trials (18), novel antioxidative strategies are needed. Oral dietary supplementation with the NAD(P)H oxidase inhibitor apocynin improved endothelial function in a recent ex-

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perimental study in cholesterol-fed mice (19). The NAD(P)H oxidase-specific peptide gp91ds-tat prevents the intracellular activation of the NAD(P)H oxidase complex by inhibiting p47phox association with gp91phox. Gp91ds-tat acts also systemically and attenuates angiotensin II-induced blood pressure elevation in mice (20). Finally, the novel non-peptide Nox inhibitor VAS2870 can block the increased NAD(P)H oxidase-mediated superoxide anion formation in response to oxLDL in human endothelial cells (21).

We are just at the beginning of discovering different molecular sources of oxidative stress in endothelial cells (22). Nevertheless, translation of basic findings into novel therapeutic strategies will be a major challenge for all disciplines of endothelial cell biology (23). The clinical importance of oxidative stress for cardiovascular diseases will accelerate the development of anti-oxidative strategies beyond synthetic vitamins in the coming years. The antioxidative properties of the aspirin-triggered lipoxin A4 analog ATL-1 add a new player to the anticipated reduction of vascular oxidative stress. This will improve our experimental and therapeutic options to substantiate the proposed beneficial effects of increased antioxidative defense in the prevention of cardiovascular diseases.

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