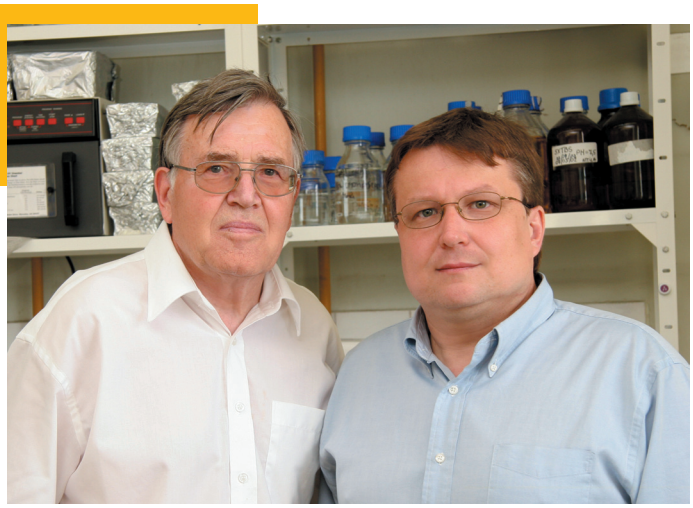
Editorial



Gerhard Spiteller (left) and László Nagy (right)

Atherosclerosis and Lipid Peroxidation

About one half of all deaths in the Western World are caused by cardiovascular disease. In contrast, atherosclerosis is rare in countries where people suffer from starvation, indicating a strong influence of Western nutrition on atherogenesis. On the other hand, atherosclerosis was found to be closely connected with oxidation of low density lipoprotein (LDL) which transports cholesterol to cells. The crucial problem how atherosclerosis, oxidation of LDL and an oversupply of fatty food might be connected unified experts in the fields of medicine, biochemistry, chemistry, and food chemistry from Europe and the United States at a meeting on "Atherosclerosis and Lipid Peroxidation" held between April 8 and 10, 2005, at Hortobagy near Debrecen, in the heart of the Hungarian Puszta. The meeting was sponsored by the Hertie Foundation, embedded in the Herder exchange program between scientists of Western and Eastern Europe, and also by the Research Center for Molecular Medicine of the University of Debrecen, Medical and Health Science Center, recognized by the European Union as a Center of Excellence.

The first paper is presented by Daniel Steinberg (University of California, La Jolla, USA). He reviews the development of research in atherosclerosis over the past fifty years, from a medical and biochemical viewpoint. The investigation of familiar hypercholesterolemia is a crucial milestone in the elucidation of the role of low density lipoproteins (LDL) in plaque formation. Emphasizing the strong relation of inflammatory events to atherogenesis characterized by the penetration of monocytes and T-cells into the developing lesions, Daniel Steinberg describes the induced activation of cytokine production and growth factors and requests which compounds are responsible for these alterations. According to this author all these effects are induced by oxidation of lipids in LDL.

His conclusion that atherosclerosis is induced by lipid oxidation is supported by Gerhard Spiteller (University of Bayreuth, Germany). He reviews chemical changes induced by atherogenesis, deducing that the most oxygen-sensitive compounds in LDL are polyunsaturated fatty acids (PUFAs). PUFAs easily undergo lipidperoxidation (LPO) in LDL and Gerhard Spiteller emphasizes the great difference between the reactivity of lipidhydroperoxide molecules generated in enzymatic reactions and the reactivity of peroxyl radicals produced in non enzymatic LPO reactions. This raises the question whether LPO might be a consequence of cell membrane alterations caused by injury. Indeed, it may be that it is not free cholesterol but direct incorporation of nutritionally derived peroxidized cholesterol PUFA esters which causes atherogenesis. The question is raised whether the protective properties of a fish diet are caused by n-3-PUFAs and it is suggested that these protective properties are based on the presence of furan fatty acids which are radical scavengers.

Hartmut Kühn et al. (Charité Berlin, Germany) give an overview of the expanding group of lipoxygenases. In their mechanism of action, the lipidhydroperoxide molecules formed are subjected to cleavage by formation of alkoxyl radicals, which requires the presence of iron ions. The question how these iron ions are generated in biological samples is outlined by Jozsef Balla (University of Debrecen, Hungary): because they are highly reactive, iron ions are extremely well shielded by complexation in biological molecules. In this paper the processes are outlined in detail which might contribute to the liberation of iron ions from hem and the protecting properties of ferritin and hem-oxygenase-1 are discussed.

The main toxic products generated in nonenzymatic lipid LPO reactions are 2,4-unsaturated aldehydic compounds. The representative of this class of compounds which has been most widely investigated is 4-hydroxynonenal. Peroxyl radicals generate a second class of toxic products, oxidized cholesterol derivatives. Giuseppe Poli (University of Turin, Italy) provides an overview of the generation of both classes of toxic products, leading to an overexpression of the proteins TGFb1, MCP-1, CD36 and b1-integrin. Moreover, he discusses the toxic actions of unsaturated aldehydes and cholesterol oxidation products.

In the course of nonenzymatic LPO processes, not only free PUFAs are attacked but also those bound to phospholipids and are cleaved to aldehydic products still connected to their glycerol skeleton. Robert Salomon *et al.* (Case Western University, Cleveland, USA) reports on the further degradation of such aldehydes to isolevuglandins. These truncated phospholipids have turned out to be important signalling molecules serving as ligands to proteins which induce an appropriate gene response. He emphasizes that although the cholesterol level is reduced by therapeutic inventions, the level of the isolevuglandin protein adduct increases, thus indicating that cholesterol levels do not reflect the oxidative state of a patient.

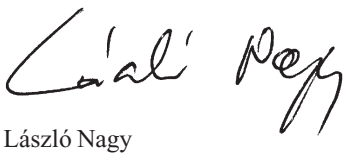
Norbert Leitinger (University of Virginia, Charlottsville, USA) continues the discussion about the action of aldehydic phospholipid derivatives on tissue samples in model studies. He recognizes that these compounds induce expression of atherosclerosis inducing genes, such as EGR-1, VCAM-1, ICAM-1, TF, and IL-6, thus contributing to vascular inflammation processes.

Macrophage gene expression and metabolism are regulated by a group of lipid-activated transcription factors: PPARγ (peroxisome proliferator activated receptor-gamma), LXR, liver X receptor and RAR (retinoic acid receptor). The role of retinoids in connecting PPARγ and LXR signaling in macrophages is the main topic discussed by László Nagy *et al.* (University of Debrecen, Hungary). Retinoids *via* the retinoic acid receptor (RAR) and PPARγ regulate the P450 enzyme CYP27, which in turn leads to an increased level of 27-hydroxysterol (a ligand of LXR) and contributes to the regulation of lipid metabolism and cholesterol efflux in macrophages.

The contribution by Ilona Staprans (University of California, San Francisco, USA) deals with the uptake of food-derived oxidized cholesterol and oxidized fatty acids in circulating lipoproteins. She was able to demonstrate in feeding experiments that toxic 5,6-epoxycholesterol is incorporated into lipoproteins, and points out that oxidized cholesterol derivatives are abundant in fast food, mentioning that these may also contribute to atherosclerosis.

The aspect of removal of radicals in tissue by scavengers is discussed by Regina Brigelius-Flohé *et al.* (University of Potsdam, Germany). She demonstrates that antioxidants act not only as scavenger molecules but also show pro-oxidant properties. Furthermore, vitamin E, for instance, has also gene-regulatory functions which have previously not been sufficiently considered. She further shows that plant constituents are able to transform SH groups to redox sensitive transcription factors which are probably more influential than their antioxidant potential.

This Issue provides convincing evidence that lipid peroxidation processes are an essential response of organisms to injury. The products formed serve apparently as ligands to proteins which in turn induce an appropriate gene response. Therefore fatty acids seem not only to be of importance for nutrition but also for signalling purposes.



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