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see original article on page 577

Multiple effects of HMG-CoA reductase inhibitors (statins) besides their lipid-lowering function

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The paper by Sharyo *et al.* shows that statins reduce the severity in a model of renal–ischemia reperfusion injury and raises the therapeutic possibility of using statins as pharmacological intervention against acute kidney injury. This, together with previous studies, indicates that statins exert a wide spectrum of anti-inflammatory, immunomodulatory, and protective effects besides their lipid-lowering function.

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Inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (statins) have become the most widely used drugs for lowering serum cholesterol levels, applied to at least 15% of patients admitted to hospitals.[1] They are mainly used for prevention of cardiovascular events, and they have proved to be highly effective. However, clinical studies demonstrated that the statin-mediated lowering of cholesterol and triglycerides appeared to account for many but not all of the beneficial effects in cardiovascular diseases.[2] Furthermore, statins improve the outcome of vascular diseases, some of which are not associated with elevated lipid levels—for example, stroke and transplantation-associated coronary vasculopathy.[2,3] These observations led to the hypothesis that statins do not only improve the lipid profile but also have direct vascular and tissue-protective actions. In this regard, Sharyo *et al.*[4] (this issue) demonstrated in a renal ischemia–reperfusion injury mouse model that pravastatin ameliorated renal function and injury independent of plasma cholesterol levels. They also report that pravastatin prevented the increase in plasma interleukin-6 levels induced by ischemic kidney injury.[4] As interleukin-6 is an important regulator of acute inflammatory reactions, these findings are in line with many other published works demonstrating anti-inflammatory actions of statins.[2] Especially *in vitro* studies with different cell types support lipid-lowering–independent functions of statins: It has been shown that statins can interfere with leukocyte–endothelial interactions and prevent the adhesion and migration of leukocytes to the inflammatory side. As Sharyo *et al.*[4] mention, simvastatin can bind directly to leukocyte function antigen-1 (LFA-1) and inhibit leukocyte adhesion.[5] This function is completely independent of blocking the activity of HMG-CoA reductase and lipid lowering (Figure 1). Additionally, statins were found to diminish the expression of various cytokines, such as interleukin-6 or tumor necrosis factor-α, in macrophages. But also in non-professional phagocytes, for example, endothelial cells and smooth muscle cells, the expression of chemotactic and proinflammatory mediators, such as monocyte chemoattractant protein-1 and interleukin-8, could be reduced by the use of statins.[2] Furthermore, statins have been shown to interfere with the generation of reactive oxygen species or to activate scavenging systems for free radicals, such as the thioredoxin system. Especially with regard to the vascular system, many additional proangiogenic and protective properties of statins have been reported, including many beneficial effects on re-endothelialization following vessel injury and inhibition of platelet aggregation in diseased vessel walls.[2,6] Because of the diverse anti-inflammatory and vasoprotective properties, it was suggested to use statins not only for the treatment of vascular diseases but also in infected or septic patients. Recent work even demonstrated antimicrobial actions of statins.[7]

Inflammatory processes, especially the release of proinflammatory cytokines, essentially regulate tissue remodeling and wound healing. The formation and deposition of fibrin is part of the hemostatic process in response to inflammation and tissue injury. However, when the fibrin is not removed because of an insufficient fibrinolytic activity, it becomes organized. This can result in fibrous tissue remodeling with loss of organ function. In different cell types, including endothelial cells, smooth muscle cells, and proximal tubular cells, statins efficiently promote the fibrinolytic activity by diminishing the expression of plasminogen activator inhibitor-1 and of the procoagulant tissue factor and by enhancing that of tissue-type plasminogen activator.[2,8,9] In this way statins might help to remove fibrin deposits and recover organ function. Furthermore, statins are supposed to interfere with matrix turnover. The breakdown of matrix is essentially mediated by a family

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of matrix-degrading enzymes, the matrix metalloproteinases (MMPs). Studies with different cell types, including endothelial cells and macrophages, demonstrate that statins lower the expression and function of a wide range of MMPs. However, the enzymatic activity of MMPs is dependent not only on the expression of the protease but also on its interaction with the endogenous tissue inhibitors of MMPs (TIMPs). As statins were found to decrease the expression of MMPs and to augment the expression of TIMPs, they probably limit extracellular matrix breakdown and function to preserve tissue.[2]

Downregulated inflammatory reactions and improved endothelial functions mediated by statins are considered to account for the better outcome of vascular diseases. However, it has not been well investigated whether statins confer similar benefits to the kidney. The work of Sharyo *et al.*[4] suggests that statins might induce similar anti-inflammatory and tissue-protective actions in the kidney. Acute kidney injury is most likely followed by multiple processes, including the generation of reactive oxygen species, nitric oxide, and the decline of antioxidant protection, which can result in dysfunction, injury, and death of the cells of the kidney. Renal inflammation involving cytokine/adhesion molecule expression with recruitment, activation, and diapedesis of circulating leukocytes is also implicated. Thus, statins might improve acute kidney injury through direct effects on the renal vasculature, protection of tubular cells, and a systemic anti-inflammatory effect.[10]

The molecular mechanisms underlying the proinflammatory and protective actions of statins are only partly known. Statins prevent the conversion of HMG-CoA to mevalonic acid, and hence also the synthesis of bioactive sterol and nonsterol metabolic intermediates deriving from this pathway (Figure 1). Proximal inhibition of this pathway reduces the production of isoprenoids such as farnesyl pyrophosphate and geranylgeranyl pyrophosphate. Isoprenoids are required for the post-translational 'prenylation' and membrane localization of small guanosine triphosphate-binding proteins. 'Prenylation' means lipid modifications with covalent binding of farnesyl or geranylgeranyl isoprenoids to conserved cysteine residues of proteins. These proteins include a wide range of signal transducers, including Ras and Ras-related guanosine triphosphate-binding (G) proteins such as Rho, which interfere with numerous inflammatory pathways. Statins inhibit the formation of farnesylated and geranylgeranylated proteins by blocking the mevalonate pathway.[2] Many anti-inflammatory and vasoprotective actions of statins can be reversed by exogenous geranylgeranyl or farnesyl pyrophosphate, demonstrating the involvement of the mevalonate pathway in the statins' mode of action. These functions include leukocyte adhesion, cell viability, cell proliferation, and the fibrinolytic activity.[2,8] In line with these findings, Sharyo *et al.*[4] report that a farnesyl transferase inhibitor improved renal dysfunction to a degree comparable to that seen with the use of statins. Furthermore, different studies show that statins downregulate the activity of the transcription factors nuclear factor-κB and activator protein-1, which also play an important role in the regulation of many inflammatory pathways.[2,9]

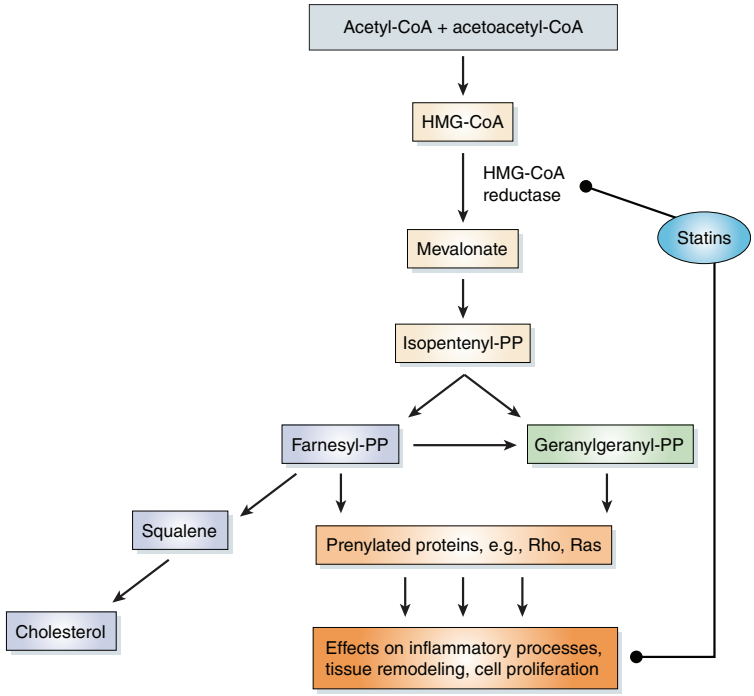

Figure 1 | Schematic illustration of the cholesterol biosynthetic pathway. Sites of action of HMG-CoA reductase inhibitors (statins) are indicated, PP pyrophosphate.

Taken together with previous work, the work of Sharyo *et al.*[4] demonstrates that statins improve renal dysfunction after acute kidney injury by a lipid-lowering–independent effect. Most likely this action of statins is due to anti-inflammatory properties and dependent on the mevalonate pathway. Further studies of the pleiotropic functions of statins may help to explain the involved mechanisms in more detail. A better understanding of the statins' mode of action may help to develop novel therapeutic strategies for various inflammatory disorders, including kidney diseases.

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see original article on page 631

Macroautophagy: a mechanism for mediating cell death or for promoting cell survival?

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Macroautophagy is a ubiquitous mechanism for the bulk removal of macromolecules and cell organelles from the cell. Periyasamy-Thandavan and colleagues report that cisplatin activates autophagy in renal tubular cells and that autophagy plays a role in decreasing apoptosis of tubular cells induced by cisplatin. This finding provides novel evidence that autophagy may play a role in ameliorating the effects of acute injury on the kidney.

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There are three types of autophagy. Microautophagy is a process that has been well characterized only in yeast; during this process cytosolic components are sequestered by lysosomes at the lysosomal membrane by septation and/or invagination. Chaperone-mediated autophagy is the direct translocation across the lysosomal membrane of cytosolic proteins that have been 'tagged' with a specific peptide sequence. This Commentary will focus entirely on macroautophagy (hereafter referred to as autophagy), which is a ubiquitous, genetically programmed and evolutionarily conserved process in which long-lived cytoplasmic components, including macromolecular aggregates and cellular organelles (such as mitochondria, peroxisomes, and endoplasmic reticulum), are sequestered into vesicles for bulk degradation by a lysosomal degradative pathway.[1–3]

The process of autophagy begins with the formation of crescent-shaped 'initiation' membranes that envelop and sequester cytosolic components before forming double-membraned vesicles called autophagosomes (Figure 1). The origin of initiation membranes remains uncertain. Autophagosomes fuse with lysosomes to form autolysosomes, which degrade the sequestered contents into their basic components (amino acids, fatty acids, and so on). These molecules are returned to the cytosol for recycling (Figure 1).[1–3] Although the proteasome provides another mechanism for mass degradation of proteins, this process requires proteins to be tagged by ubiquitination and to be unfolded so they can enter the degradative ubiquitination channel. In contrast, autophagy has the ability to degrade all forms of peptide and lipid macromolecules as well as entire cellular organelles.

Autophagy is a genetically programmed process. Autophagy-related genes (ATGs) were first isolated in yeast. Subsequently, a number of mammalian orthologues of yeast ATGs have been identified. These genes encode the proteins necessary for the complex series of events that constitute the autophagic cycle (Figure 1).[1–3] The signaling mechanisms responsible for the regulation of autophagy remain uncertain. However, it is clear that autophagy is activated by the target of rapamycin complex 1 (TORC1), as factors that activate TORC1 (insulin and growth factors) stimulate autophagy, and rapamycin-induced inhibition of TORC1 reduces autophagy.[2,4,5]

The biologic processes controlled by autophagy in mammals have not yet been clearly elucidated. Paradoxically, current evidence appears to suggest that autophagy can cause cell death in some situations while acting as a prosurvival mechanism in others.[5] 'Autophagic cell death' is presumed to result from an excessive level of cellular autophagy and is a form of programmed cell death (PCD type II) that is morphologically distinct from apoptosis (PCD type I).[3] Apoptosis is characterized by cell shrinkage, DNA fragmentation, and the rapid phagocytic removal and degradation of apoptotic cell fragments. In contrast, autophagic cell death is associated morphologically with the accumulation of autophagic vesicles (autophagosomes). A fundamental feature that distinguishes apoptosis from autophagic cell death is the source of the lysosomal enzymes used for degrading the dying cells. Apoptotic cells are degraded by the lysosomes of phagocytic cells, whereas in autophagy the endogenous lysosomal machinery of the dying cell serves this purpose.[5]

What data support the view that autophagy can cause cell death? There are morphologic studies that have demonstrated the accumulation of increased numbers of dying cells containing many autophagosomes in some disease states, such as degenerative diseases of brain and muscle.[3,4] However, these findings are only correlative in nature and cannot be considered direct

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