HMG-CoA Reductase Inhibitors Enhance Phagocytosis by Up-regulating ABCA7

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Many trials show that low-density lipoprotein (LDL) cholesterol concentration is positively associated with the risk of increase of atherosclerotic cardiovascular diseases. HMG-CoA reductase inhibitors, statins, are potent LDL cholesterol-lowering reagents and established as anti-atherogenic drugs to cardiovascular diseases. Some clinical trials with statins implicated their "anti-atherogenic" effects beyond lowering plasma cholesterol, "pleiotropic" effects, whose pharmacological grounds, however, remain ambiguous. We recently reported that the endogenous ATP-binding cassette transporter (ABC) A7 strongly associates with phagocytosis being regulated by SREBP2, rather than generates high-density lipoprotein. We examined the effects of statins on phagocytosis in vitro and in vivo based on a hypothesis that statin treatment enhances phagocytosis through SREBP-ABCA7 pathway. Phagocytosis was shown enhanced by pravastatin, rosuvastatin, simvastatin and cyclodextrin in J774, as cellular cholesterol was reduced and expressions of the cholesterol-related genes were modulated including increase of ABCA7 mRNA and decrease of ABCA1 mRNA. Knock-down of ABCA7 expression by siRNA ablated enhancement of phagocytosis by statins. In vivo study, pravastatin enhanced phagocytosis in wild-type mouse, but this reaction was ablated in ABCA7-knockout mouse. We thus concluded that statins enhance phagocytosis through the SREBP-ABCA7 pathway. These findings provide a molecular basis for enhancement of the host-defense system by statins showing that one of their so-to-speak “pleiotropic” effects is in fact achieved through their reaction to a primary target.