

Editorial Focus

Statin and endothelial cell-derived microparticles

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Microparticles (MP) are small membrane vesicles that are released from many different cell types by a process of exocytic budding of the plasma membrane (1). Because MP disseminate various bioactive effectors originating from the parent cells, they can alter vascular function and may induce biological responses involved in the vascular system (2). For example, MP can modulate coagulation via direct and indirect mechanisms. Therefore, MP concentrations are documented in almost all thrombotic diseases occurring in venous or arterial beds (3–5). Furthermore, elevated levels of MP have been found in a number of conditions associated with inflammation, cellular activation and dysfunction, angiogenesis and transport (1, 6–8).

Various factors are involved in the mechanisms of endothelial cell-derived MP (EDMP) generation (9, 10). TNF α -, lipopolysaccharide- or oxidized low-density lipoprotein (LDL)-stimulation of cultured human umbilical vein endothelial cells (HUVEC) result in an increase in the release of EDMP expressing surface tissue factor (11, 12). Several studies report the existence of EDMP generated from apoptotic endothelial cells; for example, elevation of EDMP in patients following allogeneic stem cell transplantation is associated with some transplant-related complications that include the apoptotic mechanism of endothelial cells (13–15). Furthermore, the pattern of procoagulant MP released during acute allograft rejection suggests endothelial cell activation and Fas-mediated apoptosis (16); while procoagulant MP in pulmonary arterial hypertension also show apoptotic EDMP (17). However, the clinical significance of EDMP has not been fully revealed.

A high plasma cholesterol level is a risk factor for the progression of atherosclerosis and cardiovascular disease. A high plasma level of LDL cholesterol may also promote the development of atherosclerotic disease (18). Large-scale clinical trials with 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) have shown that lowering cholesterol

levels decreases the incidence of cardiovascular events and the progression of atherosclerosis (19). Statins have additional pleiotropic effects, many of which are mediated by the vascular endothelium (20–22). These pleiotropic effects of statins, as well as their lipid lowering effects, may be responsible for the prevention of atherosclerosis. However, the distinct mechanisms of these effects of statins are poorly understood.

In this issue of *Thrombosis and Haemostasis*, Diamant et al. (23) have partially resolved the above noted problems. They found that simvastatin promotes EDMP release during the detachment of endothelial cells undergoing apoptosis (induced by this drug), whereas the adherent cells showed no signs of simvastatin-induced apoptosis. The authors also concluded that statins improve the overall condition of the remaining vascular endothelium by facilitating detachment and EDMP release. Such a defense system of MP protects parent cells, as previously reported. The release of MP protects cells against complement-induced lysis (24). EDMP are likely to be generated to maintain endothelial homeostasis.

The current view of the role of MP is changing. Freyssinet proposed that MP not only impose a potential environment threat, but may also be essential to maintain cellular homeostasis (25). Most MP in thrombotic diseases are considered to be disadvantageous because of their procoagulant and proadhesive characteristics (25, 26). However, the study by Diamant et al. (23) suggests that elevated numbers of EDMP in patients with diabetes or cardiovascular disease reflect an activated cellular mechanism to cope with the increased endothelial stress, rather than a mechanism to impose an environmental threat to other cells and tissues. Thus, their report revises our understanding about EDMP. It also suggests a new outlook for EDMP, since the detachment of endothelial cells could contribute to a better appreciation of the effect of statins on endothelial cells.

References

1. Nomura S, Ozaki Y, Ikeda Y. Function and role of microparticles in various clinical settings. *Thromb Res* 2008; in press.
2. Morel O, Toti F, Hugel B, et al. Procoagulant microparticles: disrupting the vascular homeostasis equation? *Arterioscler Thromb Vasc Biol* 2006; 26: 2594–2604.
3. Mallat Z, Benamer H, Hugel B, et al. Elevated levels of shed membrane microparticles with procoagulant potential in the peripheral circulating blood of patients with acute coronary syndromes. *Circulation* 2000; 101: 841–843.
4. Matsumoto N, Nomura S, Kamihata H, et al. Increased level of oxidized LDL-dependent monocyte-

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- derived microparticles in acute coronary syndrome. *Thromb Haemost* 2004; 91: 146–154.
5. Chirinos JA, Heresi GA, Velasquez H, et al. Elevation of endothelial microparticles, platelets, and leukocyte activation in patients with venous thromboembolism. *J Am Coll Cardiol* 2005; 45: 1467–1471.
 6. Weber A, Koppen HO, Schrör K. Platelet-derived microparticles stimulate coronary artery smooth muscle cell mitogenesis by a PDGF-independent mechanism. *Thromb Res* 2000; 98: 461–466.
 7. Boulanger CM, Scoazec A, Ebrahimian T, et al. Circulating microparticles from patients with myocardial infarction cause endothelial dysfunction. *Circulation* 2001; 104: 2649–2652.
 8. Biro E, Nieuwland R, Tak PP, et al. Activated complement components and complement activator molecules on the surface of cell-derived microparticles in patients with rheumatoid arthritis and healthy individuals. *Ann Rheum Dis* 2007; 66: 1085–1092.
 9. Sapet C, Simoncini S, Loriod B, et al. Thrombin-induced endothelial microparticle generation: identification of a novel pathway involving ROCK-II activation by caspase-2. *Blood* 2006; 108: 1868–1876.
 10. Boulanger CM, Amabile N, Guerin AP, et al. In vivo shear stress determines circulating levels of endothelial microparticles in end-stage renal disease. *Hypertension* 2007; 49: 902–908.
 11. Kagawa H, Komiyama Y, Nakamura S, et al. Expression of functional tissue factor on small vesicles of lipopolysaccharide-stimulated human vascular endothelial cells. *Thromb Res* 1998; 91: 297–304.
 12. Nomura S, Shouzu A, Omoto S, et al. Activated platelets and oxidized LDL induce endothelial membrane vesiculation: clinical significance of endothelial cell-derived microparticles in patients with type 2 diabetes. *Clin Appl Thromb Hemost* 2004; 10: 205–215.
 13. Nomura S, Ishii K, Kanazawa S, et al. Significance of elevation in cell-derived microparticles after allogeneic stem cell transplantation: transient elevation of platelet-derived microparticles in TMA/TTP. *Bone Marrow Transplant* 2005; 36: 921–922.
 14. Nomura S, Ishii K, Inami N, et al. Role of soluble tumor necrosis factor-related apoptosis-inducing ligand concentration after stem cell transplantation. *Transplant Immunol* 2007; 18: 115–121.
 15. Nomura S, Ishii K, Inami N, et al. Evaluation of angiopoietin and cell-derived microparticles after stem cell transplantation. *Biol Blood Marrow Transplant* 2008; 14: 766–774.
 16. Morel O, Ohlmann P, Epailly E, et al. Endothelial cell activation contributes to the release of procoagulant microparticles during acute cardiac allograft rejection. *J Heart Lung Transplantation* 2008; 27: 38–45.
 17. Bakouboula B, Morel O, Faure A, et al. Procoagulant membrane microparticles correlate with the severity of pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2008; 177: 536–543.
 18. Croft KD, Beilin LJ, Vandongen R, et al. Leukocyte and platelet function and eicosanoid production in subjects with hypercholesterolemia. *Atherosclerosis* 1990; 83: 101–109.
 19. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994; 344: 1383–1389.
 20. Kaneta S, Satoh K, Kano S, et al. All hydrophobic HMG-CoA reductase inhibitors induce apoptotic death in rat pulmonary vein endothelial cells. *Atherosclerosis* 2003; 170: 237–243.
 21. Feng C, Ye C, Liu X, et al. Beta4 integrin is involved in statin-induced endothelial cell death. *Biochem Biophys Res Commun* 2004; 323: 858–864.
 22. Ferrara DE, Pierangeli SS. Diverse effects of statins on endothelial cells ? *Thromb Haemost* 2005; 93: 186–188.
 23. Diamant M, Tushuizen ME, Abid-Hussein MN, et al. Simvastatin-induced endothelial cell detachment and microparticle release are prenylation dependent. *Thromb Haemost* 2008; 100: 489–497.
 24. Hamilton KK, Hattori R, Esmon CT, et al. Complement proteins C5b-9 induce vesiculation of the endothelial plasma membrane and expose catalytic surface for assembly of the prothrombinase enzyme complex. *J Biol Chem* 1990; 265: 3809–3814.
 25. Freyssinet JM. Cellular microparticles: what are they bad or good for? *J Thromb Haemost* 2003; 1: 1655–1662.
 26. Berckmans RJ, Nieuwland R, Boing AN, et al. Cell-derived microparticles circulate in healthy humans and support low grade thrombin generation. *Thromb Haemost* 2001; 85: 639–646.