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Review article

Hyperlipidemia, tissue factor, coagulation, and simvastatin

*Albert Phillip Owens III, James Robert Byrnes, and Nigel Mackman**

Department of Medicine, Division of Hematology and Oncology, McAllister Heart Institute, University of North Carolina, Chapel Hill, NC 27599, USA

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ABSTRACT

Hyperlipidemia affects millions of people worldwide and is a major risk factor for cardiovascular disease. People with hyperlipidemia have elevated levels of serum cholesterol and an increased risk of thrombosis. Studies have suggested that oxidized lipoproteins, such as oxidized low-density lipoprotein (oxLDL), contribute to the development of a pro-thrombotic state. In this review, we discuss our recent studies demonstrating a role for hematopoietic cell-derived tissue factor (TF) expression in the activation of coagulation and increased thrombosis associated with hyperlipidemia. In addition, we investigated the effect of simvastatin on TF expression and coagulation. We found that simvastatin reduced leukocyte TF expression, TF^{+} microparticles, and coagulation. These results and earlier studies suggest that the anti-coagulant activity of statins is due, in part, to their ability to reduce monocyte TF expression in patients with cardiovascular disease.

Introduction

Lipids are transported in the blood within lipoprotein particles. Hyperlipidemia describes a condition in which there are elevated levels of serum lipids. In the United States it is estimated that >30% of the adult population has elevated serum cholesterol levels (≥240 mg/dL) (Go et al., 2013). Hyperlipidemia is a risk factor for the development of atherosclerosis because the excess lipids in the blood accumulate in the walls of arteries. Oxidation of low-density lipoprotein (LDL) results in the generation of oxidized (ox) LDL, which is a heterogeneous mixture of oxidized lipids and proteins (Levitan et al., 2010). One bioactive oxidized lipid within oxLDL is oxidized 1-palmitoyl-2-arachidonoyl-*sn*-glycero-3-phosphoryl-choline (oxPAPC). OxLDL binds a variety of cellular receptors on macrophages, monocytes, vascular smooth muscle cells (VSMCs), and endothelial cells (ECs). These receptors include the scavenger receptors SRAI/II, SRBI/II, and CD36 and the immune receptor toll-like receptor 4 (TLR4) (Boullier et al., 2001; Kunjathoor et al., 2002). A recent study found that oxLDL activation of mouse macrophages and a human monocytic cell line called THP-1 is mediated by a CD36/TLR4/TLR6 heterotrimeric receptor complex (Stewart et al., 2010). OxLDL also increases TLR4 expression in macrophages, and hyperlipidemia is associated with increased TLR4 expression on circulating monocytes (Methe et al., 2005; Xu et al., 2001).

Tissue factor (TF) is a transmembrane receptor that binds factor VII/VIIa and activates the clotting cascade (Mackman, 2009). It plays an essential role in hemostasis since inactivation of the TF gene in mice is associated with embryonic lethality. Exposure of monocytes to bacterial LPS induces TF expression (Mackman et al., 1991). It is thought that TF expression by monocytes is a part of the host response to

* *Corresponding author.*
E-mail address: nmackman@med.unc.edu (N. Mackman).

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infection and helps prevent dissemination of the infection. However, monocyte TF expression can also contribute to thrombosis.

Hyperlipidemia is associated with a pro-thrombotic state (Diaz et al., 2012; Eitzman et al., 2000; Podrez et al., 2007). Recent studies have demonstrated that hyperlipidemia and oxLDL activates platelets via CD36 (Podrez et al., 2007). Studies have demonstrated that circulating monocytes from hyperlipidemic individuals have higher levels of TF compared with healthy controls (Ferro et al., 1997; Puccetti et al., 2000). In addition, acute coronary syndrome patients have elevated levels of both circulating monocyte-derived microparticles (MPs) as well as TF^+ MPs (Matsumoto et al., 2004; Morel et al., 2009; Owens and Mackman, 2011). MPs are small membrane vesicles released from activated and apoptotic cells and elevated levels are observed in the circulation in various pathological conditions (Owens and Mackman, 2011). Finally, injection of oxidized lipids also increased TF expression in blood cells in mice (Kadl et al., 2002).

Rupture of atherosclerotic plaques induces the formation of intravascular thrombi that may occlude blood flow and lead to myocardial infarction and stroke. Atherosclerotic plaques contain high levels of TF (Wilcox et al., 1989). In addition, atherosclerotic plaques contain high levels of monocyte-derived TF^+ MPs (Leroyer et al., 2007). Platelets are activated by the exposed collagen, whereas the clotting cascade is activated by TF within the plaque (Owens and Mackman, 2012). In vitro studies have shown that oxLDL induces TF expression in monocyte-derived macrophages, ECs, and VSMCs (Cui et al., 1999; Drake et al., 1991; Levitan et al., 2010; Meisel et al., 2011; Ross, 1999). Additionally, oxPAPC induces TF expression in human endothelial cells in a TLR2- and Egr-1-dependent manner (Bochkov et al., 2002).

The statin family of drugs is the most widely prescribed medication class in the world. Statins lower cholesterol levels in hyperlipidemic patients by inhibiting the rate-limiting enzyme in cholesterol synthesis 3-hydroxy-3-methylglutaryl co-enzyme A reductase (HMG-CoA reductase) that is present in the liver. However, statins also have additional activities independent of their lipid-lowering activity, including anti-oxidant, anti-inflammatory, and anti-thrombotic activities (Albert et al., 2001; Di Garbo et al., 2000; Liao and Laufs, 2005). Statins also reduce TLR4 expression in human monocytes both in vitro and in vivo (Methe et al., 2005). Recent studies have found that statins also decrease venous thrombosis in a mouse model and in humans (Glynn et al., 2009; Patterson et al., 2013).

Statins have been found to reduce TF expression in atherosclerotic plaques in hyperlipidemic mice, rabbits, pigs, and monkeys without affecting lipid levels (Aikawa et al., 2001; Bea et al., 2003; Casani et al., 2005; Monetti et al., 2007; Sukhova et al., 2002). Moreover, simvastatin reduced monocyte TF expression in hypercholesterolemic patients (Ferro et al., 1997). In the Jupiter study, the authors speculated that the decrease in venous thrombosis may be due to rosuvastatin inhibition of monocyte TF expression. In vitro studies demonstrated that statins can directly inhibit inducible TF expression in various cells types, including monocytes and macrophages (Aikawa et al., 2001; Colli et al., 1997; Ferro et al., 1997, 2000).

This review will focus on our recent study examining the role of TF in the activation of coagulation in animal models of hyperlipidemia and the effect of administration of simvastatin (Owens et al., 2012).

OxLDL induces TF expression in monocytic cells and human monocytes in vitro

We found that oxLDL, but not LDL, increased TF expression in both human THP-1 monocytic cells and human monocytes (Owens et al., 2012). OxLDL also increased the number TF^+ MPs present in the culture medium. Inhibition of TLR4 reduced oxLDL induction of monocytic TF expression and TF^+ MPs (Owens et al., 2012). We are currently investigating the intracellular signaling pathways and transcription factors that mediate oxLDL induction of TF gene expression in monocytic cells. Next, we examined the effect of simvastatin on oxLDL induction of TF expression in THP-1 cells and human monocytes. Pretreatment of THP-1 cells and human monocytes with simvastatin significantly reduced oxLDL induction of both cellular and MP TF activity (Owens et al., 2012) (Fig. 1). Previous studies have proposed that statins reduce TF expression by inhibiting geranylgeranyl pyrophosphate (GGPP)-dependent prenylation of Rho A (Eto et al., 2002; Nagata et al., 2002). An alternative possibility is that

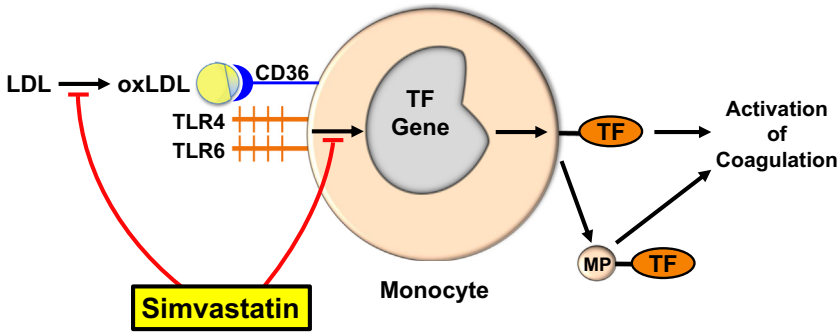

Fig. 1 – Proposed sites of simvastatin inhibition of monocytic TF expression. LDL is converted to oxLDL, which binds to a CD36/TLR4/TLR6 heterotrimeric complex on the surface of circulating monocyte that activates various intracellular signaling pathways and transcription factors that induce TF gene expression. This results in increased TF protein expression on the surface of the monocyte and release of TF^+ MPs. Simvastatin reduces the levels of oxLDL and TF expression.