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Sources of Tissue Factor that contribute to Thrombosis after Rupture of an Atherosclerotic Plaque

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Abstract

Hyperlipidemia leads to the formation of oxidized LDL (oxLDL), vessel dysfunction, atherosclerotic disease, and ultimately to plaque rupture and thrombosis. OxLDL induces tissue factor (TF) expression in various cell types, including monocytes and macrophages. High levels of TF are present in atherosclerotic plaques and this represents that major source of TF that triggers thrombosis after plaque rupture. In addition, increased levels of "circulating TF" are observed in hyperlipidemic animals and patients. This is due to induced TF expression in monocytes and monocyte-derived, TF^+ microparticles, which represents a minor source of TF that likely contributes to thrombosis after plaques rupture. This review will summarize the connections between hyperlipidemia and TF expression within atherosclerotic plaques and circulating monocytes, as well as its inhibition by statins.

Introduction

Tissue factor (TF) is a transmembrane glycoprotein that serves as the primary initiator of the coagulation cascade.[1-2] TF forms a complex with factor VII/VIIa (FVII/VIIa) that activates both FIX and FX and this leads to thrombin and fibrin generation.[3] Cross-linked fibrin then acts to stabilize thrombi in the vasculature. TF is constitutively expressed by cells surrounding the vessel wall, including vascular smooth muscle cells (VSMCs) and adventitial fibroblasts,[4-6] but is not expressed by endothelial cells and circulating cells under normal physiologic conditions. However, during hyperlipidemia, TF expression is induced in macrophages within atherosclerotic plaques and circulating monocytes.[7] Microparticles (MPs), also called microvesicles, are sub-micron sized membrane vesicles that are released from activated and apoptotic cells.[8-9] Importantly, levels of TF^+ MPs are increased in a variety of pathologic states, including hyperlipidemia.[9-11]

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This review will discuss (1) TF and atherosclerosis, (2) the link between hyperlipidemia and coagulation, (3) the contribution of monocyte TF and monocyte derived TF^+ MPs to hyperlipidemic activation of coagulation, and (4) the inhibitory effect of HMG-CoA reductase inhibitors (statins) on TF expression and thrombosis (Figure 1).

TF and Atherosclerosis

Plaque disruption and subsequent arterial thrombosis is a critical event in atherosclerosis resulting in acute vascular syndromes, such as myocardial infarction.[12] TF expression has been found to increase with the progression of human atherosclerotic lesions [13]. For instance, coronary atheroma from patients with unstable angina contained more functional TF than atheroma from patients with stable angina [14]. Furthermore, higher levels of TF activity are observed in plaques with thrombi [15]. Importantly, much of this TF appears to be in the form of TF^+ MPs. High levels of TF are also present in atherosclerotic lesions in rabbit and mouse models [16-17]. Macrophages and VSMCs appear to be the major source of TF [18]. Hyperlipidemia is associated with a shorter occlusion time in mouse carotid artery thrombosis model.[9, 19-22] We confirmed these results and further found that inhibition of TF ablates hyperlipidemic-induced thrombosis indicating a key role for TF in this enhanced thrombosis.[23] Taken together, these results suggest that atherosclerotic plaques are the major source of TF that triggers thrombosis after plaque rupture (Figure 1). [4, 18, 24]

Hyperlipidemia and Coagulation

Hyperlipidemia describes a pathological condition in which there are increased lipid concentrations in the blood. These lipids mainly consist of low density lipoprotein (LDL). Previous studies showed that the risk of arterial thrombosis is elevated in patients with increased circulating cholesterol levels in part due to the activation of platelets and the coagulation system.[25-26] Furthermore, patients with type II familial hypercholesterolemia have elevated levels of monocyte TF.[27-28] However, the mechanism of hyperlipidemic induction of systemic coagulation has not been defined.

In the early stages of atherosclerosis, it is thought that circulating LDL infiltrates into the arterial wall due to endothelial dysfunction.[29] The trapped LDL particles become progressively oxidized resulting in the modification of LDL into biologically active lipids termed oxidized LDL (oxLDL). OxLDL is rapidly internalized by infiltrating monocytes/macrophages and this results in the expression of inflammatory mediators that increase endothelial dysfunction, which further increases monocyte infiltration, macrophage foam cell formation, and production of oxLDL.[29] This vicious cycle is the foundation of atherosclerotic disease progression. While the majority of oxLDL is found in the atheroma, small amounts are also detected in the circulation of patients with acute coronary syndromes (ACS).[30-33] Moreover, elevated levels of oxLDL are observed in the plasma of hyperlipidemic mice before atherosclerotic disease is evident.[23, 34] Importantly, oxLDL and other bioactive lipids induce TF expression in monocyte/macrophages, endothelial, and VSMCs.[23, 35-39] These data suggest that oxLDL induction of TF expression may be responsible for the hypercoagulably state observed during hyperlipidemia.

Circulating TF+ MPs in Hyperlipidemic Coagulation

Several studies have reported elevated levels of TF expression in monocytes, monocyte-derived TF^+ MPs, and TF in the plasma of patients with hyperlipidemia.[9, 23, 27-28, 40] In addition, several studies have found elevated levels of monocyte/macrophage-derived TF^+ MPs and MP TF activity in patients with ACS after a myocardial infarction. These studies have been recently reviewed.[9] These data support the notion that in addition to TF within the atherosclerotic plaque TF^+ monocytes and monocyte-derived, TF^+ MPs may contribute to the formation of an occlusive thrombus after plaque rupture (Figure 1).

We recently demonstrated that hyperlipidemia resulted in a step-wise increase in plasma MP TF activity, which was associated with elevated levels of thrombin-antithrombin in both mice and monkeys fed a high-fat 'Western' diet.[23] In addition, TF expression is induced in peripheral blood mononuclear cells after prolonged hyperlipidemia. Finally, we demonstrated these events coincide with step-wise increases in oxLDL and not total cholesterol, are ablated by *in vivo* administration of an anti-TF antibody, and are dependent upon hematopoietic cell-derived TF. Together, these studies support the notion that monocyte-derived TF is responsible for hyperlipidemic systemic activation of coagulation and that MP TF activity may serve as a biomarker for this hypercoagulable state.

The carotid artery model of thrombosis is not ideal for studying the role of TF^+ MPs in thrombosis because it exposes TF within the vessel wall and hyperlipidemia increases TF expression in the vessel wall and also activates platelets.[9, 41-43] Therefore, we utilized the laser-injury cremaster arteriole model of thrombosis, which is a better model to assess the impact of hematopoietic cell-derived TF^+ MPs in thrombus formation.[9] We found that hyperlipidemia significantly augmented the accumulation of fibrin and platelets at the site of arteriole injury.[23] To assess whether hematopoietic cells contributed to this injury, we irradiated LDL receptor deficient mice and repopulated them with bone marrow from mice expressing human TF in place of mouse TF.[44] Importantly, we found that an anti-human TF antibody reduced the amount of fibrin deposition and platelet accumulation in the cremaster thrombosis model versus an irrelevant control antibody in hyperlipidemic mice (Owens, Passam, Furie, Furie and Mackman, unpublished data). These data suggest that the increased levels of monocyte-derived TF^+ MPs observed during hyperlipidemia can enhance thrombosis (Figure 1).

Statins and Thrombosis

Statins were originally developed to decrease the amount of plasma cholesterol based on the 'lipid hypothesis' of atherosclerosis.[45] However, in addition to reducing the incidence of arterial thrombosis by decreasing plasma LDL or regression of atherosclerosis,[46] statins also have pleiotrophic effects, including anti-inflammatory activity and inhibition of prenylation of intracellular signaling proteins.[47-48] Importantly, statins inhibit TF expression by monocytes and macrophages.[27-28, 36, 38, 49-51] In particular, Ferro and colleagues demonstrate simvastatin treatment of type II familial hypercholesterolemic patients reduces monocyte TF and prothrombin fragment F1+2.[28] Further, treatment of hyperlipidemic mice with either simvastatin or rosuvastatin reduced aortic and

atherosclerotic TF expression without reducing lipid levels.[47, 52] In addition, simvastatin and pravastatin treated hyperlipidemic pigs and monkeys had reduced inflammation and thrombogenicity without affecting lipids levels.[53-54] We recently demonstrated that simvastatin administration could completely attenuate hyperlipidemic-induced increases in oxLDL, peripheral blood mononuclear cell TF, MP TF activity and TAT (all independent of changes in plasma cholesterol and LDL) in both mice and monkeys.[23] These studies extend a previous study by Undas and colleagues that demonstrated lipid-independent anti-inflammatory and antithrombotic effects in human hyperlipidemic patients with short-term simvastatin therapy.[55] These data suggest that the anticoagulant activity of simvastatin during hyperlipidemia is in part due to its ability to inhibit monocyte TF expression (Figure 1).

Statin therapy can also reduce the risk of venous thromboembolism (VTE) in patients with established cardiovascular disease [56] and in healthy patients with idiopathic VTE.[57-58] Furthermore, a recent clinical trial called JUPITER evaluated preemptive administration of rosuvastatin to individuals with normal LDL but elevated levels of inflammation.[59] Statin therapy significantly reduced the incidence of major cardiovascular events and symptomatic VTE.[60] It was speculated that the reduction in thrombosis was due to statin inhibition of TF expression, but this was not analyzed.[60] Several publications concur with the findings of the JUPITER study [61-63] and when grouped together in large meta-analyses [64-66] further support the notion that statin treatment reduces the risk of VTE. Statins may reduce TF expression indirectly by inhibiting the expression of inflammatory mediators. However, this appears to be unlikely because cytokines are weak inducers of monocyte TF expression and inflammation is not a risk factor for VTE. Thus it seems more likely that statins are reducing VTE by directly inhibiting monocyte TF expression (Figure 1).

Conclusion

In summary, TF expression within the atherosclerotic plaque is the major source of TF that triggers thrombosis after plaque rupture. In addition, TF expression in circulating monocytes and monocyte-derived TF^+ MPs is also likely to contribute to formation of thrombus. TF^+ MPs may be a useful biomarker for monitoring the activation of coagulation in hyperlipidemic and atherosclerotic patients. Statin therapy can reduce hyperlipidemia, monocyte TF, TF^+ MPs, and the incidence of both arterial and venous thrombosis. This anti-coagulant activity of statins appears to be due to their ability to inhibit monocyte TF expression. However, it is possible that inflammatory mediators also contribute to pathological TF expression. In light of all the aforementioned studies, statins label as ‘the miracle drug’ and ‘new aspirin of the 21st century’ seems to be a profound and prophetic statement.

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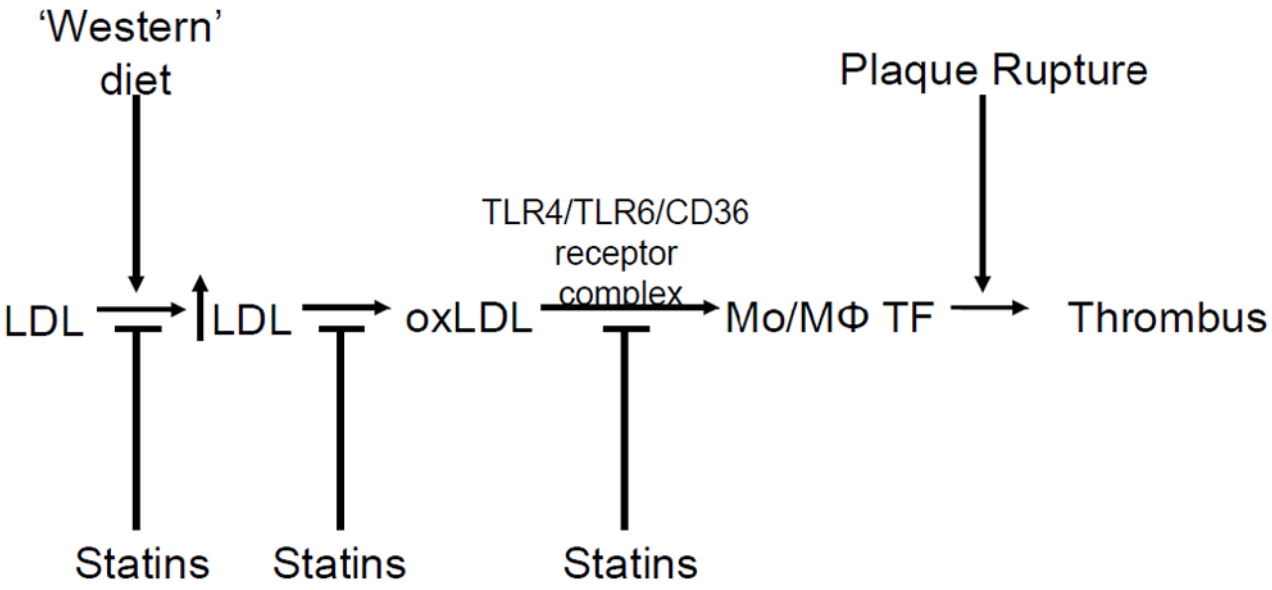

Figure 1. Pathways that lead to TF expression during hyperlipidemia

Levels of circulating low density lipoproteins (LDL) are increased with the consumption of a high fat/high cholesterol 'western' diet. This results in oxidation of LDL (oxLDL), which can increase the expression of tissue factor (TF) in macrophages (MΦ) and circulating monocytes (Mo), via a TLR4/TLR6/CD36 receptor complex, which release TF^+ MPs. Plaque rupture would exposure of high levels of TF to the blood and trigger thrombosis. TF expression in monocytes and monocyte-derived TF^+ MPs may also contribute to thrombosis. Statins inhibit increases in LDL, increases in oxLDL, induction of monocyte TF expression, and reduce thrombosis.