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The role of the CD40/CD40 ligand system in the pathogenesis of atherosclerosis

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Abstract

Increasing evidence shows that the cells associated with atherogenesis (platelets, endothelial and smooth muscle cells, fibroblasts, monocytes, macrophages and T lymphocytes) express pro-inflammatory pathways of CD40 signalling. Activation of platelets CD40/CD40L system and its counterpart CD40 receptors on vascular cell surface induces the expression of various adhesion molecules, cytokines, chemokines, growth factors, matrix metalloproteinases and reactive oxygen species, the substances which are responsible for plaque formation, destabilisation and rupture. Disturbed laminar blood flow (low wall shear stress) can mediate CD40/CD40L system signalling by increasing the residence time of the interaction between platelets and endothelium.

Experimental studies provide considerable data indicating that interruption of CD40 signalling significantly inhibits the progression of established atheroma and altered plaque composition for a lipid-poor collagen-rich stable plaque phenotype. Recent data suggest different aspects of CD40/CD40L system activation in the context of risk factors (hypercholesterolaemia, diabetes mellitus, obesity and cigarette smoking) link them into the pro-inflammatory and pro-thrombotic milieu, aggravating the atherosclerotic process. Activation of the CD40/CD40L system plays a pivotal role in acute coronary syndromes as well as acute cerebral ischaemia. After percutaneous coronary intervention the risk of restenosis increases with high levels of plasma-soluble CD40L (sCD40L). In apparently healthy women sCD40L concentration has been recognised as an independent risk factor of the first acute coronary event. Clopidogrel, aspirin, statins and some oral hypoglycaemic agents share common anti-inflammatory properties including inhibition of CD40/CD40L intercellular signalling. To prevent plaque progression, destabilisation and thrombotic complications, anti-platelet treatment strategy should be focused on inhibition of platelet activation instead of on response to platelet aggregation. (Folia Cardiol. 2006; 13: 283–292)

CD40/CD40L system, platelets, atherosclerosis

Pro-inflammatory activities of the CD40/CD40L system

Platelets are involved not only in homeostasis and thrombosis, but also, as is increasingly recognised, in atherosclerotic lesion formation and restenosis processes. "Some data indicate that at sites predisposed for atherosclerotic development like artery bifurcations, T-junctions, turbulent flow can induce endothelial overexpression of adhesion

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molecules" [1]. Numerous observations provide evidence that the pro-inflammatory CD40/CD40L system may be involved in this process.

There are continuous mechanical and humoral responses to the endothelium and blood flow [2]. Disturbed laminar blood flow (turbulent, pulsatile or reverse flow) can lead not only to endothelial cell dysfunction but also to structural modifications of cells. In low wall shear stress endothelial cells become more rounded and display a polygonal non-oriented shape. Because of high cell turnover, intracellular junctions become leaky, allowing an increase in the influx of macromolecules, platelet adhesion and leukocyte recruitment [2–6]. In contrast, the steady unidirectional laminar high blood-flow protects against atherosclerotic plaque formation [7, 8].

It has become increasingly clear that locally disturbed laminar flow is at the root of atherosclerosis and its complications. Atherosclerotic plaques are not distributed at random but there is a characteristic topographic distribution pattern. Atherosclerotic lesions tend to be found almost exclusively at specific arterial sites such as the proximal segments of coronary and renal arteries, major bifurcations and T-junctions [3, 9–11]. The progression of atheromatosus plaque is usually eccentric and the location well-defined. Sabbah at al. [13, 14] documented that the inner walls of the coronary arteries are particularly prone to artherosclerotic plaque formation. In the thoracic aorta the highest prevalence of fatty streaks occurred in the dorsal surface with the highest prevalence midway between successive pairs of intercostal ostia [11].

In spite of the fact that traditional risk factors are systemic (such as hypercholesterolaemia, diabetes mellitus, tachycardia, hypertension, cigarette smoking and obesity) the distribution of atheromatosus plaques is restricted to the specific sites mentioned above only in large and medium-size arteries in which, according to Reynolds' equation, there are suitable conditions for disturbed laminar blood flow. This means that in atherosclerotic development certain hemodynamic features like blood velocity and flow pattern should be considered [15, 16]. There is a positive association between the distribution of atheromatosus plaques and low wall shear stress, a finding that does not run contrary to the observation that accelerated flow through stenosis can promote platelet activation [17–21]. One can speculate that the initiation and evolution of atheroma is related to low shear rate, the hemodynamic factor that increases the residence time of interaction between platelets and endothelium. This can predispose to pro-inflammatory communication between the CD40/CD40L system and the endothelial cells, especially when plasma viscosity is high, as has been shown to be the case in patients with typical cardiovascular risk factors.

In arteries with a defective endothelium a paradoxical reaction is observed. At sites of early atherosclerosis acetylcholine rather than vasodilatation provokes vasoconstriction and predisposes to disturbance of laminar flow [22]. Under conditions of disturbed flow platelets and endothelial cells release adhesion molecules, chemokines, cytokines and growth factors active in pro-inflammatory and procoagulant responses. This increases the adhesiveness of the endothelium with respect to platelets as well as other morphological blood elements, aggravating the chronic inflammatory reaction of plaque formation [23]. Because of its broad biological activity, the CD40/CD40L system has emerged as one of the most important players in the atherosclerotic process.

Despite the fact that platelets are anucleate blood cells, they posses high proinflammatory properties and, upon activation, are able to release chemokines and synthesise some cytokines (interleukin-1β) [24]. The CD40 ligand (CD40L, CD154) is a transmembrane protein (39 kDa), structurally related to the cytokine TNF-α. CD40 is a 50 kDa integral membrane protein of the TNF receptor family. The CD40/CD40L system is expressed on a variety of immunological and vascular cells that are major players in atherosclerosis, namely activated T lymphocytes, monocytes, macrophages and endothelial and smooth muscle cells, but platelets are the major contributor of the soluble CD40 form (sCD40L, 18 kDa). It is estimated that 95% of the circulating sCD40L is derived from platelets [25–27] (Table 1). It is calculated that 10^8 platelets contain about 2.5 ng CD40L but the possibility cannot be excluded that some circulating sCD40L can be

Table 1. Immunological and vascular cells expressing CD40/CD40L system (adapted according to [34])

T and B lymphocytes
Polymononuclear granulocytes (basophils/eosinophils)
Mononuclear phagocytes (monocytes/macrophages)
Dendric cells
Endothelial cells
Smooth muscle cells
Fibroblasts
Platelets

derived from endothelial cells, monocytes and activated T lymphocytes [27–36].

CD40L is not stored in α-granule but in platelet cytosol. Normally absent on the surface of unstimulated platelets, CD40L is present within seconds on the platelet surface and rapidly cleaves to generate a biologically active soluble fragment (sCD40) [26, 31]. Like platelet-selectin (sP-selectin) and platelet-monocyte aggregates, soluble CD40L is regarded as a sensitive marker of in vivo platelet activation [35–37].

The low wall shear stress promotes binding of the CD40 ligand presented on activated platelets, T lymphocytes and monocytes to the CD40 receptors expressed on vascular cells. As a consequence of CD40 ligation to its receptor, several pro-atherogenic processes are initiated [38].CD40L binding enhances synthesis of adhesion molecules [39]. Activated platelets aggregate with leukocytes and more easily adhere to endothelium [40, 41]. The cells associated with atherosclerotic lesion exhibit abundant expression of CD40 on their surface. CD40/CD40L signalling is a crucial mediator not only in the initial events of atherogenesis but also in the progression and thrombotic complications of atheroma. Ligation of CD40L expressed on platelets and immunological cells to the endothelium, smooth muscle cells and fibroblasts not only results in abundant expression of adhesion molecules (selectin, VCAM-1, ICAM-1) [26, 42–46] on those cells but also stimulates chemokine production (IL-8, RANTES MCP-1, MIP-1α) [47–51]. In vitro CD40/CD40L activation in endothelial and smooth muscle cells and monocytes increases the generation of atherogenic cytokines (IL-1, IL-6, IL-12, IFN-γ, TNFα) and growth factors (Table 2) [38, 52]. Key elements of atherosclerotic lesions, adhesion molecules, are expressed mainly in areas of low wall shear stress, promoting the recruitment of platelets, monocytes and lymphocytes to dysfunctional endothelium.

The importance of adhesion molecules in atherogenesis has been demonstrated in experimental models. In apolipoprotein E-deficient mice (ApoE$^{-/-}$) inhibition of different adhesion molecules attenuates or protects against atherosclerosis [53–55]. In mouse models engineered for accelerated atherosclerosis administration of the CD40L blocking antibody or targeting of the CD40L gene greatly inhibits the initiation of lesions and makes the plaque phenotype more stable. The lesions of anti-CD40L--treated mice exhibit more smooth muscle cells and interstitial collagen and have reduced lipid-content, fewer macrophages and T lymphocyte. Disruption of CD40/CD40L signalling is associated with downregulation of the expression of adhesion molecules such as VCAM-1 and matrix metalloproteinases [56–58].

The long-term blockade of CD40/CD40L suppress murine cardiac allograft arteriopathy, improve graft function and decrease allograft endothelial activation by downregulation of the expression of adhesion molecules [59].

Thrombotic activity of CD40/CD40L system

sCD40L is a bifunctional protein, being involved in both thrombosis and inflammation. CD40/CD40L interaction promotes thrombotic activity by means of matrix metalloproteinase-enhanced function. This leads to more a fragile plaque phenotype, prone to rupture and thrombus formation. Activation of CD40/CD40L increases tissue factor expression on macrophages and endothelial cells and this is the second reason why the CD40/CD40L system is engaged in procoagulant activity [60, 61]. The thrombotic sCD40 ligand properties are also due to a KGD sequence located near the amino

Table 2. Pro-inflammatory molecules stimulated by CD40/CD40L signalling in atheroma-associated cells (adapted according to [34])

Cytokines: IL-1α/β, IL-2, IL-5, IL-8, IL-10, IL-12, IL-15, IL-18, TNF-α/β, INF-γ
Adhesion molecules: P-selektin, E-selektin, ICAM-1, VCAM-1
Growth factors: VEGF, FGF, M-CSF, GM-CSF
Chemokines: IL-8, MCP-1, RANTES, MIP-1α/β
Metalloproteinases: MMP from 1 to 13
Procoagulant: TF

IL — interleukin, TNF — tumour necrosis factor, INF — interferon, ICAM — intercellular adhesion molecule, VCAM — vascular cell adhesion molecule, VEGF — vascular endothelial growth factor, FGF — fibroblast growth factor, M-CSF — monocyte colony stimulating factor, GM-CSF — granulocyte/monocyte colony stimulating factor, MCP — monocyte chemotactic protein, RANTES — regulated on activation normal T cell expressed and secreted, MIP — macrophage inflammatory protein, MMP — matrix metalloproteinases, TF — tissue factor

terminus that allows the protein to bind to $\alpha_{IIb}\beta_3$ receptors, promoting stable platelet aggregate formation [62]. The absence of CD40L affects the stability of arterial thrombi and delays arterial occlusion in vivo. Infusion of recombinant soluble CD40L restores normal thrombosis [62].

Activation of endothelial cell CD40 receptors enhances reactive oxygen species production and inhibits endothelial cell migration. The reactions may play a crucial role when vessel injury occurs (plaque erosion or PTCA). Because the activation of CD40 receptors inhibits re-endotheliasation, the risks of thrombus formation or the restenosis process are increased [63].

CD40/CD40L as a marker of inflammation

The risk factors of atherosclerosis are features which are more frequently present in patients who are ill in comparison to healthy persons. The correlation between atherosclerosis and risk factors is, in fact, not causal but strictly statistical. Hypertension, hypercholesterolaemia or cigarette smoking double the risk of coronary artery disease. The risk in diabetic patients is even higher, but hypertension and hypercholesterolaemia concomitant with diabetes multiply the risk. It can safely be speculated that the risk factors promote the atherosclerotic process through a common pathological mechanism. Such an assumption can explain why the global risk is not the sum of single risk factors and indicates that they act synergically.

There is a considerable overlap in predicted risk between those subjects who did and those who did not develop acute coronary syndromes and well-known risk factors can account for the occurrence of acute episodes in the minority of them [64–65]. Atherosclerosis is a multi-factorial dynamic and progressive disease and there is increasing evidence to show that various inflammatory markers and agents (sedimentation rate, fibrinogen, CRP protein, interleukin 6, amyloid and ICAM-1) are involved in this process [66–71]. The CD40/CD40L system has recently joined this extensive list. In a prospective nested case-control study of apparently healthy middle-aged women, (Women's Health Study) an elevated plasma concentration of sCD40L at baseline foretold a significantly increased risk of future cardiac events [72].

Epidemiological data has consistently demonstrated a statistical correlation between different markers of inflammation and atherosclerotic complications but it remains unknown whether this represents a marker or consequence of cardiovascular disease. Elevated sCD40L concentration can be rendered an "innocent bystander" or, because of its broad function in vivo, can exacerbate clinical symptoms [73].

CD40/CD40L and well-known risk factors

The plasma levels of CRP and interleukin-6 in patients with non-insulin-dependent diabetes mellitus correlate positively with glucose level and insulin resistance [74, 75]. Plasma TNF, plasminogen activator inhibitor-1 (PAI-1) levels and platelet activation are increased in diabetic patients with a concomitant high level of sCD40L [76–80]. Varo at al. [80] revealed that type 2 and type 1 diabetic patients had a significantly higher sCD40 concentration. Furthermore, high sCD40L levels positively correlate with interleukin-6, tissue factor and diabetes control (HbA_{1c}) [81]. CD40/CD40L system activation in diabetics is manifested not only in a high level of sCD40L but also in overexpression of CD40 ligand and CD40 receptors on the platelets surface [81].

Patients with hypercholesterolaemia, in common with those with diabetes, exhibit overproduction of different cytokines, chemokines and adhesion molecules and platelet activation is observed. CD40 and P-selectin expression on platelets correlate with LDL cholesterol concentration [82–85]. The sCD40L levels are higher in patients with low HDL cholesterol and correlate with sICAM, apolipoprotein B and a prothrombotic state [86–90]. Schönbeck at al. [91] suggest that oxidised LDL can provide an initial signal for overexpression of the CD40 receptor/ligand dyad in atherosclerotic plaque.

The clinical data linking hypertension and inflammation are scarce. In one study patients with essential hypertension showed a significant overexpression of CD40 on platelets as well as increased sCD40L levels compared with controls [92].

Presumably, CD40/CD40L system may combine with other risk factors such as cigarette smoking [93] and obesity [94–95]. Tobacco use upregulates the CD40 expression on monocytes and CD40L on the surface of platelets and favours the platelet-monocyte aggregation involved in the inflammatory and thrombotic process [96]. High levels of sCD40L and concentrations of adhesion molecules (sICAM-1, sVCAM-1, sE-selectin, sP-selectin) have been demonstrated in obese children [95].

CD40/CD40L interaction promotes atherosclerosis independently of its vascular localisation [97].

Evidence of CD40/CD40L activation accompanies thrombotic complications of atherosclerosis (unstable angina, myocardial infarction and acute cerebral ischaemia) [61, 73, 80, 98] and is associated with percutaneous coronary interventions [73, 99, 100] as well as cardiopulmonary bypass [29]. In patients with chronic heart failure, soluble CD40L concentration correlates with clinical severity, neurohormonal dysregulation and left ventricular dysfunction [101]. The high concentration of sCD40L, IL-6 and MCP-1 in pulmonary arterial hypertension may suggest the involvement of CD40/CD40L signalling in chemokine-related pathogenic mechanisms [102].

CD40/CD40L system overexpression may be involved in the pathogenic mechanism of atherosclerosis in patients from high-risk groups such as those with Crohn's disease, ulcerative colitis and Kawasaki disease [32, 103]. Enhanced CD40/ /CD40L signalling and elevated serum concentrations of cytokines are found in patients with the autoimmune diseases of systemic lupus erythematosus and rheumatoid arthritis. This may be a pivotal mechanism in the creation of a pro-inflammatory micro-environment which promotes the development of accelerated atherosclerotic vascular disease in this group of patients, especially when well-known risk factors are absent [104–109].

CD40/CD40L in acute coronary syndromes

Platelets from patients with unstable angina are characterised by markedly decreased intracellular CD40L levels as well as a decreased release of sCD40L on stimulation. This indicates that in acute coronary syndromes platelets are the source of high concentrations of soluble CD40L [73]. Enhanced activation of the CD40/CD40L system during thrombotic complications of atherosclerosis confirms not only elevation of sCD40L concentration but also overexpression of the CD40 ligand and CD40 receptors on platelets and the CD40 ligand on the surfaces of monocytes [61, 98, 99]. Concentrations of sCD40L correlate with the formation of aggregates of monocyte-platelets [110]. There is a positive correlation between MMP-9, MMP-3, and CD40L expression on platelets as well as sCD40L levels [61]. Patients with myocardial infarction have higher concentrations of soluble CD40L compared with patients with unstable angina. This finding indicates that the patients with myocardial infarction have increased hydrolysis of surface CD40L, but overexpression of CD40L on platelets in unstable angina can be a marker of platelet activation and an increased risk of acute thrombotic complications [98].

The OPUS-TIMI 16 (Orbofiban in Patients with Unstable coronary syndromes) [110] and CAPTURE (Chimeric c7E3 AntiPlatelet Therapy in Unstable angina REfractory to standard treatment) [111] studies confirm that the intensity of CD40/CD40L system activation is a powerful clinical marker for the identification of the high-risk group among patients with unstable angina. Patients with elevated serum levels of sCD40L have a significantly greater risk of major adverse cardiovascular events, including acute myocardial infarction, sudden death and recurrent angina [112]. In patients with unstable angina who are negative for troponin, elevation of soluble CD40L identifies a subgroup that is more likely to benefit from anti-platelet treatment with abciximab [110].

CD40/CD40L and restenosis after coronary angioplasty

Clopidogrel pretreatment reduces platelet activation and CD40/CD40L signalling after mechanically induced plaque rupture by percutaneous transluminal coronary angioplasty (PTCA) [73, 99, 113]. After coronary angioplasty the concentration of inflammatory markers (IL-6, CRP and sCD40L) is increased [114]. The overexpression of adhesion molecules (VCAM-1, ICAM-1, E-selectin) on endothelial and smooth muscle cells is observed and a high concentration of monocyte chemoattractant protein-1 (MPC-1) is an independent strong predictor of late restenosis [115, 116]. Elevated sCD40L at baseline is significantly correlated with adhesion molecules and MCP-1 generation after angioplasty [117]. A high preprocedural level of sCD40L is an independent predictor of late lumen loss. In addition, increased concentrations of sCD40L after a procedure are more manifest and prolonged in restenotic patients [117]. In vitro sCD40L may activate monocyte and endothelial cells to release MIP-1 and reactivate oxygen species generation and inhibit endothelial cell migration, a process considered critical for the re-endotheliasation of the injured vessel. The sCD40L-dependent endothelium and monocyte-mediated inflammatory reaction after PTCA may be one of the most important mechanisms of enhancing the restenotic process [63, 117].

Therapeutic modalities that downregulate the CD40/CD40L system

During past decades anti-platelet treatment concentrated on the inhibition of platelet aggregation,

but increasing evidence shows that an equal or even more critical issue in anti-platelet therapy is inhibition of platelet activation. Results from the CAPRIE (Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events) and CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trials indicate that clopidogrel therapy results in downregulation of CD40/CD40L interaction with a concomitant anti-inflammatory and antithrombotic effect [118, 119]. There are four groups of drugs: clopidogrel, aspirin, statins and some oral hypoglycaemic agents which have in the common the ability to inhibit CD40/CD40L signalling [31, 79, 91, 120, 121].

Intravenous glycoprotein IIb/IIIa antagonists inhibit hydrolysis of sCD40L from the surface of activated platelets. However, this does not prevent translocation of intraplatelet CD40L stores to the platelet surface [63, 64]. In the CAPTURE study patients with the highest level of sCD40L benefited more from abciximab therapy [110]. Because they protect against acute thrombotic complications, intravenous glycoprotein GP IIb/IIIa blockers remain an adjunctive therapy for percutaneous coronary intervention or a rescue therapy when thrombotic complications occur.

The inhibitory effect of glycoprotein IIb/IIIa antagonists is dose-dependent and suboptimal platelet aggregation inhibition unexpectedly potentiates the release of sCD40L from platelets CD40L [121, 122]. Glycoprotein IIb/IIIa blockers given in a sufficient dose, however, inhibit platelet aggregation but do not prevent the platelet stimulation induced by platelet agonists [123].

Despite their promise as active potent inhibitors of platelet aggregation, oral platelet glycoprotein IIb/IIIa inhibitors have failed to bring about a reduction in ischaemic events. In view of the risk of increased bleeding events, sub-optimal inhibition of platelet aggregation was probably one of the reasons why this therapeutic group of drugs has been disappointing. A 16% increase in myocardial infarction was observed with oral glycoprotein IIb/IIIa blockade without concurrent aspirin, together with a statistically significant increase in bleeding complications [124, 125]. Platelet aggregation affected by lack of platelet glycoprotein GPIIb/IIIa complexes in patients with Glanzmann thrombasthenia does not protect against the development of atherosclerosis [126]. These observations have argued persuasively that ongoing platelet activation plays an integral role in the pathophysiology of atherosclerosis and shifts the focus of anti-platelet therapy from aggregation inhibition to prevention of platelet activation. In addition, relatively weak platelet antagonists, such as aspirin and the thienopyridines, have brought about a relative reduction of about 25% in cardiovascular-event risk when administered as secondary prevention.

Surface expression of CD40L is stimulated by a variety of platelet agonists including ADP, collagen, thrombin and tromboxane A2 [31]. As a result of the cytoplasmatic localisation of platelet CD40L, platelet stimulation by weak agonists may trigger CD40L-dependent pathology even in the absence of platelet secretion [26, 38]. Clopidogrel, by blocking platelet $P2Y_{12}$ purineric receptors, inhibits ADP-induced CD40L expression and aspirin collagen-induced sCD40L release [121, 127, 128].

Blockade of $P2Y_{12}$ receptors can diminish communication between platelets and monocytes, which leads to a reduction in circulating platelet-leukocyte aggregates, monocyte tissue factor generation and CD40L, P-selectin and GP IIb/IIIa receptor expression on the surface of platelets, with a subsequent antithrombotic and anti-inflammatory effect [63, 129]. Aspirin use (325 mg for 7 days) results in a 50% decrease in the release of sCD40L from collagen-induced platelet aggregates [121]. These observations provide new insight into the mechanism of anti-platelet therapy strategy.

Inhibition of platelet activation by aspirin and clopidogrel downregulate pro-inflammatory and prothrombotic platelet communication with vascular cells and lymphocytes and protect against the release of various mediators of CD40/CD40L system signalling. More pronounced platelet activation inhibition can explain the prevalence of the combined therapy of aspirin and ticlopidine rather than that of aspirin and warfarin for the prevention of the serious complication of stent thrombosis [130]. The COMMIT/CCS-2 (CLOpidogrel and Metoprolol in Myocardial Infarction Trial/Second Chinese Cardiac Study) and CLARITY-TIMI 28 (Clopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis in Myocardial Infarction) trials revealed that the addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction is superior with regard to the patency rate of the infarct-related artery and reduces ischaemic complications without any increase in haemorrhagic complications [131,132].

Lipid-lowering therapy downregulates CD40L expression in atherosclerotic plaque [133] and even after short periods of therapy statins diminish CD40/CD40L signalling in monocytes, endothelial and smooth muscle cells and lower plasma MCP-1 concentration [84, 91]. Long lasting, lipid-lowering therapy is associated with a reduction in sCD40 plasma level [88]. The pleiotropic effect of statins

provides a novel insight into their anti-inflammatory properties, which can be especially important for patients with high sCD40L concentrations [120].

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