Upregulation of CD40-CD40 Ligand (CD154) in Patients With Acute Cerebral Ischemia

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Background and Purpose—Inflammation and hypercoagulability contribute to the development of acute cerebral ischemia. Both can be mediated by the CD40 system. This study investigated whether the CD40 system and related mediators are upregulated in patients with transient ischemic attack (TIA) or stroke.

Methods—Seventeen patients with TIA, 60 patients with complete stroke, and 15 control subjects were investigated. CD154 and P-selectin were analyzed on platelets and CD40 on monocytes during and 3 months after acute cerebral ischemia by double-label flow cytometry. Blood concentrations of soluble CD154 and monocyte chemoattractant protein-1 (MCP-1) were evaluated.

Results—Our main findings are as follows: (1) patients with acute cerebral ischemia showed a significant increase of CD154 on platelets and CD40 on monocytes compared with controls; (2) plasma levels of soluble CD154 were significantly higher in these patients; (3) these patients had significantly higher numbers of prothrombotic platelet-monocyte aggregates; (4) the chemoattractant MCP-1 was significantly elevated in cerebral ischemia; and (5) at 3 months’ follow-up, upregulation of CD154 still persisted in patients with previous acute cerebral ischemia.

Conclusions—Patients with acute cerebral ischemia show upregulation of the CD40 system, which might contribute to the known proinflammatory, proatherogenic, and prothrombotic milieu found in these patients. (Stroke. 2003;34:1412-1418.)

Key Words: blood platelets ■ CD40 ■ CD154 ■ cerebral ischemia ■ inflammation

Acute cerebral ischemia is a major cause of human suffering, hospitalization, chronic disability, and death. The past few years have shown the crucial role of inflammation in the pathophysiology of atherosclerosis and its clinical manifestations, ie, coronary artery disease, peripheral artery disease, and stroke. Atherosclerosis involves inflammatory cells (ie, T cells, monocytes/macrophages) in the vasculature as well as the systemic elevation of proinflammatory cytokines, chemokines, adhesion molecules, and tissue factor.

Another important feature of advanced stages of atherosclerosis is the formation of an intravascular thrombus, which plays a central role, particularly in the setting of acute coronary or cerebral ischemia, as shown by histopathologic and interventional studies. Interestingly, the intricate interface between inflammation and thrombosis is currently becoming apparent. Platelets produce a variety of inflammatory mediators, such as platelet-derived growth factor, platelet factor 4, thrombospondin, transforming growth factor-β, and nitric oxide, thus contributing to the vascular inflammation during the formation of an intravascular thrombus. Hereby, antithrombotic treatment might suppress inflammation.

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1412
factor or activates matrix metalloproteinases.\textsuperscript{6,7} In addition, CD154 is strongly upregulated on platelets constituting a fresh thrombus.\textsuperscript{8} Thus, the CD40-CD154 system appears to be a critical pathway for local inflammation of the vascular wall and the hemostatic system.

Whereas the role of CD40-CD154 in acute coronary syndromes has been proven recently,\textsuperscript{9,10} no study has addressed the potential relation between acute cerebral ischemia and the CD40 system. Therefore, the present study was designed to investigate whether the CD40-CD154 dyad is modified in patients with transient ischemic stroke (TIA)/stroke with regard to platelets, monocytes, and T cells. In addition, prothrombotic and proinflammatory parameters, such as platelet-monocyte aggregates and C-reactive protein (CRP) were determined.

### Methods

#### Patients and Controls

The study contained 60 patients with ischemic stroke and 17 patients with a TIA who were admitted to the stroke unit of the Department of Neurology at the University of Erlangen-Nuremberg within 24 hours after the onset of symptoms. Patients with symptoms lasting for \(>24\) hours were excluded from the study. Further exclusion criteria were infections, malignancies, autoimmune diseases, acute coronary syndromes, surgery within the previous 12 months, and intracerebral hemorrhage. A detailed history was obtained (see Table 1). Blood concentrations of leukocytes, platelets, and CRP were determined.

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#### Blood Sampling Protocol

Peripheral venous blood was drawn by physicians into blood-collection tubes containing sodium citrate within 6 hours after admission and before the administration of any medications, including thrombolytic agents. Blinded blood samples were either centrifuged (190 \(g\), 10 minutes, room temperature [RT]) by the laboratory assistants to obtain platelet-rich plasma or immediately fixed with 1% formaldehyde (1:1, vol/vol). Noncitrated blood was immersed in melting ice and allowed to clot for 1 hour before centrifugation (1500g, 10 minutes, 4\(^\circ\)C). The supernatant was stored at \(-80\)^\(\circ\)C until analysis. Samples were thawed only once.

#### Immunofluorescence

The following antibodies were used: fluorescein isothiocyanate (FITC)-conjugated anti-CD154 (B-B29, mouse IgG\(_2\), anti-CD62P (FITC; AK-4, mouse IgG\(_1\)), mouse IgG (FITC), phycoerythrin (PE)-conjugated anti-CD61 (PM6, mouse IgG\(_1\)), and anti-CD4 (PE; RFT-4, mouse IgG\(_1\)) from Dianova and anti-CD40 (FITC; 5C3, mouse IgG\(_1\)), anti-CD14 (PE; M5E2, mouse IgG\(_2\)), and anti-CD25 (FITC; M-A251, mouse IgG\(_1\)) from Pharmingen.

Platelet immunostaining was performed as previously described.\textsuperscript{14} Fixed blood was diluted 1:200 with phosphate-buffered saline and incubated with the antibodies for 30 minutes at RT. In some experiments, we used platelet-rich plasma for the stimulation of platelets (20 000/\(\mu\)L) with ADP (5 \(\mu\)mol/L, for 10 minutes at RT; ADP from Sigma). Thereafter, platelets were diluted to 2500/\(\mu\)L and incubated with the antibodies (anti-CD154, anti-CD62P [directed at P-selectin] and anti-CD61 [directed at the membrane glycoproteins \(\alpha\IIb\beta3\) and \(\alpha\IIa\beta3\) on platelets]) for another 30 minutes at RT. A total number of 10 000 cells was measured by flow cytometry (FACSCalibur, Becton-
trol, P stroke, 18.2/H11006 the control subjects (control, 4.9
percentage of platelets positive for expression of CD154 in each
patient with TIA or stroke was also significantly higher than in
blood was incubated with anti-CD4 (for identification of CD4
1:5 and incubated with anti-CD40 and anti-CD14 (for identification of
variability was <10%. Before starting the study, experiments had
excluded the possibility that the fixation procedure with 1% formalde-
hyde significantly altered the expression of any of the epitopes
measured.1

For the evaluation of CD40 on monocytes, fixed blood was diluted
1:5 and incubated with anti-CD40 and anti-CD14 (for identification of
monocytes) for 30 minutes at RT. To determine T-cell activation, fixed
blood was incubated with anti-CD4 (for identification of CD4+ T cells)
and anti-CD25 (for identification of interleukin-2 receptor as a marker
of T-cell activation). Erythrocytes were removed by adding 2 mL FACS
lysis solution (PharMingen) for 10 minutes at RT. Leukocytes were
washed twice with phosphate-buffered saline and fixed in 1% formalde-
hyde in phosphate-buffered saline. Monocytes were identified by
gating for CD14+ cells and T cells, by gating for CD4+ cells.

Adhesion of platelets to monocytes was measured as previously
described.15 In brief, 100 μL citrate-anticoagulated blood was diluted
with HEPES-Tyrode’s buffer (1:2, vol/vol). Samples were incubated
with anti-CD61 or isotype-matched control. After 30 minutes of
incubation at RT, 1 mL FACS lysis solution was added for 10 minutes
to lyse erythrocytes before analysis by flow cytometry. Platelet-
monocyte aggregates were identified by gating on the monocyte
population.

Measurement of Soluble CD154 and MCP-1
Serum (MCP-1) levels and plasma (sCD154) levels were analyzed in
duplicates by using commercially available ELISAs (sCD154 detection
limit, 95 pg/mL, Bender MedSystems; MCP-1 detection limit, 5
pg/mL, R&D) according to the manufacturers’ instructions.

Statistics
The data were analyzed by nonparametric methods to avoid assump-
tions about the distribution of the measured variables. Comparisons
between groups and within groups were made with the Mann-
Whitney U test and Kruskal-Wallis test, respectively. The differ-
ences between baseline and posttreatment values were analyzed with
the Wilcoxon signed-rank test. The association of measurements
with other biochemical parameters was assessed by the Spearman
rank correlation test. All values are reported as mean±SD. Statistical
significance was considered to be indicated by a value of P<0.05.

Results
The data in Table 1 show the baseline characteristics of the
study groups. Etiology of stroke according to the TOAST
criteria was large-artery atherosclerosis in 26.7% (16 of 60
patients) of all patients with stroke, cardioembolism (21.7%,
13/60 patients), small-artery occlusion (30%, 18/60 patients),
stroke of other determined cause (5%, 3/60 patients),
and stroke of undetermined cause (16.7%, 10/60 patients).

CD154 on platelets was significantly increased in
formaldehyde-fixed blood samples from patients with TIA and
stroke compared with those obtained from control subjects
(CD154: control, 9.5±5.8; TIA, 32.3±20.7; and stroke,
25.8±16.3; all net MFI; TIA vs control, P<0.001; stroke vs control,
P<0.001; and TIA vs stroke, P=0.09; Figure 1A). The
percentage of platelets positive for expression of CD154 in each
patient with TIA or stroke was also significantly higher than in
the control subjects (control, 4.9±4.3%; TIA, 17±5.6%; and
stroke, 18.2±11.8%; TIA vs control, P<0.001; stroke vs control,
P<0.001; and TIA vs stroke; P=0.8, Kruskal-Wallis test).

Next to CD154, P-selectin on platelets was significantly upregu-
lated in patients with stroke but not significantly upregulated in
patients with TIA compared with controls (control, 1.2±0.6;
TIA, 2.3±1.8; and stroke, 3.5±3.5 MFI; TIA vs control, P<0.01;
stroke vs control, P<0.01; and TIA vs stroke, P=0.2, Kruskal-
Wallis test). Upregulation of both CD154 and P-selectin
on platelets did not depend on the etiology of stroke (data not
shown). Furthermore, stimulation of unfixed platelets with the
agonist ADP increased the expression of CD154 as well as of
P-selectin in platelets obtained from patients with stroke or
TIA were compared separately with controls.

At 3-month follow-up, expression levels of CD154 in patients
with TIA were even more elevated at this time (24.3±7.3 vs
39.3±13.7 MFI; P=0.01), whereas patients with stroke showed
no significant change in CD154 expression levels at follow-up
(20.9±15.8 vs 29.3±26.2 MFI; P=0.3). In addition, P-selectin
expression was unchanged, elevated expression level in patients
with TIA and stroke at the 3-month follow-up (for TIA, initial event,
2.3±0.9 vs follow-up, 2.9±3.9 MFI, P=0.8; for stroke, 3.4±2.5
vs 4.1±2.9 MFI, P=0.4). Interestingly, throughout the study
groups, the expression of CD154 on platelets showed a signifi-
cant correlation with the expression of P-selectin (r=0.29,
P<0.05).

The soluble and biologically active form16 of CD154
(sCD154) showed significantly higher plasma levels in patients
with TIA and stroke compared with controls (control, 3.4±1.6;
TIA, 16.9±7; and stroke, 17.1±7.5 ng/mL; TIA vs control,
P<0.001; stroke vs control, P<0.001; and TIA vs stroke,
P=0.9; Figure 1B). At the 3-month follow-up, plasma levels of
sCD154 did not decline significantly (TIA initial event,
17.5 ± 7.4 vs follow-up, 15.6 ± 4.7 ng/mL, P = 0.5; stroke initial event, 17.2 ± 6.3 vs follow-up, 18.6 ± 6.2, P = 0.5).

On monocytes, the receptor CD40 was significantly upregulated in patients with TIA and stroke compared with controls (control, 5.3 ± 4.3; TIA, 12.0 ± 4.1; and stroke, 12.5 ± 4.3 MFI; TIA vs control, P < 0.001; stroke vs control, P < 0.001; and TIA vs stroke, P = 0.9; Figure 2). At 3 months’ follow-up, expression of CD40 on monocytes had significantly declined in patients with TIA (10.7 ± 2.9 vs 6.4 ± 4.1 MFI; P < 0.05) as well as in patients with stroke (11.9 ± 4.7 vs 8.8 ± 2.9 MFI; P < 0.01). Activation of platelets with consecutive upregulation of CD154 and/or P-selectin led to an enhanced adhesion of platelets to monocytes (control, 35.9 ± 21.6; TIA, 53.4 ± 16.7; and stroke, 55.1 ± 20.1 MFI; TIA vs control, P < 0.001; stroke vs control, P < 0.001; and TIA vs stroke, P = 0.8; Figure 3) but not to granulocytes (control, 9.8 ± 8.9 vs TIA, 14 ± 5.6 MFI, P = 0.1; control vs stroke 15.2 ± 11.3, P = 0.06; and TIA vs stroke, P = 0.07, Kruskal-Wallis test). The 3-month follow-up showed persistently high numbers of platelet-monocyte aggregates in patients with TIA (initial event, 51.9 ± 18.2 vs follow-up, 61.9 ± 23.7 MFI, P = 0.5), whereas the number of aggregates in patients with stroke had even increased within 3 months (55.6 ± 18.7 vs 72.5 ± 15.5 MFI, P < 0.002).

Upregulation of CD40-CD154 might enhance the release of MCP-1 from endothelial cells or monocytes in vitro. Accordingly, patients with TIA (278.7 ± 184.1 pg/mL) and stroke (267.2 ± 117.6) showed significantly higher serum levels of MCP-1 than did controls (158.7 ± 100.6; TIA or stroke vs control, P < 0.05; and TIA vs stroke, P = 0.5; Figure 4). At the 3-month follow-up, serum concentrations of MCP-1 were almost unchanged in the patient groups (acute ischemic event, 267.2 ± 117.6 vs 3-month follow-up, 246.7 ± 102.2 pg/mL, P = 0.6). Correlation analysis, however, revealed no significant correlation among platelet CD154, number of CD154+ platelets, or sCD154 and serum concentrations of MCP-1 (CD154: r = 0.05, P = 0.7; and sCD154: r = 0.16, P = 0.3).

Next to platelets and monocytes, patients with acute cerebral ischemia showed a significant higher activation of CD4+ T cells, as measured by CD25, compared with T cells of controls (control, 3.4 ± 0.7; and TIA, 10.1 ± 4.2 MFI; TIA vs control, P < 0.001; stroke 10.4 ± 5.8, stroke vs control, P < 0.001; and TIA vs stroke, P = 0.8, Kruskal-Wallis test). At the 3-month follow-up, activation of T cells was still persisting in patients with previous acute cerebral ischemia (initial event, 10 ± 4.9 vs follow-up, 8.9 ± 3.9 MFI, P = 0.4).

**Discussion**

The present study shows CD40-CD154 upregulation in patients with acute cerebral ischemia: patients showed a significant increase of CD4+ T cells, as measured by CD25, compared with T cells of controls when compared with sex- and age-matched controls. Activation of platelets and monocytes led to significantly higher numbers of platelet-monocyte aggregates. The role of the CD40 system in acute cerebral ischemia was further supported by the finding of significantly elevated plasma levels of the soluble form of CD154 in patients with TIA and with stroke. Both forms of CD154 might be responsible for the elevation of MCP-1, which we found to be significantly elevated in acute cerebral ischemia. Although activation of the CD40

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**TABLE 2. Expression of CD154 and P-Selectin on Platelets in Patients With TIA and Stroke and 15 Age- and Sex-Matched Controls (Platelet-Rich Plasma): Expression Before and After Stimulation With 5 μmol/L ADP (Net Mean Fluorescence Intensity)**

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>TIA</th>
<th>Stroke</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=15)</td>
<td>(n=17)</td>
<td>(n=60)</td>
<td></td>
</tr>
<tr>
<td>CD154</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Without</td>
<td>9.9±7.4</td>
<td>19.9±6.8+</td>
<td>17.3±7.2+</td>
<td>+P&lt;0.01 (vs controls without)</td>
</tr>
<tr>
<td>ADP</td>
<td>25.6±18.1*</td>
<td>33.6±23.8</td>
<td>33±27.8*</td>
<td>*P&lt;0.01 (vs without of the group)</td>
</tr>
<tr>
<td>P-Selectin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without</td>
<td>3.2±2.7</td>
<td>8.8±5.3+</td>
<td>8.8±6.5+</td>
<td>+P&lt;0.02 (vs controls without)</td>
</tr>
<tr>
<td>ADP</td>
<td>63.2±29.4*</td>
<td>86.3±37.2*</td>
<td>84.3±29.2*</td>
<td>*P&lt;0.001 (vs without of the group)</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

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**Figure 2.** CD40 on monocytes in 15 controls as well as in patients with TIA (n=17) and with stroke (Insult, n=60). Bars represent mean levels, and the error bars, SD. *P<0.001 vs controls, P=NS, TIA vs stroke (Kruskal-Wallis test). Patients with stroke or TIA were compared separately with controls.

**Figure 3.** Platelet-monocyte aggregates in 15 controls as well as in patients with TIA (n=17) and with stroke (Insult, n=60). Bars represent mean levels, and the error bars, the SD. *P<0.001 vs controls, P=NS, TIA vs stroke (Kruskal-Wallis test). Patients with stroke or TIA were compared separately with controls.
system has been observed in atherosclerosis-related diseases,16,6 our findings represent the first in vivo evidence of CD40-CD154 upregulation in patients with acute cerebral ischemia. These data represent an additional pathophysiological pathway for the prothrombotic and proatherogenic state found in patients with TIA and stroke.

Our results confirm several studies that have shown that acute cerebral ischemia is associated with persistent platelet activation in vivo.17,18 The upregulation of CD154 on platelets, however, represents a new pathophysiological aspect in acute cerebral ischemia.7 P-selectin and CD154 derived from platelets share common features but show biologic differences: both can be immediately expressed on platelets on stimulation with platelet activators. In contrast to previous reports,7 CD154 in platelets is not stored in the α-granule, as is the case for P-selectin, but in the cytosol of platelets and follows a different expression pattern on platelet activation compared with P-selectin.19 Moreover, enzymatic cleavage of membrane-bound CD154 on platelets leads to a rise in soluble CD154, because it was detected in the plasma of our patients with TIA and with stroke.20 Given its strong capability of inducing proinflammatory, prothrombotic, and proatherosclerotic effects in the vasculature, a prominent role for CD154 as a major pathophysiological contributor has to be assumed in the setting of acute cerebral ischemia.

The activation of monocytes in acute cerebral ischemia with consecutive release of proinflammatory mediators has been reported previously.21 Particularly CD40 engagement on monocytes induces many procoagulant and proatherosclerotic effects.22 CD40 on monocytes might be upregulated by proinflammatory mediators, such as CRP.16 The latter was found to be elevated in acute cerebral ischemia.23

CD40 engagement on monocytes might also occur through enhanced platelet-monocyte interaction, because monocytes rapidly adhere for prolonged periods of time to activated platelets that display P-selectin.25 This enhanced interaction between platelets and monocytes increases, through the engagement of CD40, the release of proinflammatory and thrombogenic factors. Moreover, elevated numbers of platelet-monocyte aggregates have been shown to be a stronger predictor of thrombosis compared with P-selectin.25

Our finding of an activation of T cells in acute cerebral ischemia indicates that T cell–derived CD154 might contribute to inflammation in this setting. The observed significant elevation of serum levels of sCD154 in patients with acute cerebral ischemia might therefore not only derive from activated platelets but also from activated T cells.

In addition, we found significantly elevated serum levels of MCP-1, an important chemokine that specifically attracts leukocytes to sites of inflammation. This result stands in contradiction to the study of Losy and Zaremba,26 in which patients with ischemic stroke showed significantly elevated MCP-1 levels in their cerebrospinal fluid but not in their sera. In our larger study, the finding of elevated serum levels of MCP-1 fits into the pathophysiological concept of an ongoing inflammatory process in the setting of acute ischemic syndromes.23 For example, CRP as an established marker of inflammation in these states induces MCP-1 from endothelial cells.23 The MCP-1 release might also be the result of CD40 engagement on endothelial cells27 or on monocytes.28 In an in vitro platelet–endothelial cell coculture model, CD154 on platelets proved its biologic potency by significantly enhancing the release of MCP-1 from human endothelial cells,16,17

An important finding of our study is the persistence of upregulation of CD154 and MCP-1 even 3 months after the initial event. Van Kooten et al29 have reported persistent platelet activation in the chronic phase after stroke as a parameter of poor clinical outcome. Persistent upregulation of CD154 with its known prothrombotic and proinflammatory effects might possibly be another determinant for poor clinical outcome, as has been shown for patients with acute coronary syndromes.10

Specific therapeutic interventions can suppress CD40-mediated proatherogenic effects, because it has been already shown in animal models.6 With regard to platelets, ADP-receptor agonists such as clopidogrel completely abolish CD154 upregulation, whereas aspirin, the most widely used “antiplatelet” agent in acute cerebral ischemia, does not inhibit CD154 expression.19 This observation further supports the potential benefit of new developed antithrombotic substances in the setting of acute cerebral ischemia.30 With regard to monocytes and the endothelium, CD40 upregulation can be effectively suppressed by statins.16 Our present data provide another rationale for the potential benefit of statins in the acute phase of cerebral ischemic disease, as has been recently proven in the setting of acute coronary syndromes.31 Current studies in patients with acute cerebral ischemia treated with statins will prove this.32 A possible limitation of our present study consists of the rather small control group. Hypertensive subjects were particularly underrepresented compared with the study groups.

In conclusion, we have shown that acute cerebral ischemia is associated with activation of the CD40-CD154 system. Because upregulation of this system is particularly involved in the advanced stage of atherosclerosis, including plaque rupture, we propose that activation of the CD40-CD154 system might create and/or maintain the proinflammatory and prothrombotic milieu found in patients with TIA or stroke. Targeting the CD40-CD154 system in acute cerebral ischemia through specific pharmacologic interventions might result in a clinical benefit for these patients.

Acknowledgment

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Mounting evidence indicates that procoagulant and inflammatory pathways intertwine in complex networks and that inflammation contributes in an important way to atherogenesis and arterial thrombosis, ultimately leading to diseases such as ischemic stroke. Among the most intriguing recent findings was the detection of an important role of the potent immune mediator CD40 and its counterpart CD40 ligand (CD154) in thrombosis and atherosclerosis. Initially thought of as solely mediating T lymphocyte–B lymphocyte interactions, CD40 was later also detected on monocytes/macrophages, smooth muscle cells, and endothelial cells. CD40 is an important activation receptor, whose engagement via CD40L endows these cells with powerful functions including the release of proinflammatory cytokines, adhesion receptors, tissue factor, metalloproteinases, and prostaglandins. CD40L, a transmembrane protein structurally related to tumor necro-

**References**


**Editorial Comment**

**Stroke and the CD40-CD40 Ligand System: At the Hinge Between Inflammation and Thrombosis**

Mounting evidence indicates that procoagulant and inflammatory pathways intertwine in complex networks and that inflammation contributes in an important way to atherogenesis and arterial thrombosis, ultimately leading to diseases such as ischemic stroke. Among the most intriguing recent findings was the detection of an important role of the potent immune mediator CD40 and its counterpart CD40 ligand (CD154) in thrombosis and atherosclerosis. Initially thought of as

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In the article entitled “Upregulation of CD40-CD40 Ligand (CD154) in Patients With Acute Cerebral Ischemia” by Garlitsch et al.,1 the name of R. Handschu, MD, was omitted from the list of authors. The publisher regrets the error.