Association Between Polymorphism in the Chemokine Receptor CX3CR1 and Coronary Vascular Endothelial Dysfunction and Atherosclerosis

David H. McDermott,* Julian P.J. Halcox,* William H. Schenke, Myron A. Waclawiw, Maya N. Merrell, Neal Epstein, Arshed A. Quyyumi, Philip M. Murphy

Abstract—Fractalkine, a chemokine expressed by inflamed endothelium, induces leukocyte adhesion and migration via the receptor CX3CR1, and the CX3CR1 polymorphism V249I affects receptor expression and function. Here we show that this polymorphism is an independent risk factor for atherosclerotic coronary artery disease (CAD). Genotyping of the CX3CR1-V249I polymorphism was performed in a cohort of 339 white individuals who underwent cardiac catheterization (n=197 with and n=142 without CAD, respectively). In 203 patients, intracoronary acetylcholine 15 \( \mu \)g/min and sodium nitroprusside (20 \( \mu \)g/min) were administered to test endothelium-dependent and -independent coronary vascular function, respectively. Change in coronary vascular resistance (ΔCVR) was measured as an index of microvascular dilation. An association was observed between presence of the CX3CR1 I249 allele and reduced prevalence of CAD, independent of established CAD risk factors (odds ratio=0.54 [95% confidence interval, 0.30 to 0.96], \( P=0.03 \)). Angiographic severity of CAD was also lower in these subjects (\( P=0.01 \)). Furthermore, endothelium-dependent vasodilation was greater in these individuals compared with individuals homozygous for the CX3CR1-V249 allele (ΔCVR during acetylcholine = −46±3% versus −36±3%, respectively, \( P=0.02 \)), whereas ΔCVR with sodium nitroprusside was similar in both groups (−55±2% versus −53±2%, \( P=0.45 \)). The association between CX3CR1 genotype and endothelial function was independent of established risk factors and presence of CAD by multivariate analysis (\( P=0.02 \)). Thus, the CX3CR1 I249 allele is associated with decreased risk of CAD and improved endothelium-dependent vasodilation. This suggests that CX3CR1 may be involved in the pathogenesis of CAD. (Circ Res. 2001;89:401-407.)

Key Words: genetics ■ fractalkine ■ acetylcholine ■ inflammation ■ epidemiology

Atherosclerotic coronary artery disease (CAD) is a multifactorial process that involves inflammation in response to progressive vascular injury.1 Vascular endothelium plays a key role in this process by secreting factors that can directly regulate vascular tone, induce accumulation and activation of platelets and leukocytes at the vessel wall, and cause proliferation of vascular smooth muscle cells.2,3 Hypertension, diabetes, smoking, and hypercholesterolemia are established risk factors for CAD and appear to work in part by causing endothelial injury, resulting in reduced bioavailability of NO. This state can be clinically characterized by demonstrating impaired vasodilation in response to endothelium-dependent pharmacological probes such as acetylcholine (ACH).4–6 In vivo measurement of coronary vascular endothelial function not only correlates with coronary vasomotion during physiological stress, but also appears to be an independent predictor of long-term progression of atherosclerosis and adverse cardiovascular events.3,7

Genetic factors also appear to be important determinants of cardiovascular disease.8–11 In particular, specific genetic polymorphisms that modulate blood pressure, coagulation, and lipid metabolism have been identified that are associated with increased risk of CAD.12–17 However, none of these associations has identified the precise molecular basis of pathological accumulation of leukocytes in the vessel wall.

In general, leukocyte trafficking is regulated by specific sets of adhesion molecules, chemoattractants, and chemoattractant receptors. The chemokines are a large family of chemoattractant peptides that differentially attract subsets of leukocytes.18,19 Several chemokines have been identified in atherosclerotic lesions, and experiments in knockout mice have revealed a role for one of these, monocyte chemoattractant protein-1 (MCP-1), and its receptor CCR2 (CC chemo-
kine receptor 2).20–22 However, the importance of chemokines in human CAD has not been established.

Fractalkine (CX3CL1 in the systematic chemokine nomenclature)19 is an unusual chemokine markedly upregulated on inflamed endothelium that can function as a chemoattractant and a direct adhesin via its specific receptor CX3CR1. CX3CR1 is expressed on monocytes, T lymphocytes, and natural killer (NK) cells.23 We have previously reported two common nonsynonymous single nucleotide polymorphisms of CX3CR1 that are in complete linkage disequilibrium (V249I and T280M).24,25 The I249 allele has been associated with reduced number of fractalkine binding sites and reduced fractalkine binding affinity on peripheral blood mononuclear cells, as well as with reduced risk for acute coronary events, suggesting that CX3CR1 may participate in the pathogenesis of atherosclerosis by affecting fractalkine-mediated inflammatory events.26 Here we further test this hypothesis by analyzing the association of CX3CR1 polymorphism with angiographically defined atherosclerosis and coronary vascular function.

Materials and Methods

Study Subjects

We studied all 339 white subjects enrolled as of April 2000 in an ongoing clinical protocol to evaluate coronary vascular function. Inclusion criteria for entry to the protocol were chest pain or noninvasive tests consistent with myocardial ischemia and age greater than 21. Patients with significant valvular heart disease and those with recent unstable angina or myocardial infarction were excluded from enrollment. All enrolled subjects underwent cardiac catheterization. A subset of these (n=203) who consented to the procedure and did not have safety exclusion criteria (left main stem disease or 3-vessel disease in whom it would be unsafe to instrument any coronary artery) and were able to tolerate withdrawal of cardiac medications also underwent endothelial function tests. The National Heart, Lung, and Blood Institute Investigational Review Board approved the study, and informed consent for catheterization and genotyping was obtained from all patients.

Clinical Definitions

CAD was defined as angiographic evidence of stenosis in any epicardial coronary artery of ≥50%. Conversely, a participant was defined as having no significant CAD if all epicardial coronary arteries had <50% stenoses.27 We also studied the subgroup with angiographically smooth coronary arteries (n=117) versus those with any evidence of plaquing or stenosis (n=222). CAD severity was defined as the number of major epicardial coronary vessels with angiographic evidence of one or more stenoses of ≥50% severity.

Risk factors for atherosclerosis that were analyzed included age, male gender, body mass index, tobacco smoking, diabetes, hypercholesterolemia, and hypertension. Smoking was defined as a current or a prior history of tobacco use. Diabetes was defined as a fasting blood glucose level >7.8 mmol/L (140 mg/dL), or treatment with dietary modification, insulin, or oral hypoglycemic agents at the time of the study. Hypertension was defined as a seated systolic blood pressure ≥140 mm Hg and/or diastolic pressure ≥90 mm Hg on at least three occasions, or if such a diagnosis had been made in the past and the patient was being treated with medication or lifestyle modification. Hypercholesterolemia was defined as a fasting cholesterol ≥6.2 mmol/L (240 mg/dL) or treatment with lipid-lowering medication. Clinical characteristics are shown in Table 1.

Cardiac Catheterization Protocol

All subjects enrolled in the protocol underwent diagnostic coronary angiography using standard techniques. Two hundred three of these patients subsequently underwent assessment of coronary vascular function. In these subjects, all cardiac medications were withdrawn ≥48 hours before the study, and aspirin or other cyclooxygenase inhibitors were discontinued 7 days before. After diagnostic coronary angiography, a 3F infusion catheter was introduced using a 7F guiding catheter into the aortocoronary ostium of a major epicardial artery, and blood flow velocity was measured, as previously described, using a 0.014- or 0.018-inch wire equipped with a Doppler crystal at its tip (FloWire, EndoSonics).5,28,29

Coronary blood flow was measured and coronary vascular resistance (CVR) was calculated during intracoronary infusions of ACH followed by sodium nitroprusside and then adenosine, to test endothelium-dependent and -independent coronary microvascular function and vasodilator reserve, respectively.5,28,29 Further details of the coronary vascular function testing protocol are provided in the online data supplement available at http://www.circresaha.org.

Genotyping

Laboratory personnel who had no knowledge of the coronary angiographic or vascular function data performed CX3CR1 genotyping. The following two CX3CR1 polymorphisms have been identified: I249, a guanine-to-adenine substitution at nucleotide 745 of the open reading frame changing valine at position 249 in the reference sequence to isoleucine, and M280, a cytosine-to-thymidine substitution at nucleotide 839 changing a threonine at position 280 in the reference sequence to methionine.24,25 These two variants are in complete linkage disequilibrium such that there are only 3 haplotypes and 6 compound genotypes of the 4 and 9 that are possible, respectively. Further details of our CX3CR1 genotyping protocol are provided in the online data supplement available at http://www.circresaha.org. A third chemokine receptor polymorphism, CCR5Δ32, was genotyped as previously described.30

Statistical Analysis

Data are mean±SEM, and differences between means were compared by the 2-tailed unpaired Student t test. Univariate correlations

<table>
<thead>
<tr>
<th>TABLE 1. Association of Conventional Risk Factors With CAD</th>
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<tbody>
<tr>
<td><strong>Risk Factors</strong></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Mean age, years*</td>
</tr>
<tr>
<td>Male gender</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
</tbody>
</table>

*Age considered as a continuous variable (mean±SEM).†Odds ratio for age represents the increased risk of CAD for each 10-year increase in age.
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Association of CAD severity with CX3CR1 genotype.

It has been previously demonstrated that CX3CR1 expression and fractalkine binding affinity on peripheral blood mononuclear cells are greater for CX3CR1-V249 homozogotes (genotype 1) compared with those with the CX3CR1 I249 allele, and given the limited numbers of individuals in genotypes 2 to 4, we compared individuals with genotype 1 with all other genotypes as a combined group (genotypes 2 to 6, Table 2). Thus our primary comparisons are limited to subjects homozygous for the V249 allele compared with those heterozygous or homozygous for the I249 allele.

Individuals with an I249 allele were less frequent in the CAD group compared with those without CAD (38% versus 51%, univariate odds ratio 0.74 [95% confidence interval, 0.58 to 0.95]), and given the limited numbers of individuals in genotypes 2 to 4, we compared individuals with genotype 1 with all other genotypes as a combined group (genotypes 2 to 6, Table 2). Thus our primary comparisons are limited to subjects homozygous for the V249 allele compared with those heterozygous or homozygous for the I249 allele.

Results

Association Between CAD and Established Risk Factors

Of the 339 white subjects studied, 197 had CAD, and 142 did not (117 of these had smooth-appearing coronary arteries, and 25 had evidence of mild plaquing). By univariate analysis, increasing age, male gender, hypercholesterolemia, hypertension, diabetes, and smoking were significantly associated with the presence of CAD (Table 1). Age, male gender, hypercholesterolemia, diabetes, and smoking remained as independent risk factors for CAD after multivariate analysis (Table 1).

Distribution of CX3CR1 Genotypes in Study Participants

Consistent with our previously published results, we found that the CX3CR1-V249I and -T280M polymorphisms were in complete linkage disequilibrium such that there are only three haplotypes and 6 genotypes (Table 2). Twenty-seven percent of our white subjects were CX3CR1-V249I homozygotes (genotype 1) as compared with 53% of 176 white random blood donors, as previously reported. The proportion of genotypes for each allele considered separately was consistent with Hardy-Weinberg predictions for all groups.

Table 2. Prevalence of CAD According to CX3CR1 Genotype

<table>
<thead>
<tr>
<th>Genotype</th>
<th>CX3CR1</th>
<th>CAD</th>
<th>NSCAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>V/V</td>
<td>70</td>
<td>49</td>
</tr>
<tr>
<td>2</td>
<td>I/I</td>
<td>96</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>I/I</td>
<td>81</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>I/I</td>
<td>75</td>
<td>74</td>
</tr>
<tr>
<td>5</td>
<td>V/I</td>
<td>73</td>
<td>72</td>
</tr>
<tr>
<td>6</td>
<td>I/I</td>
<td>73</td>
<td>72</td>
</tr>
</tbody>
</table>

NSCAD indicates no significant coronary artery disease; V, valine; I, isoleucine; T, threonine; and M, methionine. 249 and 280 are amino acid positions of CX3CR1.

*P=0.03 vs genotype 1.

Differences in genotypic frequencies for the CX3CR1 and CCR5Δ32 polymorphisms were examined for significance using the Pearson χ² test. The independent contribution of CX3CR1 genotype to the presence of CAD was determined using a stepwise logistic regression model with traditional CAD risk factors such as age, male gender, body mass index, cigarette smoking, diabetes, hypercholesterolemia, and hypertension entered as covariates, and the odds ratio was calculated using this model (the Logistic procedure of SAS).

The association between genotype and severity of CAD was determined using a stepwise logistic regression model with traditional CAD risk factors such as age, male gender, body mass index, cigarette smoking, diabetes, hypercholesterolemia, and hypertension entered as covariates, and the odds ratio was calculated using this model (the Logistic procedure of SAS). The independent contribution of CX3CR1 genotype to the presence of CAD remained significant after multivariate adjustment for established CAD risk factors (odds ratio =0.58 [0.30 to 0.96], P=0.03, Table 2). Established cardiac risk factors were very similar in both genotype subgroups (Table 3), and the observed association between CX3CR1 genotype and presence of CAD remained significant after multivariate adjustment for established CAD risk factors (odds ratio =0.54 [0.30 to 0.96], P=0.03, Table 2). We also compared only those 117 subjects with angiographically smooth coronary arteries versus all others (n=222). Individuals with an I249 allele were also less frequent among those with angiographic evidence of atherosclerosis (40% versus 50%, univariate odds ratio =0.65 [0.41 to 1.01], P=0.06; adjusted odds ratio =0.58 [0.32 to 1.07], P=0.08). Angiographic severity of atherosclerosis was also less in subjects with an I249 allele compared with those heterozygous or homozygous for the I249 allele.

Table 3. Prevalence of Conventional Risk Factors According to CX3CR1 Genotype

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Genotype*</th>
</tr>
</thead>
<tbody>
<tr>
<td>249-V/V</td>
<td>249-V/I or -I/I</td>
</tr>
<tr>
<td>Mean age, years</td>
<td>52±1</td>
</tr>
<tr>
<td>Male gender</td>
<td>68%</td>
</tr>
<tr>
<td>Hypcholesterolemia</td>
<td>53%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>49%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>20%</td>
</tr>
<tr>
<td>Smoking</td>
<td>58%</td>
</tr>
</tbody>
</table>

*P=NS in all categories.

Figure 1. Distribution of CAD severity with CX3CR1 genotype. Shown is percentage of individuals with the CX3CR1 I249 allele (genotypes 2 to 6) vs number of diseased coronary vessels defined as ≥50% stenosis on diagnostic cardiac catheterization. P value is from Mann-Whitney U test of all 3 categories.
CX3CR1 Genotype and Coronary Endothelial Function

Endothelium-dependent coronary microvascular dilation with ACH was greater in subjects with an I249 allele compared with V249 homozygotes (P=0.02, Figure 2). Thus, subjects with an I249 allele had a 27% greater fall in CVR in response to ACH than V249 homozygotes. Moreover, when the population was divided into two equal groups with either “normal” (mean ΔCVR=−62±1% or “depressed” (mean ΔCVR=−20±3%) response to ACH, the proportion of subjects with an I249 allele was lower in those with depressed compared with those with normal endothelial function (35% versus 54%, respectively, P=0.01).

Univariate predictors of endothelial function, measured as percentage reduction in CVR with ACH, were age (P=0.01), presence of CAD (P=0.009), smoking (P=0.01), and the CX3CR1-V249I polymorphism (P=0.02). By multivariate analysis, smoking (P=0.03) and the CX3CR1-V249I polymorphism (P=0.02) remained significant predictors of the ACH response, independent of all other risk factors for endothelial dysfunction including the presence of CAD. In contrast, microvascular vasodilation observed during infusions of the endothelium-independent vasodilators sodium nitroprusside and adenosine was similar in patients with and without the I249 allele (Figure 2). Furthermore, when we defined CAD as any visible plaquing or stenosis, after multivariate adjustment the independent relationship between the I249 allele and better vasodilation in response to ACH remained (P=0.015). There was no significant difference between the genotypes with respect to sodium nitroprusside or adenosine responsiveness (P=0.32 and P=0.97, respectively).

CCR5Δ32 Genotype, Coronary Atherosclerosis, and Coronary Vascular Function

We also stratified study participants on the basis of the CCR5Δ32 polymorphism in the CCR5 gene, which encodes another chemokine receptor. This mutation is a 32-bp deletion in the CCR5 open reading frame that prevents expression of CCR5 on the cell surface. Like CX3CR1, CCR5 is also expressed on lymphocytes and monocytes. CCR5Δ32 is found at an allele frequency of 10% in North American whites.30,32

In this cohort, the frequency of the CCR5Δ32 allele was 10% and the genotypes were in Hardy-Weinberg equilibrium. The frequency of subjects heterozygous or homozygous for the CCR5Δ32 allele was similar in the CAD and NSCAD groups (18% versus 16%, P=0.63). Likewise, the change in CVR in response to ACH was similar in subjects without compared with those with the CCR5Δ32 allele (ΔCVR=−41±2% versus −41±5% respectively, P=0.84), as were the responses to sodium nitroprusside (ΔCVR=−54±2% versus −53±4% respectively, P=0.94) and adenosine (ΔCVR=−72±1% versus −73±2% respectively, P=0.88).

Discussion

The major findings of this study are that human subjects with the fractalkine receptor, CX3CR1 I249 allele have a reduced risk of developing CAD and have less severe disease than individuals homozygous for the CX3CR1-V249I reference allele. Endothelium-dependent, but not independent, coronary vasodilation is also better in subjects with the I249 allele. Thus, presence of the I249 allele was associated with lower risk of both structural (presence and angiographic severity of atherosclerosis) and functional (endothelium-dependent vasodilation) measures of atherogenesis. In contrast, CCR5Δ32, a mutation that inactivates the chemokine receptor CCR5, did not affect risk of coronary endothelial dysfunction or atherosclerosis. This does not support a role for CCR5 in human atherosclerosis.

CX3CR1 Genotype and CAD

CAD is a complex multifactorial process that involves an inflammatory/immune response to ongoing vascular injury that may be metabolic, physical, infectious, oxidative, and/or auto-
The role of fractalkine and CX3CR1 in leukocyte trafficking in vivo is not yet clear, although unambiguous effects on both chemotaxis and cell adhesion have been shown in vitro. Fractalkine is an unusual chemokine in that it possesses a transmembrane domain and seems to mediate a particularly strong and rapid flow arrest of cells such as resting monocytes, IL-2-activated CD8+ T lymphocytes, and NK cells on endothelial cells. Fractalkine can also be cleaved to release a free chemokine domain that stimulates monocyte, NK cell, and T-lymphocyte chemotaxis. Fractalkine-mediated adhesion does not require G-protein activation or integrin upregulation. Inflammatory cytokines such as tumor necrosis factor-α, IL-1β, and lipopolysaccharide markedly upregulate endothelial expression of fractalkine via a nuclear factor κB–dependent mechanism, and fractalkine-mediated adhesion of circulating NK cells leads to endothelial cell injury, an effect that can be blocked by soluble fractalkine or anti-CX3CR1 antibody. Furthermore, fractalkine enhanced adhesion of macrophage-like THP-1 cells and monocytes to fibronectin and ICAM-1 presumably via CX3CR1-mediated signaling. These properties suggest that any factor that modulated CX3CR1 expression level and/or affinity for ligand may affect leukocyte trafficking and associated disease processes, including atherosclerosis. In this regard, it is noteworthy that the CX3CR1 alleles that we have analyzed in the present study have already been reported to differ in both these parameters.

**CX3CR1 Genotype and Coronary Vascular Function**

Coronary vasodilation in response to ACH is predominantly due to stimulation of NO release. Depression of this response is a marker of an impaired vasodilator response during physiological stress, increased platelet aggregability, an accelerated progression of atherosclerosis, and an adverse cardiovascular prognosis. In experimental animal models, reduced NO bioavailability and endothelial dysfunction precipitate accelerated atherosclerosis, and increased oxidative stress associated with exposure to risk factors reduces NO bioavailability and promotes vascular inflammation. Moreover, endothelium-dependent vasodilator capacity is depressed in patients with evidence of increased systemic inflammation. Thus, factors that facilitate the inflammatory process would be expected to contribute to endothelial dysfunction. We observed that endothelium-dependent coronary vasodilation is greater in subjects with the CX3CR1 I249 allele, and that this genotype predicts the endothelium-dependent coronary vasodilator response to ACH, independently of the presence of CAD and other risk factors for endothelial dysfunction. Potential mechanisms for this finding, supported by current experimental evidence, include direct NK cell–mediated endothelial cell injury and/or increased leukocyte adhesion and infiltration into the vascular wall facilitated by increased expression and fractalkine binding affinity of CX3CR1 in V249 homozygotes.

In contrast, the coronary vascular responses to the endothelium-independent vasodilators adenosine and sodium nitroprusside were similar, indicating equivalent smooth muscle vasodilator capacity in both genotypic subsets. This further supports our hypothesis that reduction in vasodilator response to ACH associated with CX3CR1-V249 reflects a selective decrease in endothelial function and not a generalized abnormality of vasodilator tone. These observations are consistent with our findings of endothelial dysfunction in subjects homozygous for V249, independent of the presence of angiographic evidence of CAD, and provide a mechanistic insight into the potential role of fractalkine and the CX3CR1 receptor in the pathogenesis of endothelial dysfunction and atherosclerosis.

**Limitations**

Additional independent studies of atherosclerosis and endothelial function as endpoints will be needed to confirm the present study. We limited our analysis to white participants because we had found previously that the frequencies of both variants are not equivalent in different racial groups. Further studies will also be needed to address the impact of these polymorphisms in other racial groups. Our cohort was not designed to test whether CX3CR1 polymorphism is a risk factor for acute clinical coronary events; however, our recent study of a myocardial infarction/unstable angina cohort from France, which has been reported separately, has demonstrated this. Importantly, the relative risk for acute coronary events attributable to possession of 249I in that study was similar to that for atherosclerosis reported here. That study did not report angiographic and endothelial function parameters. Thus, the two studies are complementary and consistent.

As in any genetic association study, it is difficult to completely ensure that the result is not secondary to another closely linked site. The disease association with I249 reported here may be influenced by M280 or other as-yet-unknown variants in the CX3CR1 gene promoter. Some of the CX3CR1 genotypes are rare, making it difficult to distinguish the independent contribution of these polymorphisms in other racial groups. Our cohort was not designed to test whether CX3CR1 polymorphism is a risk factor for acute clinical coronary events; however, our recent study of a myocardial infarction/unstable angina cohort from France, which has been reported separately, has demonstrated this. Importantly, the relative risk for acute coronary events attributable to possession of 249I in that study was similar to that for atherosclerosis reported here. That study did not report angiographic and endothelial function parameters. Thus, the two studies are complementary and consistent.

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exists between epicardial and microvascular reactivity to endothelium-dependent and -independent agonists.5

Conclusions

We have demonstrated an independent association between CX3CR1 genotype and prevalence and severity of CAD, and endothelial dysfunction in white subjects. Our findings suggest that subjects with the CX3CR1 I249 allele have a reduced risk of developing atherosclerosis as a consequence of improved endothelial function probably as a result of a lower susceptibility to vascular inflammation. This suggests that fractalkine-CX3CR1 interaction may be a useful target for designing future therapies for CAD.

References

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