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Human Low-Affinity IgG Receptor FcγRIIA Polymorphism H131R Associates with Subclinical Atherosclerosis and Increased Platelet Activity in Systemic Lupus Erythematosus

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Abstract

Background: Systemic lupus erythematosus (SLE) is a complex autoimmune disease associated with an elevated risk for premature cardiovascular disease. Platelets express receptors contributing to inflammation and immunity including FcγRIIA, the low affinity receptor of the Fc portion of IgG antibodies. The variation at a single amino acid substitution, H131R, in the extracellular binding domain alters the affinity for IgG, which may account for individual variation in platelet activity and platelet mediated disease.

Objectives: This study was performed to investigate the association between FcγRIIA genotype, preclinical atherosclerosis, platelet reactivity, and vascular health.

Methods: FcγRIIA was genotyped in 80 SLE patients and 30 healthy controls. Carotid ultrasound plaque, soluble E-selectin, and platelet aggregability were evaluated in SLE and matched controls.

Results: Carotid plaque was significantly more prevalent in SLE patients carrying a variant allele compared to those who were homozygous ancestral (58% vs. 25%, P=0.04). In contrast, prevalent carotid plaque was not associated with genotype in controls. Consistently, SLE variant FcγRIIA carriers vs. ancestral had a significant increase in the levels of soluble E-selectin, which was not observed in controls. Monocyte and leukocyte-platelet aggregation and platelet aggregation in response to submaximal agonist stimulation were significantly elevated in SLE patients with the variant vs. ancestral genotype.

Conclusions: Carotid ultrasound plaque, soluble E-selectin levels and platelet activity were more frequently prevalent in SLE patients carrying variant FcγRIIA. The interplay between

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Addendum

R. Clancy, J. P. Buyon, and J. S. Berger had the concept

R. Clancy, S. E. Rasmussen, N. Bornkamp, N. Allen, R. Dann, H. Reynolds carried out the experiments.

H. El Bannoudi, H. Reynolds, R. Clancy, J. P. Buyon, and J.S. Berger drafted and edited the manuscript.

Disclosure of conflict of interests

H. Reynolds reports non-financial support from Abbott Vascular, outside the submitted work. The other authors state that they have no conflict of interest.

FcγRIIA-mediated platelet activation and endothelial cells might represent a mechanism underlying the pathogenesis of cardiovascular disease in SLE patients.

Keywords

Atherosclerosis; cardiovascular disease; FcγRIIA; platelets; systemic Lupus Erythematosus (SLE)

Introduction

Systemic lupus erythematosus (SLE) is a complex autoimmune disease with an elevated risk for premature cardiovascular disease (CVD). A growing body of evidence supports the notion that CVD is the cause of death in the majority of patients with longstanding SLE [1–3]. Indeed, the rate of myocardial infarction in women with SLE aged 35–44 years is ~50 times greater than expected [1]. Subclinical CVD, including intima-media thickness (IMT), carotid plaque and coronary artery calcium is significantly higher in SLE than controls [4, 5]. Increased atherosclerotic risk in SLE remains despite adjustment for traditional Framingham risk factors [2]. Additional risk factors may include longer duration of disease and lower likelihood of treatment with prednisone, cyclophosphamide, or hydroxychloroquine [4], a combination that may promote persistent inflammation leading to vascular tissue damage and induction of CVD.

Among the expanding list of nontraditional biomarkers, platelets have been understudied as a relevant contributor to premature atherosclerosis in SLE. Pathological and clinical studies consistently demonstrate that platelets play a key role in atherosclerosis and thrombosis. Platelets, which contain transcripts and the necessary molecular machinery to conduct translation, are intercellular regulators of inflammation and immune activation. Increasing evidence suggests the contribution of platelets to the pathogenesis of SLE. As such, platelets isolated from subjects with SLE compared to controls reveal evidence of hyperactivity as supported by increased membrane expression of P-selectin and CD40 ligand [6, 7], higher binding of Annexin V [7, 8], complement deposition [9, 10] and platelet-leukocyte complexes [6, 8, 11]. In a lupus murine model, depletion of platelets or administration of a potent antiplatelet drug, clopidogrel, improved various measures of disease severity and overall survival [6]. A recent study by our group demonstrated that platelets are hyperreactive in SLE and can contribute to the pathogenesis of vascular disease in these patients by activating endothelial cells in an IL1-β dependent manner [12].

Platelets express immune receptors such the activating Fcγ receptor IIA (FcγRIIA), which binds with low affinity to the Fc portion of immunoglobulin G (IgG) [13]. IgG binding to cognate antigens form immune complexes (ICs) that have been shown to activate platelets. Recent studies of influenza and heparin induced thrombocytopenia, have identified a hyperactive platelet phenotype in subjects with persistent and elevated circulating ICs and a putative role of FcγRIIA signaling. FcγRIIA harbors a functional polymorphism due to a single amino acid substitution, H131R, in the extracellular binding domain resulting in altered affinity to IgG_2 [14]. Functional variation in this family of receptors has been associated with SLE and lupus nephritis across diverse populations [15, 16].

Based on the plausible contribution of platelet activity to atherosclerotic risk in SLE, this study was initiated to determine the functional consequences of variation at FcγRIIA in SLE platelets. The approach leveraged a previously reported cohort of SLE patients in whom carotid IMT with inflammatory biomarkers and banked DNA was available for FcγRIIA genotyping [4, 5]. In addition, a newly assembled cohort was genotyped and platelet activity phenotyped to assess functional associations.

Materials and Methods

Study Population

Patients were recruited from the NYU Langone Medical Center and Bellevue Hospital. Written informed consent approved by the NYU institutional review board (IRB) was obtained from all subjects. All patients fulfilled at least 4 of the American College of Rheumatology (ACR) Criteria for the diagnosis of SLE [17]. The first cohort was previously published [5] and comprised patients with SLE and healthy controls evaluated by carotid ultrasound to determine the prevalence of atherosclerosis and associated inflammatory markers. This group was available for the determination of rs1801274 genotypes in FcγRIIA. The second cohort included patients enrolled based on consecutive attendance in either of two specialized lupus clinics or Rheumatology private practices as well as healthy controls. These patients and controls contributed fresh platelets for functional evaluations and genotyping. Exclusion criteria in this second cohort included the use of over-the-counter or prescribed non-steroidal anti-inflammatory drugs (NSAIDs), aspirin, or any anticoagulation, thrombocytopenia or anemia.

Phlebotomy and Sample Processing

Blood was collected using a 21-gauge needle. Following a 2cc discard, blood was collected into vacutainer tubes containing EDTA for complete blood count (CBC), 3.2% (0.105 moles/L) sodium citrate for platelet collections, platelet activity measures, and plasma aliquots (Becton Dickenson, Franklin Lakes, NJ). Serum separator tubes were used to collect serum (SST; Becton Dickinson). After phlebotomy, blood was immediately transported to the laboratory for processing. Sodium citrate anti-coagulated blood was centrifuged within 15 minutes of phlebotomy at 200g for 10 minutes, yielding platelet rich plasma (PRP) that was used for light transmission aggregometry. To obtain serum, blood in SST tubes was allowed to clot for 30 minutes at room temperature and then centrifuged at 2500g for 10 minutes. Plasma and serum were aliquoted immediately after completion of centrifugation, flash frozen in liquid nitrogen, and stored at −80°C until the time of assay. From a purified DNA fraction, genotyping of FcγRIIA was performed by the allelic exclusion technique using assays and reagents purchased from Applied Biosciences (SNP ID: rs1801274, Assay ID: C___9077561_20), and assignments were confirmed by direct sequencing.

Measurement of soluble E-Selectin

As described previously [5], sE-selectin levels were measured using an enzyme-linked immunosorbent assay (ELISA) according to the instructions of the manufacturers (R&D Biosystems).

Light Transmission Aggregometry

Light transmission aggregation (LTA) was performed using AggRAM light transmission aggregometer, reagents, cuvettes, and stir bars (Helena Laboratories, Beaumont, Texas). Agonists were purchased from a single lot at the onset of the study. LTA was performed according to manufacturer's specification and tests ran for 10 minutes. As described previously [18], citrate-anticoagulated blood was centrifuged at 200g for 10 minutes to obtain platelet rich plasma (PRP). LTA was immediately performed, and platelet aggregation was assessed in response to submaximal epinephrine, collagen, adenosine diphosphate (ADP), and arachidonic acid (AA), in that respective order. Testing of the latter agonists was dependent on availability of PRP, as the amount of PRP isolated from each subject varied.

Flow Cytometry

To assess Leukocyte-Platelet Aggregates (LPA) and Monocyte-Platelet Aggregates (MPA), citrate anti-coagulated blood was fixed with 1% formaldehyde in a 1:1.2 ratio and stained with fluorescently conjugated antibodies; CD61-FITC (platelets) and either CD14-APC (monocytes) or CD45-APC (leukocytes) for 10 minutes in the dark at room temperature. Monocytes and leukocytes were collected based on side-scatter properties and positive staining for CD14 or CD45, respectively. Monocyte-platelet aggregates were identified as having a positive stain for CD14 and CD61, and LPA were identified as having a positive stain for CD45 and CD61. Data are expressed as a percentage of at least 25,000 leukocytes or 2,000 monocytes positive for adherent platelets. Data were acquired on BD Accuri C6 Cytometer (BD Biosciences) and were analyzed using FlowJo (Tree Star) software.

Statistical Analysis

The Student unpaired *t*-test was used in 2-group comparisons of normally distributed data, whereas the Mann-Whitney nonparametric test was used when the normality assumption was not met. Fisher's exact test was performed to evaluate bivariate associations between categorical variables. Statistical significance was performed using GraphPad Prism version 6.0g (GraphPad Software, La Jolla, California, USA). All *P* values were considered significant at $P < 0.05$.

Results and discussion

The demographic and clinical profile of the SLE patients and controls are shown in Table 1 (Page 17). Subjects were mostly female and nearly 50% white. Controls were matched by age, sex, and race/ethnicity. Approximately two-thirds of the population fulfilled the renal ACR classification criteria for SLE. As reported previously, SLE patients had a significantly higher prevalence of carotid intima thickness (CIT).

Overall, allelic frequencies of FcγRIIA were not significantly different between SLE patients or healthy controls. Minor allele frequency (MAF) of rs1801274 was found in ≈40% of subjects with SLE and controls. There was no difference in demographics by FcγRIIA genotype. Among the 49 SLE subjects with carotid ultrasound assessment, 17 of 29 (58%) SLE patients with the allelic variant had carotid plaque compared to 5 of 20 (25%) SLE patients without the variant had carotid plaque (P=0.039, Figure 1A). In contrast, the

presence of the FcγRIIA rs1801274 variant did not associate with carotid plaque in healthy controls (Figure 1A).

There are biologic consequences of allelic variation in the Fc receptors. These include differences in immune complex clearance by phagocytic cells as well as downstream signaling pathways [15, 16]. Zhou and coworkers demonstrated that FcγRIIA receptor signaling in platelets induced by FcγRIIA triggering, directly contributed to a hyperreactive phenotype and was dependent on the H131R polymorphism. Specifically, platelets isolated from R/R131 homozygotes (variant) were highly responsive and H/H 131 homozygotes (ancestral) platelets were weakly responsive to stimulation via FcγRIIA [19]. In support of this concept, Chen and coworkers demonstrated that the H131R polymorphism of FcγRIIA is important for fibrinogen binding to the $\alpha_{IIb}\beta_3$ [20]. In addition to platelets, FcγRIIA is also expressed by other immune cells and as such could potentially contribute to the development of atherosclerosis.

We previously showed that patients with SLE have elevated soluble E-selectin, and among SLE patients, soluble E-selectin was higher in those with (versus without) CIT [5]. In this cohort, the levels of soluble E-selectin were higher in SLE subjects carrying a variant allele compared to those with ancestral alleles (P=0.036, Figure 1B). In contrast, soluble E-selectin did not differ by allelic frequencies of FcγRIIA rs1801274 among healthy controls. A non-specific marker of inflammation, C-reactive protein, did not differ significantly among SLE patients or controls carrying the variant allele compared to those with the homozygous ancestral genotype (data not shown).

SLE is characterized by an abundance of ICs, which contribute to systemic and tissue inflammation. Platelets which are in close interaction with endothelial cells of the vascular wall, can promote CVD by functioning as a bridging link between ICs and endothelial cells. By cross linking the variant FcγRIIA, IgG-containing ICs can increase platelet aggregation, which in turn enhances the activation of endothelial cells. Indeed, we have recently demonstrated that platelets induce endothelial inflammation in an IL-1β dependent manner [12]. Elevation of sE-selectin in subjects carrying the variant FcγRIIA, is consistent with the notion that this biomarker reflects activation of the endothelium and high levels have been previously associated with atherosclerosis and cardiovascular risk in both SLE and non SLE cohorts [5, 21–23]

Given prior data from our group demonstrating that platelets from SLE patients exhibit an activated phenotype and an ability to induce proinflammatory endothelial cell phenotype [12], platelet aggregation and platelet-leukocyte interaction were explored. Since platelet aggregation in response to submaximal epinephrine stimulation is a robust marker of platelet activity that generalizes to a global hyperreactive platelet phenotype, we investigated platelet aggregation in response to low-epinephrine. Patients with SLE and the allelic variant had increased aggregation in response to epinephrine 0.1 μM, 0.4 μM and 2 μM compared to SLE patients with the homozygous ancestral genotype (P<0.05 for each assessment; (Figure 2A, B and C). Consistently, SLE patients with the allelic variant had a higher percent aggregation to low-dose (160 μM) arachidonic acid (data not shown). While numerically higher, no significant difference was detected in platelet aggregation in response to low-dose

collagen (0.2 μg/ml) or ADP (0.4 μM) (data not shown). Cross-talk between platelets and leukocytes is a crucial pathophysiological mechanism linking atherothrombosis, immunity and inflammation, and e*x vivo* measurement of monocyte- (and leukocyte) platelet aggregation in the circulation has been proposed to represent a robust biomarker of platelet activation *in vivo*. Both MPA and LPA were significantly higher in SLE patients carrying the variant allele compared to those with the homozygous ancestral genotype (Figure 2D and E).

Several limitations exist when interpreting the results of our study. First, the findings include two separate cohorts and individuals with IMT and measurement of E-selectin, did not have evaluations of platelet function (and vice versa). Second, atherosclerosis develops over years and our data on platelet and vascular functional parameters were limited to cross sectional analyses. Finally, our population was not large enough to look at heterozygous carriers (R/H) of the variant form of Fcγ RIIA.

Altogether, the data of this study supports the contributing role of FcyRIIA genotype in premature atherosclerosis, vascular impairment and increased platelet activity in patients with SLE.

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Essentials

- Systemic lupus erythematosus (SLE) patients are at increased risk for premature CVD.
- Platelet activity, vascular dysfunction and carotid artery plaque are associated with FcγRIIA genotype in SLE.
- FcγRIIA genotype was not associated with platelet activity or carotid plaque in healthy controls.
- FcγRIIA represents a link that connects platelet activity, vascular health and CVD in SLE.

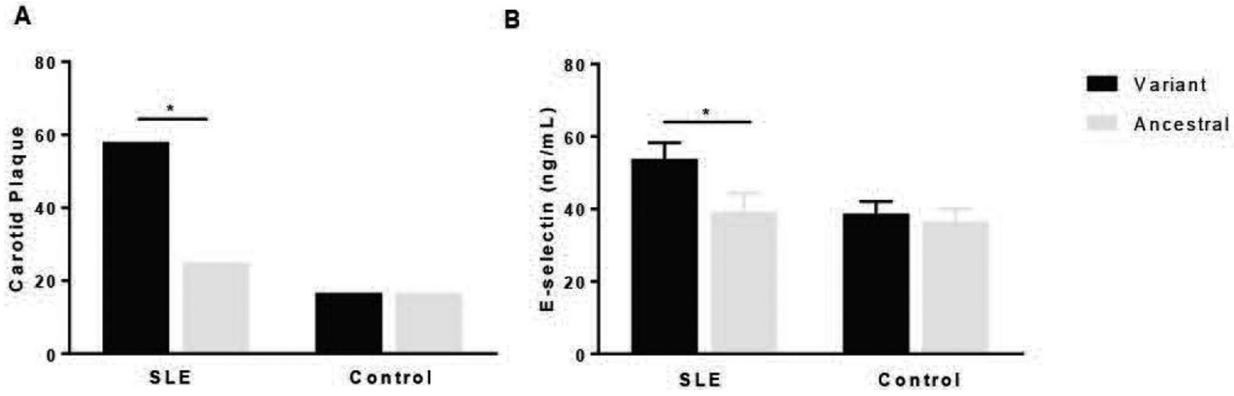

Figure 1.

Increased prevalence of atherosclerotic plaque and E-selectin levels in systemic lupus erythematosus (SLE) with FcγRIIA variant. (A) Atherosclerotic plaque was measured using ultrasonography in SLE patients (n= 49) and controls (n= 30). Increased prevalence of plaque was observed in SLE patients with variant FcγRIIA compared to SLE patients with ancestral FcγRIIA. In contrast, there was no significant difference in plaque prevalence in controls with or without the variant FcγRIIA. (B) Soluble E-selectin (sE-selectin) was measured in serum of patients with SLE (n= 34) and healthy controls (n= 42) carrying either the variant or ancestral form of FcγRIIA. P-value was calculated using Unpaired t-Test (*, $p < 0.05$).

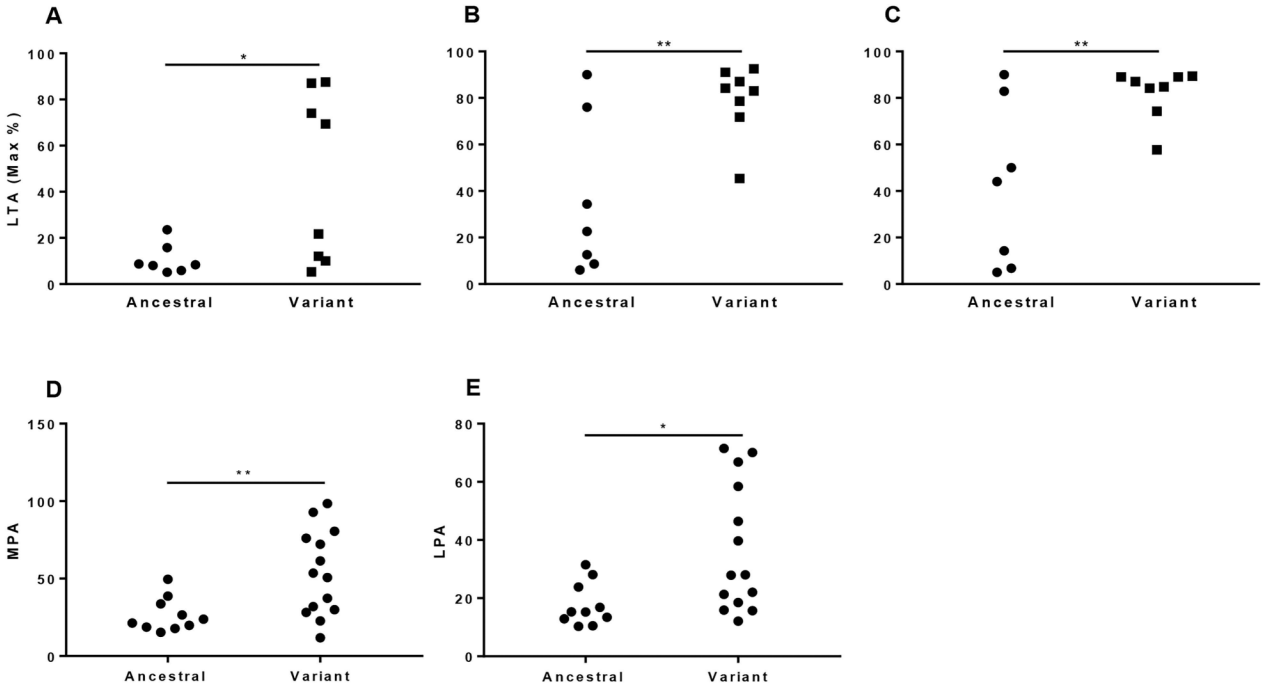

Figure 2.

Increased platelets activity in SLE patients with the variant FcγRIIA. Light transmission aggregation (LTA) was measured following treatment of platelet-rich plasma of SLE patients with 0.1 μM (A), 0.4 μM (B) or 2 μM (C) epinephrine by using Helena AggRAM light transmission aggregometer. The percentage of monocyte-platelet aggregates (MPA, D)) and leukocyte-platelet aggregates, (LPA, E) assessed by flow cytometry. Single dots in the graphs represent measurement of individual patients. Statistical significance was determined using Unpaired t-Test (*, $p < 0.05$; **, $p < 0.01$).

Table 1.

Demographics of Patients and Controls

Cohort	SLE-1	Control-1	SLE-2
Evaluation	Carotid IMT	Carotid IMT	Platelet activity
N	49	30	31
Age, mean	45.0 ± 7.5	42.6 ± 8.3	40 ± 12.4
Female, n (%)	44 (95.6)	25 (86.2)	20 (83..3)
White, %	43.4	51.7	46.6
Malar rash*, %	63.1		53.3
Discoid rash*, %	36.8		50
Photosensitivity*, %	56.7		50
Oral ulcers*, %	47.3		36.6
Arthritis*, %	94.8		73.3
Serositis*, %	35.1		33
Renal*, %	58.3		73.3
Neurological, %	5.5		0
rs1801274 MAF	0.41	0.41	0.38

*ACR criteria