Elevated Plasma Level of Soluble F11 Receptor/Junctional Adhesion Molecule-A (F11R/JAM-A) in Hypertension

Article *in* American Journal of Hypertension · February 2009

DOI: 10.1038/ajh.2009.23 · Source: PubMed

CITATIONS
18

READS
35

13 authors, including:

Kwok Leung Ong
UNSW Sydney
106 PUBLICATIONS **4,007** CITATIONS
SEE PROFILE

Ray Leung
The University of Hong Kong
43 PUBLICATIONS **805** CITATIONS
SEE PROFILE

Anna Babinska
State University of New York Downstate Medical Center
49 PUBLICATIONS **615** CITATIONS
SEE PROFILE

Moro O Salifu
State University of New York Downstate Medical Center
130 PUBLICATIONS **1,572** CITATIONS
SEE PROFILE

nature publishing group

Elevated Plasma Level of Soluble F11 Receptor/ Junctional Adhesion Molecule-A (F11R/JAM-A) in Hypertension

Kwok Leung Ong[1], Raymond Y.H. Leung[1], Anna Babinska[2], Moro O. Salifu[2], Yigal H. Ehrlich[3], Elizabeth Kornecki[2], Louisa Y.F. Wong[1], Annette W.K. Tso[1], Stacey S. Cherny[4], Pak Chung Sham[4], Tai Hing Lam[5], Karen S.L. Lam[1] and Bernard M.Y. Cheung[6]

BACKGROUND
The F11 receptor (F11R, also known as junctional adhesion molecule A (JAM-A)) plays a role in the development of hypertension in rat. Genetic variants in the human F11R gene were demonstrated to influence systolic blood pressure. In the present study, we investigated the relationship between F11R and hypertension by examining the levels of a circulating soluble form of F11R (sF11R) in hypertensive patients.

METHODS
Plasma sF11R was measured by enzyme-linked immunosorbent assay in 152 hypertensive and 166 normotensive subjects in whom seven tagging single-nucleotide polymorphisms (SNPs) in the F11R gene had been genotyped.

RESULTS
Plasma sF11R levels were significantly higher in hypertensive subjects than in normotensive subjects (median (interquartile) range): 162.8 (85.5–293.2) vs. 116.5 (74.1–194.8) pg/ml, $P = 0.004$), which remained significantly higher after adjusting for age, sex, body mass index (BMI), and homeostasis model assessment of insulin resistance (HOMA-IR) ($P = 0.028$). In stepwise multiple logistic regression, sF11R level (log-transformed) ($P = 0.040$), triglycerides (log-transformed) ($P = 0.024$), and HOMA-IR (log-transformed) ($P < 0.001$) were independently associated with hypertension. Plasma sF11R level correlated with systolic and diastolic blood pressures ($r = 0.15$, $P < 0.001$, and $r = 0.13$, $P = 0.024$, respectively). In stepwise multiple linear regression, hypertension ($P = 0.013$) and fibrinogen levels ($P = 0.027$) were significant independent predictors of sF11R level. A seven-locus haplotype, present in 2.1% of the subjects, was associated with higher sF11R level ($P = 0.024$).

CONCLUSIONS
These results further support a role of F11 receptor in the pathophysiology of human hypertension.

Am J Hypertens 2009; **22**:500-505

The F11 receptor (F11R) was first identified and characterized in 1990 as a glycoprotein expressed on the surface of human platelets.[1] The presence of the F11R protein was described later in 1998 at tight junctions of vascular endothelial and epithelial cells, and referred to as Junctional Adhesion Molecule (JAM-1 or JAM-A).[2] F11R has been shown to play a role in platelet activation, aggregation, and adhesion.[1,3] An association between F11R and inflammatory thrombosis was reported,[3,4] and enhanced levels of F11R were detected in atherosclerotic plaques of coronary artery disease (CAD) patients and in the plaques obtained from arteries of atherosclerosis-prone apoE$^{-/-}$ mice.[3] The F11R was recently shown to play a novel role in the etiology of hypertension in rats.[5,6] Overexpression of F11R in the brain of rats increased systolic blood pressure and decreased heart rate without significant change in spontaneous cardiac baroreflex gain.[5] The expression of F11R in spontaneously hypertensive rats was significantly higher than that in Wistar-Kyoto rats, not only in the brain but also in other organs, such as heart, kidney, lung, spleen, liver, and skeletal muscle.[5] We previously reported the significant association of genetic variants (rs790056 and rs2774276) in the F11R gene with systolic blood pressure.[7] Salifu *et al.* recently reported that circulating levels of a soluble, released form of F11R (sF11R) were elevated in hemodialysis patients and correlated positively with inflammatory markers known to be elevated in cardiovascular diseases, including tumor necrosis factor-α, interleukin-6, and interleukin-10.[8] Plasma sF11R levels were also elevated in CAD patients.[9] Since the activity of F11R in initiating plaque formation leading to atherosclerosis

[1]Department of Medicine, University of Hong Kong, Hong Kong, People's Republic of China; [2]Department of Anatomy/Cell Biology and the Department of Medicine, State University of New York, Downstate Medical Center, Brooklyn, New York, USA; [3]Biology Department, Program in Neuroscience, CSI/City University of New York, Staten Island, New York, USA; [4]Genome Research Centre and Department of Psychiatry, University of Hong Kong, Hong Kong, People's Republic of China; [5]Department of Community Medicine, University of Hong Kong, Hong Kong, People's Republic of China; [6]Department of Clinical Pharmacology, University of Birmingham, Birmingham, UK. Correspondence: Bernard M.Y. Cheung (b.cheung@bham.ac.uk)

Received 28 September 2008; first decision 21 December 2008; accepted 14 January 2009; advance online publication 12 February 2009. doi:10.1038/ajh.2009.23

is triggered by inflammatory agents[3,4] and as inflammatory cytokines are involved in the pathogenesis of hypertension,[10] we examined the association between circulating F11R and hypertension by measuring the levels of sF11R in hypertensive individuals.

METHODS

Subjects. The study included 318 unrelated Chinese subjects living in Hong Kong. The sample consisted of 152 hypertensive subjects and 166 normotensive controls drawn from the Hong Kong Cardiovascular Risk Factor Prevalence Study.[11] They had been previously genotyped for seven tagging single-nucleotide polymorphisms (SNPs) (rs790056, rs2481084, rs6695707, rs7546890, rs11576837, rs3737787, and rs2774276) in the F11R gene. These seven SNPs captured all the 26 SNPs in the F11R gene with $r^2 \geq 0.9$ and minor allele frequency ≥ 0.10 in the HapMap Han Chinese population (Phase II data, release 22), from the 3kb region upstream to 1kb downstream of the gene (position 159, 231, 608–159, 278, 358, GenBank accession number NC_000001).[7] The study protocol was approved by the University of Hong Kong Faculty of Medicine Ethics Committee, and written informed consent was obtained from all participants. Hypertension was defined as blood pressure ≥140/90 mm Hg or taking antihypertensive medication.[12] Blood pressure was measured in the right arm manually three times at 5-min intervals using a mercury sphygomomanometer. The first blood pressure measurement was performed to familiarize the patient with the procedure. The mean of the two subsequent readings was used for data analysis. Plasma fibrinogen level was measured using a photo-optical end-point clot detection method on a Cobas Fibro instrument (Roche Diagnostics, Basle, Switzerland) with an interassay coefficient of variation of 4.7%. Other clinical characteristics and physical examinations had been described earlier.[7,11]

Blood sampling. Subjects were studied in the morning after overnight fasting. After resting for at least 5 min in the sitting position, venous blood was taken from a forearm vein in the sitting position, placed in an ethylenediaminetetracetic acid bottle, and immediately placed on ice. The blood was immediately centrifuged at 4 °C, and the plasma was frozen at –70 °C until the time of assay.

sF11R level measurement. The enzyme-linked immunosorbent assay for plasma sF11R was performed using recombinant F11R/Fc chimera (R&D Systems, Minneapolis, MN) as standard, M.Ab.F11 monoclonal antibody as capture antibody (BD Biosciences, San Jose, CA), and biotinylated antihuman F11R antibody (R&D Systems, Minneapolis, MN) as detection antibody according to the conditions described earlier.[8,9] The sensitivity of the sF11R assay was 9.8 pg/ml, and the interassay coefficient of variation was <12%.

Statistical analysis. Statistical analysis was performed using SPSS 15.0 for Windows (SPSS, Chicago, IL). Comparisons of clinical characteristics were performed using unpaired Student's *t*-test or nonparametric Mann–Whitney *U*-test for continuous variables, where appropriate, and Fisher's exact test was performed for categorical variables. Plasma sF11R level is presented as median and interquartile range due to its skewed distribution. The sF11R levels in normotensive, untreated hypertensive, and treated hypertensive subjects were compared using Kruskal–Wallis test. For bivariate correlations, Spearman correlation coefficients were calculated. Stepwise forward multiple logistic and linear regression analyses were performed with hypertension or sF11R level as the dependent variable, respectively. Variables with skewed distributions were log-transformed in the regression models. Haplotype analysis of SNPs with log-transformed sF11R level was performed using --chap and --each-vs-others commands in the software program PLINK (version 1.0.3).[13] A two-tailed *P* value <0.05 was considered statistically significant.

RESULTS

Our study consisted of 152 hypertensive and 166 normotensive subjects. The baseline characteristics of these subjects are shown in Table 1. Hypertensive subjects exhibited significantly higher blood pressure, body mass index (BMI), waist circumference, plasma triglycerides, fasting glucose, fasting insulin, homeostasis model assessment of insulin resistance index

Table 1 | Baseline characteristics of normotensive and hypertensive subjects

	Normotensive	Hypertensive	
n	166	152	*P*
Age (year)	56.8 ± 10.9	57.7 ± 10.5	0.44
Female (%)	42.2	44.7	0.65
Systolic blood pressure (mm Hg)	118.4 ± 10.8	145.5 ± 17.9	<0.001
Diastolic blood pressure (mm Hg)	73.1 ± 7.8	85.6 ± 11.2	<0.001
BMI (kg/m^2)	23.9 ± 3.6	25.6 ± 3.2	<0.001
Waist circumference (cm)	80.6 ± 10.3	86.1 ± 9.2	<0.001
LDL cholesterol (mmol/l)	3.36 ± 0.83	3.38 ± 0.82	0.79
HDL cholesterol (mmol/l)	1.40 ± 0.44	1.25 ± 0.35	0.001
Triglycerides (mmol/l)	1.1 (0.8–1.6)	1.5 (1.1–2.3)	<0.001
Fasting glucose (mmol/l)	5.3 (4.9–5.9)	5.4 (5.1–6.3)	0.048
Fasting insulin (mIU/l)	7.0 (4.6–9.3)	9.9 (6.7–14.0)	<0.001
HOMA-IR	1.7 (1.1–2.5)	2.6 (1.6–3.9)	<0.001
Fibrinogen (g/l)	2.97 ± 0.54	3.09 ± 0.65	0.06
Current smoker (%)	22.3	15.1	0.12
Diabetes (%)	24.1	32.9	0.11
sF11R level (pg/ml)	116.5 (74.1–194.8)	162.8 (85.5–293.2)	0.004
sF11R level (pg/ml, log-transformed)	2.08 ± 0.46	2.20 ± 0.48	0.027

Data are expressed as mean ± s.d. or median (interquartile range).
BMI, body mass index; HDL, high density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance index; LDL, low density lipoprotein; sF11R, soluble form of F11 receptor.

Table 2 | Forward stepwise regression analysis for hypertension

	All		Males		Females	
	Odds ratio	*P*	Odds ratio	*P*	Odds ratio	*P*
Triglycerides (mmol/l, log-transformed)	4.50	0.024	NS	NS	NS	NS
Fasting insulin (mIU/l, log-transformed)	NS	NS	14.36	<0.001	NS	NS
HOMA-IR (log-transformed)	11.92	<0.001	NS	NS	45.62	<0.001
Fibrinogen (g/l)	NS	NS	1.76	0.036	NS	NS
sF11R level (pg/ml, log-transformed)	1.77	0.040	NS	NS	2.21	0.033

Age, sex, body mass index, waist circumference, low density lipoprotein cholesterol, high density lipoprotein cholesterol, fasting glucose (log-transformed), current smoker (yes and no), and diabetes (with and without) were excluded from the stepwise model ($P > 0.05$).
HOMA-IR, homeostasis model assessment of insulin resistance index; NS, not significant ($P > 0.05$); sF11R, soluble form of F11 receptor.

Table 3 | Forward stepwise regression analysis for plasma sF11R

	All		Normotensive		Hypertensive	
	β	*P*	*β*	*P*	*β*	*P*
Fibrinogen (g/l)	−0.13	0.027	−0.19	0.014	NS	NS
Hypertension (with and without)	0.14	0.013	—	—	—	—

Age, sex, systolic blood pressure, diastolic blood pressure, body mass index, waist circumference, low density lipoprotein cholesterol, high density lipoprotein cholesterol, triglycerides (log-transformed), fasting glucose (log-transformed), fasting insulin (log-transformed), homeostasis model assessment of insulin resistance index (log-transformed), current smoker (yes and no), and diabetes (with and without) were excluded from the stepwise model ($P > 0.05$).
NS, not significant ($P > 0.05$); sF11R, soluble form of F11 receptor.

Table 4 | Relationship of sF11R level with genetic variants

Genotypes		*n*	sF11R level (pg/ml)	*P*
rs790056	TT	230	130.1 (81.9–260.0)	0.53
	TC + CC	88	134.3 (75.5–195.6)	
rs2481084	TT	219	130.2 (77.4–248.5)	0.85
	TC + CC	99	141.4 (78.0–249.4)	
rs6695707	AA	191	136.5 (73.3–242.2)	0.52
	AC + CC	127	124.0 (85.6–249.4)	
rs7546890	TT	145	127.3 (81.7–292.6)	0.46
	TC + CC	173	135.9 (76.4–228.9)	
rs11576837	AA	139	132.6 (79.2–256.7)	0.86
	AG + GG	179	131.5 (77.3–247.4)	
rs3737787	GG	220	129.4 (77.3–254.0)	0.91
	GA + AA	98	142.9 (78.0–247.2)	
rs2774276	CC	228	122.7 (74.0–248.3)	0.21
	CG + GG	90	146.7 (80.1–258.6)	

Data are expressed as median (interquartile range). Subjects homozygous for the minor allele were grouped with heterozygotes for comparison with those homozygous for the major allele to increase the sample size for comparison, assuming a dominant inheritance model.
sF11R, soluble form of F11 receptor.

(HOMA-IR), and significantly lower high-density lipoprotein cholesterol, as expected. We determined that both the median of the plasma sF11R level and mean of the log-transformed level were significantly higher in hypertensive subjects than in normotensive subjects ($P = 0.004$ and 0.027, respectively). The association between the log-transformed sF11R level and hypertension remained significant after adjusting for age, sex, BMI, and HOMA-IR (log-transformed) ($P = 0.028$). The association was even greater in strength when subjects within the upper (>502.8 pg/ml) and lower (<41.6 pg/ml) 10% of the sF11R level were excluded ($P = 0.004$ after adjustment) so that the observed difference between sF11R level was not due to extreme outliers. Moreover, the association remained significant after excluding subjects on drug treatment for diabetes ($P = 0.022$ after adjustment).

Among the 152 hypertensive subjects, 81 (53.3%) of the individuals were on antihypertensive medication, and 35 (43.2%) of these individuals had a blood pressure <140/90 mm Hg. There was no significant difference in sF11R level between treated and untreated hypertensive subjects (154.5 (83.7–279.2) vs. 184.5 (86.7–350.6) pg/ml, $P = 0.54$). The plasma sF11R level was elevated in both untreated and treated hypertensive subjects ($P = 0.011$ and 0.032, respectively, vs. normotensive controls, using the Mann-Whitney U test and $P = 0.014$ using the Kruskal-Wallis test). Among the 81 treated hypertensive subjects, plasma sF11R level did not differ significantly between subjects whose blood pressure was <140/90 mm Hg and those with inadequate control (145.9 (72.8–271.1) vs. 166.4 (91.8–304.3) pg/ml, $P = 0.47$). Of the 81 subjects treated with antihypertensive medications, 73 had reported the names of the antihypertensive drugs used: angiotensin II receptor antagonists ($n = 3$), angiotensin-converting enzyme inhibitors ($n = 11$), beta-blockers ($n = 31$), calcium antagonists ($n = 25$), diuretics ($n = 18$), other hypertensive drugs ($n = 13$), and 22 individuals reported use of more than one class of antihypertensive drugs. Plasma sF11R level did not differ significantly between subjects taking or not taking a specific type of drug ($P > 0.05$), although subjects taking more than one class of antihypertensive drugs had significantly higher plasma sF11R levels than those taking only one class of hypertensive drugs (254.6 (105.3–419.3) vs. 139.0 (79.2–186.0) pg/ml, $P = 0.033$).

Among all subjects, plasma sF11R level was not related to sex, smoking, or diabetes ($P > 0.05$ using Mann-Whitney *U*-tests). In univariate Spearman correlation analysis, plasma sF11R level correlated with both systolic and diastolic blood pressures ($r = 0.15$, $P = 0.006$, and $r = 0.13$, $P = 0.024$, respectively) as well as plasma triglycerides ($r = 0.11$, $P = 0.044$). The correlation remained significant for systolic blood pressure after exclusion of hypertensive subjects on drug treatment ($r = 0.15$,

$P = 0.026$) but not for diastolic blood pressure ($r = 0.11$, $P = 0.10$). No significant correlation was found for the other variables as shown in **Table 1**.

In forward stepwise logistic regression analysis with hypertension as a dichotomous dependent variable and all the other 14 variables except blood pressure from **Table 1** as independent variables, sF11R level, plasma triglycerides, and HOMA-IR were independent predictors, accounting for 21.6% of the total variance among all subjects (**Table 2**). However, in sex-specific analysis, sF11R level was an independent predictor of hypertension in women but not in men.

In forward stepwise linear regression analysis with sF11R level (log-transformed) as the dependent variable and all the other 16 variables (including hypertension) shown in **Table 1** as independent variables, only hypertension ($\beta = 0.14$, $P = 0.013$) and fibrinogen levels ($\beta = -0.13$, $P = 0.027$) were significant independent predictors among all subjects (**Table 3**). However, this stepwise model could only account for 2.5% of the variance in sF11R level, suggesting that there were unidentified factors influencing sF11R levels. The independent association of hypertension with sF11R (log-transformed) remained significant after adjusting for age, sex, BMI, plasma triglycerides, fibrinogen, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, fasting glucose, fasting insulin, HOMA-IR, diabetes, smoking, and antihypertensive drug treatment ($P = 0.041$), whereas replacement of BMI with waist circumference in the regression model did not appreciably affect the P value ($P = 0.038$). Fibrinogen was significantly associated with sF11R level in the subgroup of normotensive subjects (**Table 3**).

We further investigated the effects of seven tagging SNPs. Individually, these seven SNPs were not significantly associated with sF11R level (all $P > 0.05$) (**Table 4**). Haplotype analysis suggested a nominally significant association of the seven-locus haplotype TTATAGG, comprising all the seven SNPs, rs790056, rs2481084, rs6695707, rs7546890, rs11576837, rs3737787, and rs2774276, with sF11R level (regression coefficient = 0.25, $P = 0.024$, haplotype frequency = 2.1%). The association remained significant after adjusting for age, sex, fibrinogen, and hypertension ($P = 0.040$).

DISCUSSION

The sF11R was first found in circulation by Salifu *et al.*[8] who demonstrated an elevation in sF11R level in the sera of hemodialysis patients that was positively correlated with inflammatory cytokines, such as tumor necrosis factor-α, interleukin-10, and interleukin-6, in these patients. In another study, Cavusoglu *et al.*[9] demonstrated increased plasma sF11R levels in the circulation of CAD patients to levels that suggested that circulating sF11R can serve as a potential marker of human atherosclerosis. Here, we report for the first time that the level of plasma sF11R is elevated in hypertension and correlates positively with blood pressures and more strongly with systolic blood pressure. This finding is consistent with the *in vivo* experiment in rats showing increased systolic blood pressure after overexpression of F11R in the brain.[5] Individually, none of the SNPs in the F11R gene was significantly associated with sF11R level. However, there was a nominal association of sF11R level with the TTATAGG haplotype. This is an uncommon haplotype found in 2% of the subjects. Our finding needs to be confirmed in a larger sample in another population with different ethnic groups.

Plasma sF11R level does not appear to correlate with other traditional cardiovascular risk factors, such as age, BMI, insulin resistance, and lipid profile. In a study of CAD patients, the plasma sF11R level did not relate to diabetes, obesity, or hyperlipidemia, but it correlated positively with fasting insulin and was significantly lower in current smokers.[9] Interestingly, plasma sF11R level did not differ significantly between CAD patients with or without hypertension.[9] In this study, we did not find any gender difference in the plasma sF11R level. However, the association of sF11R level with hypertension was significant in women but not in men in the stepwise regression analysis. Sex hormones have been suggested to contribute to the gender difference in blood pressure regulation.[14] The expression level of F11R has been shown to be affected by sex hormones, at least in the female genital tracts in mice.[15]

The causative role of sF11R in hypertension of humans is unknown at present. Rodent models may shed light on mechanisms by which F11R may elevate blood pressure. Expression of F11R in the nucleus tractus solitarii of the rat brain stem was shown to increase prior to the onset of hypertension, and overexpression of F11R increased systolic blood pressure with the effect lasting for more than 14 days.[5] It has been demonstrated that F11R serves to promote the adherence of leukocytes to the endothelium resulting in vascular inflammation[16] and thus may be responsible in part for the increase in the total peripheral resistance observed in spontaneously hypertensive rats.[17] Moreover, the mediation by F11R in the arrest and transendothelial migration of T cells may further suggest a role for the involvement of F11R in the pathogenesis of hypertension.[18,19] However, the relationship between brain F11R with plasma sF11R is unknown. Our study did not find a significant difference in sF11R level between treated hypertensive subjects with or without normalized blood pressure, suggesting that sF11R may not be the cause of elevation in blood pressure, although the lack of a significant difference could also be due to an insufficiently large sample size.

It has been suggested that the soluble form(s) of F11R, detected in circulating plasma at the pg/ml level,[9] may arise by sheddings from endothelial cells and/or platelets by a protease[20] or other mechanisms[21] resulting in the release of the extracellular domain of F11R into the circulation as sF11R. In addition to endothelial cells and platelets, F11R is also expressed in erythrocytes, monocytes, lymphocytes, neutrophils, and antigen-presenting cells.[18,22] Thus, the concentration of sF11R in the circulation would be dependent on the level of expression of the native, transmembrane F11R and on the rate of the release of its extracellular domain into the circulation. Interestingly, in spontaneously hypertensive rats, enhanced proteolyic activity in endothelium and in plasma increases cleavage of cell membrane receptors, including

insulin receptors and CD18 membrane adhesion molecules.[23] Whether the low level of circulating (pg/ml range) sF11R has active biological functions or is an inactive degradation product is still unknown. Pharmacological concentrations of a recombinant soluble extracellular portion of rsF11R, at the μg/ml level, were shown to inhibit platelet aggregation induced by the stimulatory monoclonal antibody, M.Ab.F11, and the adhesion of platelets to immobilized rsF11R.[24] Such high concentrations of rsF11R were also shown to inhibit mononuclear cell recruitment on inflamed or atherosclerotic endothelium.[16] Whether the generated level of sF11R may provide a negative feedback mechanism that regulates the activity of the native F11R is speculative at the present time. Further study using F11R antagonists in animal models may be needed to validate the functional relevance of sF11R to hypertension.

Our finding of an association of sF11R with hypertension, a major risk factor of cardiovascular diseases, is consistent with a previous report showing an association with CAD. However, the sF11R level in normotensive subjects measured in the present study is significantly higher than that measured in normal subjects in a previous report.[9] The cause of this difference lies in the study population itself, the sites, or sample handing, although stringent adherence to the protocols was followed. However, this difference between studies in normotensive levels does not detract from the final conclusion of the present study regarding the significant correlation with sF11R levels in people with hypertension. Further prospective studies are needed to investigate the ability of sF11R to predict the development of hypertension and hence its causative role.

The independent association of sF11R level with fibrinogen, an acute phase protein, in stepwise multiple linear regression analysis is consistent with its correlation with inflammatory cytokines such as tumor necrosis factor-α[8,9] and its role in inflammation.[18] The sF11R could be another inflammatory cytokine involved in the pathogenesis of hypertension.[10] It is interesting that the direction of association between sF11R level and fibrinogen is negative. Besides fibrinogen, fibronectin is another molecule that mediates platelet aggregation.[25] Soluble fibronectin can attenuate the effects of tumor necrosis factor-α on the disassembly of F11R from intercellular junctions.[26] Measurement of inflammatory cytokines may help to elucidate the role of the F11 receptor in human hypertension.

The direct role of F11R in the induction of plaque formation was attributed to the homologous adhesion of F11R expressed constitutively on the surface of circulating platelets with the newly expressed F11R on the surface of the endothelium treated with inflammatory cytokines.[3,4] Inflammatory cytokines induce *de novo* expression and redistribution of F11R, leading to inflammatory thrombosis.[3,4,24] Similar mechanisms may be involved in the action of inflammatory cytokines in the pathogenesis of hypertension.[10] This possibility suggests also that F11R antagonists developed for the prevention and treatment of atherosclerosis[3,4,24] may also be useful for the prevention and treatment of human hypertension.

In conclusion, plasma sF11R is elevated in hypertension and is related to fibrinogen level. Its use as a novel biomarker of hypertension and other related cardiovascular risk merits further study.

Acknowledgments: The Hong Kong Cardiovascular Risk Factor Prevalence Study-2 (CRISPS2) was supported by a Hong Kong Research Grants Council Grant (#7229/01M) and the Sun Chieh Yeh Heart Foundation. The study of SNPs was supported by a Hong Kong Research Grants Council Grant (#7626/07M).

Disclosure: The authors declared no conflict of interest.

1. Kornecki E, Walkowiak B, Naik UP, Ehrlich YH. Activation of human platelets by a stimulatory monoclonal antibody. *J Biol Chem* 1990; 265:10042–10048.
2. Martìn-Padura I, Lostaglio S, Schneemann M, Williams L, Romano M, Fruscella P, Panzeri C, Stoppacciaro A, Ruco L, Villa A, Simmons D, Dejana E. Junctional adhesion molecule, a novel member of the immunoglobulin superfamily that distributes at intercellular junctions and modulates monocyte transmigration. *J Cell Biol* 1998; 142:117–127.
3. Babinska A, Azari BM, Salifu MO, Liu R, Jiang XC, Sobocka MB, Boo D, Al Khoury G, Deitch JS, Marmur JD, Ehrlich YH, Kornecki E. The F11 receptor (F11R/JAM-A) in atherothrombosis: overexpression of F11R in atherosclerotic plaques. *Thromb Haemost* 2007; 97:272–281.
4. Babinska A, Kedees MM, Athar H, Batuman O, Ehrlich YH, Hussain MM, Kornecki E. F11-receptor (F11R/JAM) mediates platelet adhesion to endothelial cells: role in inflammatory thrombosis. *Thromb Haemost* 2002; 88:843–850.
5. Waki H, Liu B, Miyake M, Katahira K, Murphy D, Kasparov S, Paton JF. Junctional adhesion molecule-1 is upregulated in spontaneously hypertensive rats: evidence for a prohypertensive role within the brain stem. *Hypertension* 2007; 49:1321–1327.
6. Paton JF, Waki H. Is neurogenic hypertension related to vascular inflammation of the brainstem?. *Neurosci Biobehav Rev* 2009; 33:89–94.
7. Ong KL, Leung RY, Wong LY, Cherny SS, Sham PC, Lam TH, Lam KS, Cheung BM. Association of F11 receptor gene polymorphisms with central obesity and blood pressure. *J Intern Med* 2008; 263:322–332.
8. Salifu MO, Kolff Q, Murty P, Haria DM, Zimpa M, Shakeel M, Lee H, Kornecki E, Babinska A. Relationship between the soluble F11 receptor and markers of inflammation in hemodialysis patients. *J Investig Med* 2007; 55:115–119.
9. Cavusoglu E, Kornecki E, Sobocka MB, Babinska A, Ehrlich YH, Chopra V, Yanamadala S, Ruwende C, Salifu MO, Clark LT, Eng C, Pinsky DJ, Marmur JD. Association of plasma levels of F11 receptor/junctional adhesion molecule-A (F11R/JAM-A) with human atherosclerosis. *J Am Coll Cardiol* 2007; 50: 1768–1776.
10. Sesso HD, Buring JE, Rifai N, Blake GJ, Gaziano JM, Ridker PM. C-reactive protein and the risk of developing hypertension. *JAMA* 2003; 290:2945–2951.
11. Cheung BM, Wat NM, Man YB, Tam S, Thomas GN, Leung GM, Cheng CH, Woo J, Janus ED, Lau CP, Lam TH, Lam KS. Development of diabetes in Chinese with the metabolic syndrome: a 6-year prospective study. *Diabetes Care* 2007; 30: 1430–1436.
12. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ. Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. *Hypertension* 2003; 42:1206–1252.
13. Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D, Maller J, Sklar P, de Bakker PI, Daly MJ, Sham PC. PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet* 2007; 81:559–575.
14. Reckelhoff JF. Gender differences in the regulation of blood pressure. *Hypertension* 2001; 37:1199–1208.
15. Yu M, Cao X, Wang X, Xu J, Yang M, Ben K. Migration of mouse antibody-secreting hybridoma cells from blood to genital tract and its regulation by sex hormones are associated with the differential expression patterns of adhesion molecules and chemokines in the tract rather than in the antibody-secreting cells. *J Reprod Immunol* 2007; 74:78–89.
16. Ostermann G, Fraemohs L, Baltus T, Schober A, Lietz M, Zernecke A, Liehn EA, Weber C. Involvement of JAM-A in mononuclear cell recruitment on inflamed or atherosclerotic endothelium: inhibition by soluble JAM-A. *Arterioscler Thromb Vasc Biol* 2005; 25:729–735.
17. Fukuda S, Yasu T, Kobayashi N, Ikeda N, Schmid-Schonbein GW. Contribution of fluid shear response in leukocytes to hemodynamic resistance in the spontaneously hypertensive rat. *Circ Res* 2004; 95:100–108.

18. Weber C, Fraemohs L, Dejana E. The role of junctional adhesion molecules in vascular inflammation. *Nat Rev Immunol* 2007; 7:467–477.
19. Guzik TJ, Hoch NE, Brown KA, McCann LA, Rahman A, Dikalov S, Goronzy J, Weyand C, Harrison DG. Role of the T cell in the genesis of angiotensin II induced hypertension and vascular dysfunction. *J Exp Med* 2007; 204: 2449–2460.
20. Kornecki E, Ehrlich YH, DeMars DD, Lenox RH. Exposure of fibrinogen receptors in human platelets by surface proteolysis with elastase. *J Clin Invest* 1986; 77: 750–756.
21. Kedees M, Babinska A, Swiatkowska M, Deitch J, Ehrlich YH, Hussain MM, Kornecki E. Expression of a recombinant protein of the platelet F11 receptor (F11R) (JAM-1/JAM-A) in insect cells: F11R is naturally phosphorylated in the extracellular domain. *Platelets* 2005; 16:99–109.
22. Sobocka MB, Sobocki T, Banerjee P, Weiss C, Rushbrook JI, Norin AJ, Hartwig J, Salifu MO, Markell MS, Babinska A, Ehrlich YH, Kornecki E. Cloning of the human platelet F11 receptor: a cell adhesion molecule member of the immunoglobulin superfamily involved in platelet aggregation. *Blood* 2000; 95:2600–2609.
23. DeLano FA, Schmid-Schönbein GW. Proteinase activity and receptor cleavage: mechanism for insulin resistance in the spontaneously hypertensive rat. *Hypertension* 2008; 52:415–423.
24. Babinska A, Kedees MH, Athar H, Sobocki T, Sobocka MB, Ahmed T, Ehrlich YH, Hussain MM, Kornecki E. Two regions of the human platelet F11-receptor (F11R) are critical for platelet aggregation, potentiation and adhesion. *Thromb Haemost* 2002; 87:712–721.
25. Ni H. Unveiling the new face of fibronectin in thrombosis and hemostasis. *J Thromb Haemost* 2006; 4:940–942.
26. Martinez-Estrada OM, Manzi L, Tonetti P, Dejana E, Bazzoni G. Opposite effects of tumor necrosis factor and soluble fibronectin on junctional adhesion molecule-A in endothelial cells. *Am J Physiol Lung Cell Mol Physiol* 2005; 288:L1081–L1088.