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Resistin level is positively correlated with thrombotic complications in Southern Chinese metabolic syndrome patients

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ABSTRACT. ***Background:*** **The metabolic syndrome (MetS) has been found to be closely related with thrombotic diseases. The mechanism, however, is far from elucidated.** ***Aim:*** **This study was designed to investigate the relationship between endogenous resistin and thrombosis mediating factors, as well as its potential effects on the gene expression of cardiovascular disease biomarkers.** ***Methods:*** **Ninety patients satisfied the MetS criteria, and 55 healthy subjects were recruited as part of a single-center clinical study. Plasma levels of resistin, tissue factor (TF), tissue factor pathway inhibitor (TFPI), tissue plasminogen activator (tPA), plasminogen activator inhibitor-1 (PAI-1) were measured by enzyme-linked immunosorbent assays. The effect of resistin on the expression of cardiovascular disease biomarkers in human umbilical vein endothelial cells (HUVEC) was assayed by gene microarray.** ***Results:*** **1) The average levels of resistin in MetS patients with or without acute myocardial or cerebral infarction were significantly higher than those of the controls. 2) The TF and TFPI increase was higher in MetS with infarction patients than in MetS patients. 3) In MetS with infarction patients, resistin was positively correlated with TF and PAI-1 (r=0.313, *p*=0.008; r=0.401, *p*=0.002, respectively). 4) In HUVEC, the microarray showed that apolipoprotein C-I, ACE, tumor necrosis factor receptor superfamily member 1A (TNFRSF1A) and member 5 (CD40) genes expression were dramatically increased by resistin.** ***Conclusion:*** **In patients with MetS, resistin is strongly associated with hypercoagulative and hypofibrinolitic activities. Moreover, resistin may induce thrombotic complications *via* mediating the lipoprotein metabolism and stimulating inflammation.**

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INTRODUCTION

Metabolic syndrome (MetS), a constellation of metabolic abnormalities, including the clustering of abdominal obesity, insulin resistance (IR), dyslipidemia and elevated blood pressure (BP) (1), is one of the risk factors for Type 2 diabetes and cardiovascular disease (CVD), and its pathogenesis is closely linked to IR and inflammation (2). The risk of coronary artery disease and acute thrombotic events, such as myocardial infarction and stroke, are found to be 2- to 4-fold higher in individuals with MetS compared with those without MetS (3-5).

Resistin, a newly discovered adipokine, belongs to a family of polypeptides mainly produced by adipose tissue-related leucocytes and mononuclear cells in human (6), and was originally reported to be secreted by adipocytes, linking obesity to IR and diabetes in mice (7). Some clinical studies revealed that elevated resistin levels were associated with MetS (8-10). Subsequent studies showed that elevated resistin levels were associated with the presence and severity of coronary artery disease (11, 12) and the increasing coronary artery calcification (13). Recent data further demonstrated that resistin is also secreted by macrophages in atheroma, thus raising the hypothesis of resistin being a contributor to atherogenesis (6). It is still controversial, however, to confirm the pathophysiological role of resistin in MetS and its complications (14, 15), which may be partly due to the different sources of circulating resistin in humans and rodents.

Thrombus formation was viewed as a consequence of the imbalance of blood coagulation and fibrinolysis, which is regulated mainly by tissue factor (TF), tissue factor pathway inhibitor (TFPI), plasminogen activator inhibitor-1 (PAI-1), and tissue-type plasminogen activator (tPA). TF, the key initiator of coagulation is widely expressed in atherosclerotic plaques and found in macrophages, smooth muscle cells, and extracellular matrix (16). TFPI is known to inhibit the potentiation of TF by factor Xa-dependent binding to the factor VIIa-TF complex (17). Taking all data into consideration, the purpose of the present investigation is to assess the correlation of circulating resistin levels with other metabolic parameters and markers of coagulation and fibrinolysis system in Southern Chinese subjects with MetS, and investigate the effect of resistin on some CVD biomarkers expression in endothelial cells to reveal the role of endogenous resistin in the pathophysiological process of thrombotic complications in MetS.

SUBJECTS AND METHODS

Study participants

Ninety patients (45 men and 45 women), who were not taking any medication at the time of study, were recruited to participate in this study from October 2008 to August 2009. They were admitted to Emergency, Endocrinology or Cardiovascu-

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Key-words: metabolic syndrome, resistin, thrombosis.

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lar Departments of the First Affiliated Hospital of Shantou University Medical College; those who did not satisfy the criteria below were excluded. In addition, 55 individuals were recruited from the Medical Examination Center of the First Affiliated Hospital of Shantou University Medical College. Only those who were age-matched and did not have a history of myocardial infarction or ischemic stroke, and whose chemical examinations did not suggest diabetes, hyperlipemia or other characteristics of MetS were enroled as healthy people. After exclusion of 5 individuals due to hyperglycemia and hypertension, 50 healthy subjects (21 men and 29 women) remained as control subjects. All subjects provided written informed consent to participate in the study, and procedures were approved by the Hospital Ethics Committee.

Subjects completed a self-administered questionnaire that included demographic characteristics, general health status, smoking history, and current medications. Anthropometric and body composition measurements including height, waist and hip circumference were performed in all study participants before breakfast, with the subjects wearing light clothing and without shoes. Their body mass index (BMI) (kg/m^2) was calculated as an index of their overall adiposity. BP was measured from the right arm subsequent to the participant sitting at rest for a period of 20 min. The mean of two consecutive BP recordings was used for statistical analysis. One observer performed all of the anthropometric and BP measurements. The blood samples of patients were collected on the day of admission before taking any medication. The control blood samples were collected after a 12-h fast. All the blood samples were collected in tubes containing natrium citricum (1:9), and the plasma samples were collected from blood samples after centrifugation at 1500 rpm for 10 min, and were processed immediately, coded, and then stored at –80 C until analysis.

Definition of acute myocardial infarction, stroke, and metabolic syndrome

Acute myocardial infarction and ischemic stroke case definitions were based on published international clinical criteria (18). MetS was defined based upon the International Diabetes Federation (IDF) criteria for Chinese (19) as presenting the first of the following components and at least 2 of others:

- waist circumferences ≥90 cm in men or ≥80 cm in women;
- triglycerides ≥1.7 mmol/l;
- HDL cholesterol <1.03 mmol/l in men or <1.30 mmol/l in women;
- BP≥130/85 mmHg, or current use of anti-hypertensive medications;
- fasting plasma glucose ≥5.6 mmol/l, or previously diagnosed Type 2 diabetes, or use of oral anti-diabetic agents or insulin.

Laboratory measurement

The measurements of fasting plasma glucose, total cholesterol, triglyceride, HDL cholesterol, glycosylated hemoglobin, platelet, C-reactive protein (CRP), prothrombin time (PT), activated partial thromboplastin time (APTT) and fibrinogen (Fbg) were as previously described (11). Plasma resistin concentration was measured by commercial enzyme-linked immunosorbent assays (ELISA) (Invitrogen, Camarillo, CA, USA), plasma C peptide of insulin concentration was assayed with ELISA kits (BlueGene, ShangHai, China), plasma TF and TFPI concentrations were assayed with ELISA kits (ADI, Stamford, CT, USA), plasma PAI-1, tPA and von Willebrand Factor (vWF) concentrations were assayed with ELISA kits (SunBiote, ShangHai, China).

Cell culture

Primary human umbilical vein endothelial cells (HUVEC), culture medium, growth factors, and supplements were obtained from

Table 1 - *Comparisons of clinical parameters among control group, metabolic syndrome (MetS) group, and MetS with infarction group.*

Parameters	Control group (no.=50)	MetS group (no.=50)	MetS with infarction group (no.=40)
Age (yr)	67.39±3.18	67.50±3.15	66.68±5.98
Men-women ratio	1.5:1	1:1.38	1.5:1
Height (cm)	164.78±5.40	160.75±7.55	164.48±7.94
Weight (kg)	60.72±6.39	63.08±6.22[a]	68.45±9.13[b]
Waist-to-hip ratio	0.81±0.07	0.90±0.09[a]	0.85±0.06[a]
BMI (kg/m^2)	22.32±1.57	24.43±2.09[b]	25.26±2.57[b]
SBP (mmHg)	126.72±13.87	138.33±11.36[a]	155.25±22.33[b,c]
DBP (mmHg)	69.94±6.46	89.83±12.22[b]	90.25±11.08[b]
Fasting plasma glucose (mM/l)	5.87±1.25	8.54±2.18[b]	8.26±3.44[b]
Total cholesterol (mM/l)	4.75±1.22	7.32±1.16[b]	5.18±1.02[a,d]
Triglyceride (mM/l)	1.04±0.34	1.87±0.65[b]	1.98±0.25[b]
HDL cholesterol (mM/l)	1.23±0.56	1.27±0.56	1.17±0.31
Glycosylated hemoglobin	4.38±0.94	7.77±1.77[b]	6.14±1.33[b,d]
C peptide of insulin (ng/ml)	13.88±3.89	16.60±4.35[a]	21.57±5.47[b,d]
Platelet (*10E9/l)	230.11±51.74	221.25±53.78	254.50±89.81
CRP (mg/l)	2.41±0.70	2.36±0.93	18.04±11.08[b,d]
PT (sec)	11.91±0.71	12.33±1.59	10.44±0.71[b,d]
APTT (sec)	35.46±2.22	33.86±4.31	26.78±3.73[b,d]
Fbg (g/l)	3.06±0.53	2.94±0.41	3.33±0.95[c]

Data are presented as means±SD. [a]$p<0.05$ *vs* control group; [b]$p<0.01$ *vs* control group. [c]$p<0.05$ vs MetS group. [d]$p<0.01$ *vs* MetS group. MetS: metabolic syndrome; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; CRP: C-reactive protein. PT: prothrombin time. APTT: activated partial thromboplastin time; Fbg: fibrinogen.

Table 2 - *Comparisons of laboratory parameters among control group, metabolic syndrome (MetS) group, and MetS with infarction group.*

Parameters	Control group (no.=50)	MetS group (no.=50)	MetS with infarction group (no.=40)
Resistin (ng/ml)	6.87±2.75	10.73±6.60[b]	11.95±6.04[b]
TF (ng/ml)	676.97±374.83	623.51±520.57	975.14±897.50[a,d]
TFPI (pg/ml)	96.37±48.83	74.62±44.40[a]	129.14±60.04[b,d]
PAI-1 (ng/ml)	202.42±66.05	280.06±69.69[b]	323.29±155.50[b,c]
tPA (ng/ml)	35.19±34.36	31.71±25.07	35.19±20.10
vWF release (%)	12899.26±5959.17	11105.75±5311.31	9182.34±3653.57[b]

Data are means±SD. [a]$p<0.05$ *vs* control group; [b]$p<0.01$ vs control group. [c]$p<0.05$ *vs* MetS group; [d]$p<0.01$ *vs* MetS group. TF: tissue factor; TFPI: tissue factor pathway inhibitor; PAI-1: plasminogen activator inhibitor-1; tPA: tissue plasminogen activator; vWF: von Willebrand Factor.

ScienCell Research Laboratories (San Diego, CA, USA), and the cells were cultured and maintained according to the manufacturer's instructions. HUVEC within 3rd to 5th passage were cultured in 75-cm^2 flasks at a density of 10^5 cells/ml (20).

Superarray gene microarray

HUVEC were treated with either media alone as controls, or 50 ng/ml resistin for 48 h. The experiment was performed according to Oligo GEArray assay protocol (SupperArray, MD, USA). Briefly, total RNA was isolated from HUVEC by use of TRIzol reagent according to the manufacturer's recommendations (Invitrogen, CA, USA). A total of 6 μg RNA was used to synthesize cDNA. The cRNA was then labeled and amplified using a TrueLabeling- AMP™ linear RNA amplification kit. The Oligo GEArray was processed for chemiluminescent detection on X-ray film and an image was acquired on a flatbed desktop scanner.

Statistical analysis

The intra-assay reproducibility was calculated on 3 plasma samples of healthy subjects, the MetS patients and the MetS with infarction patients, respectively. Each sample was analyzed 4 times. The same plasma samples were used also to calculate the inter-assay reproducibility: each sample was divided into 4 aliquots, then each aliquot was analyzed separately. The SD of the measured amounts was divided for the mean value and the reproducibility was expressed as a percentage of the coefficient of variation (CV) (intra- and inter-assay CV%).

SPSS 13.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Results are presented as means±SD. A $p<0.05$ was considered statistically significant. We used the one-way analysis of variance to analyze difference in the body composition and biochemical parameters. Correlation coefficients between resistin, coagulated and fibrinolytic markers (TF, TFPI, tPA, PAI-1, and vWF) and metabolic feature were calculated by partial correlation analysis. Coagulated and fibrinolytic markers (TF, TFPI, tPA, and PAI-1) on plasma resistin concentrations were tested in multivariate linear regression analyses. Analyses were controlled for potential confounders including age and BMI.

RESULTS

Clinical characteristics of the study participants

The demographic, anthropometric, and metabolic parameters of subjects enroled in this study are summarized in Table 1.

The increase in weight, BMI, waist-to-hip ratio, systolic and diastolic BP, fasting plasma glucose, C peptide of insulin, total cholesterol, triglyceride, and glycosylated hemoglobin levels was significantly higher in the two MetS groups than in controls.

The increase in systolic BP, C peptide of insulin, CRP, and Fbg was higher in the MetS with myocardial or cerebral infarction group than in the MetS group.

Total cholesterol, glycosylated hemoglobin, PT, and APTT levels in the MetS with myocardial or cerebral infarction group were much lower than in the MetS group.

Laboratory characteristics of the study participants

The median plasma resistin concentration was 9.85 ng/ml (CV=1.7%) in the study population (Table 2). The increase in plasma resistin level was significantly higher in the MetS patients compared to the control subjects, and the MetS with infarction patients had a significantly higher concentration of resistin than the control subjects. There was no significant difference between the MetS and the MetS with infarction patients. The median plasma TF concentration was 758.54 ng/ml (CV=2.5%) in the study population. The MetS with infarction patients had a significantly higher level of TF than MetS alone patients or the control subjects. There was no significant difference between the control and the MetS groups. However, the MetS with acute infarction patients had a significantly higher level of TFPI than the control subjects or the MetS patients. The median plasma TFPI concentration was 100.04 pg/ml (CV=1.9%) in the study population. The median plasma PAI-1 concentration was 268.59 ng/ml (CV=1.4%) in the study population. The PAI-1 plasma level increased greatly in subjects with MetS compared to the control subjects. The MetS with infarction patients had a significantly higher level of PAI-1 than the control subjects or the MetS patients. The median plasma tPA concentration was 34.03 ng/ml (CV=2.4%) in the study population; there was no significant difference among 3 groups. The median plasma vWF concentration was 11062.45 ng/ml (CV=1.8%) in the study population. The release level of vWF decreased more in the MetS with infarction patients than in the control subjects, there was no significant difference between the control and the MetS groups (Table 2).

Associations of resistin with metabolic features and coagulation regulating factors

We investigated the relationships between plasma concentrations of resistin and metabolic features, and concentrations of coagulation regulating factors. The plasma

Table 3 - *Partial correlation coefficients between plasma levels of resistin, and the variables of clinical, laboratory and anthropometric parameters in all subjects examined and according to presence/absence of the metabolic syndrome or infarction.*

Parameters	Control group (no.=50)		MetS group (no.=50)		MetS with infarction group (no.=40)	
	r	*p*	r	*p*	r	*p*
Waist-to-hip ratio	0.042	0.027	0.054	0.043	0.095	<0.001
SBP (mmHg)	0.149	0.581	–0.356	0.032	–0.199	0.231
DBP (mmHg)	–0.118	0.686	0.282	0.108	–0.140	0.401
Fasting plasma glucose (mM/l)	0.798	<0.001	–0.223	0.194	0.047	0.780
Triglyceride (mM/l)	–0.285	0.271	0.482	0.004	–0.084	0.616
HDL cholesterol (mM/l)	–0.636	0.008	–0.215	0.214	0.275	0.094
Glycosylated hemoglobin (%)	–0.106	0.682	–0.318	0.739	0.090	0.591
CRP (mg/l)	0.513	0.040	0.126	0.473	–0.245	0.138
PT (sec)	0.397	0.134	0.585	<0.001	–0.061	0.717
APTT (sec)	0.368	0.172	0.240	0.161	0.161	0.334
C peptide of insulin (ng/ml)	–0.035	0.902	0.091	0.609	–0.125	0.454
TF (ng/ml)	0.237	0.372	0.157	0.394	0.313	0.008
TFPI (pg/ml)	0.239	0.389	0.158	0.396	–0.071	0.651
PAI-1 (ng/ml)	–0.163	0.546	0.193	0.279	0.401	0.002
tPA (ng/ml)	–0.284	0.280	–0.441	0.008	–0.156	0.351
vWF release (%)	0.113	0.551	–0.272	0.172	–0.152	0.334

All correlation coefficients were calculated after adjustment for age and body mass index (BMI). SBP: systolic blood pressure; DBP: diastolic blood pressure; CRP: C-reactive protein; PT: prothrombin time; APTT: activated partial thromboplastin time; Fbg: fibrinogen; TF: tissue factor; TFPI: tissue factor pathway inhibitor; PAI-1: plasminogen activator inhibitor-1; tPA: tissue plasminogen activator; vWF: von Willebrand Factor.

resistin levels were significantly correlated with age and BMI of all subjects (Pearson's correlation coefficient, r=0.269, *p*=0.015; r=0.078, *p*=0.048, respectively). Thus, the correlation of resistin levels with other metabolic and anthropometric parameters was investigated with a partial correlation analysis adjusted for age and BMI. Partial correlation analysis (Table 3) showed that, after adjustment for age and BMI, in the control group, resistin was positively correlated with waist-to-hip ratio, fasting plasma glucose, CRP, and was negatively correlated with HDL. In the MetS group, resistin was positively correlated with waist-to-hip ratio, triglyceride, and PT. In the MetS with infarction group, resistin was positively correlated with waist-to-hip ratio, TF, and PAI-1 (r=0.095, *p*<0.001; r=0.313, *p*=0.008; r=0.401, *p*=0.002, respectively). The relationships between plasma concentrations of resistin and TF and PAI-1 in subjects with the MetS and infarction are shown in Figures 1 and 2, respectively. Further analysis in multivariate linear regression, as presented in Table 4, showed that TF and PAI-1 in the MetS with infarction group were independent predictors of plasma resistin level.

Resistin up-regulated CVD biomarkers' gene expression

We observed the effect of resistin on some CVD biomarkers' gene expression by SuperArray Oligo GEArray. Punctiform figures (Fig. 3) showed the results of Oligo GEArray. The expression of 12 biomarkers was significantly different between the control group and the resistin treatment group; we are especially interested in 4 of these: tumor necrosis factor receptor superfamily, member 1A (TNFRSF1A); tumor necrosis factor receptor superfamily,

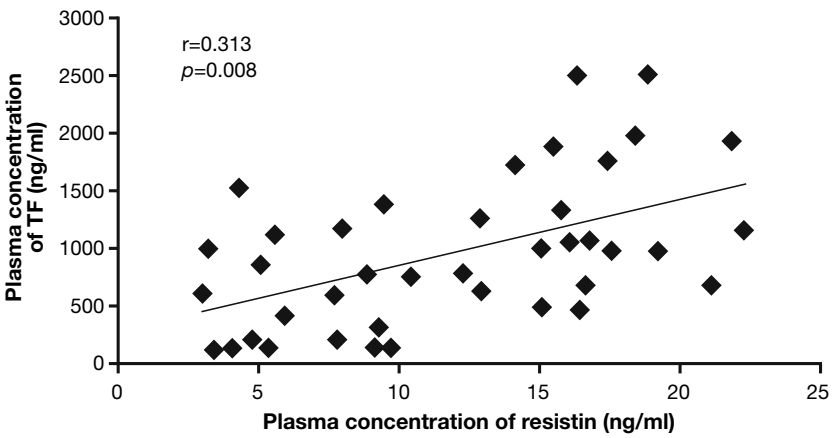

Fig. 1 - *Correlation between plasma levels of resistin and tissue factor (TF) of the metabolic syndrome with infarction patients.*

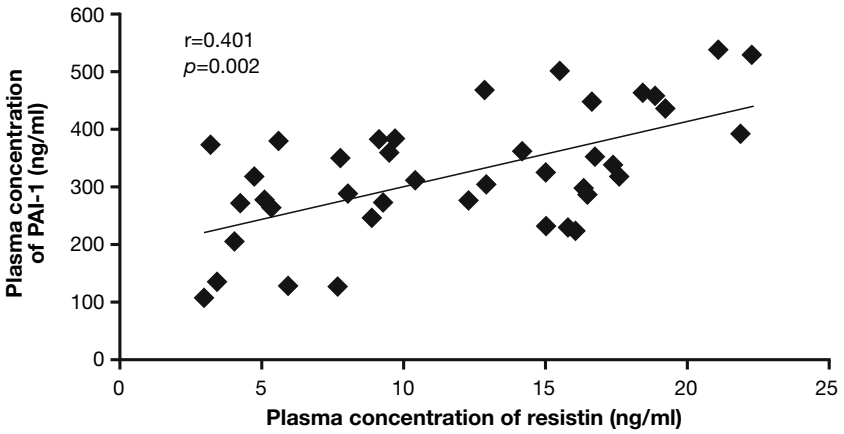

Fig. 2 - *Correlation between plasma levels of resistin and plasminogen activator inhibitor-1 (PAI-1) of the metabolic syndrome with infarction patients.*

member 5 (CD40); ACE and apolipoprotein C-I (ApoC-I), which are obviously up-regulated by resistin compared to medium treated alone group (Fig. 4).

DISCUSSION

Individuals with MetS are reported to have a higher risk of thrombotic events, such as myocardial infarction or ischemic stroke (21-23). The mechanism, however, is far from elucidated. Our observations demonstrate that in patients with MetS, resistin is positively associated with TF and PAI-1 after adjustment for age and BMI, which are important mediators of coagulation and fibrinolysis system. Furthermore, the multivariate regression analyses suggest that TF and PAI-1 may also play important roles in determining the plasma resistin level and their associations with MetS.

Our findings in Southern Chinese are consistent with a previous study carried out in Northern Chinese population (24), which also reported a strong relationship between resistin and PAI-1 levels, but other researchers did not subdivide the category of diseases. In support to some of the clinical investigations, we found that the MetS patients had significantly higher resistin concentrations than control subjects (6, 15, 16, 25), although there was no diversity between the 2 MetS patients groups with or without thrombotic infarction. Similarly, Lubos et al. (26) reported that resistin levels were elevated in patients presenting with unstable angina, non-ST-elevation myocardial infarction, and ST-elevation myocardial infarction, and might play a role as a diagnostic marker. More recently, one prospective cohort study concluded that resistin was an independent risk factor of coronary heart disease after adjustment for usual risk factors (27).

On the other hand, although evidence indicates that elevated levels of blood-borne or circulating TF have been associated with MetS (28), we did not find such elevation in the MetS patients, nevertheless, TF and TFPI, as well as plasma PAI-1 concentrations were obviously increased in the MetS with infarction patients, which are commonly present in acute thrombosis development. As the major initiator of coagulation, TF plays a central role in the pathogenesis of thrombus (29), whose expression is found to be increased at sites of carotid and coronary plaque. Interestingly, in accordance with our results, its inhibitor TFPI, expressed by a variety of cell types including macrophages and smooth muscle cells, has also been reported to be up-regulated in plaques which may be a result of the compensatory mechinisms (30).

PAI-1, one of the remarkably elevated cytokines secreted by adipose tissue as well as vascular endothelial cells in MetS, is the main physiologic inhibitor of tPA and is recognized as a primary inhibiting mediator on fibrinolytic activities (31). The positive relationship between resistin and TF, and PAI-1 observed in this study may reflex that high level of resistin in MetS patients may influence the balance between coagulation and fibrinolysis system to accelerate thrombotic complications.

In human beings, resistin is considered as an inflammatory marker with potent proinflammatory properties, and

Table 4 - *Multivariate regression analyses of coagulation and fibrinolysis regulating factors on plasma resistin level.*

Parameters	Control group (no.=50)			MetS group (no.=50)			MetS with infarction group (no.=40)		
	β	(SEM)	*p*	β	(SEM)	*p*	β	(SEM)	*p*
TF (ng/ml)	0.001	(0.001)	0.195	–0.008	(0.009)	0.388	0.048	(0.011)	<0.001
TFPI (pg/ml)	0.022	(0.009)	0.020	0.074	(0.071)	0.305	–0.108	(0.117)	0.356
PAI-1 (ng/ml)	–0.001	(0.003)	0.654	0.024	(0.021)	0.274	0.123	(0.035)	0.001
tPA (ng/ml)	–0.001	(0.004)	0.829	–0.210	(0.205)	0.313	–0.405	(0.215)	0.064

All correlation coefficients were calculated after adjustment for age and body mass index (BMI). TF: tissue factor; TFPI: tissue factor pathway inhibitor; PAI-1: plasminogen activator inhibitor-1; tPA: tissue plasminogen activator.

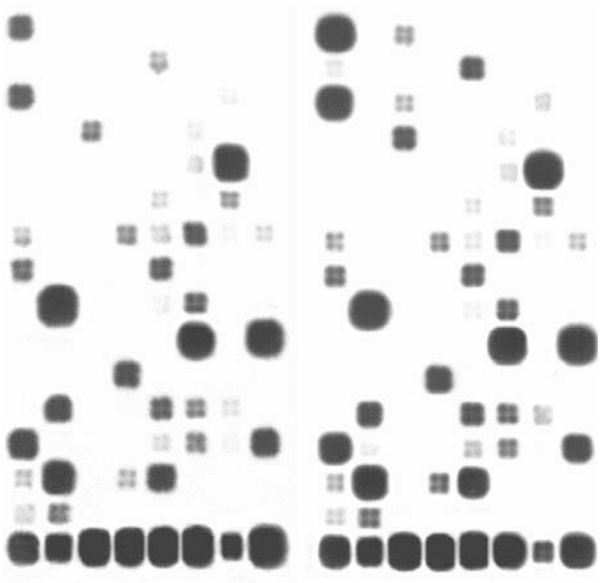

Fig. 3 - *Discrepancy of the expression of cardiovascular disease biomarkers in human umbilical vein endothelial cells treated with resistin (the gray scale of point lattice stand for the expression of genes).*

is associated positively with inflammatory markers such as CRP, interleukin-6 and tumor necrosis factor-α receptor 2 (25, 32). Then, in our *in vitro* experiment, we investigated the effect of resistin on mRNA levels of some of the CVD and thrombosis development relevant genes, including apolipoprotein, endothelin, interleukin, integrin by using gene microarray assay. In cultured vascular endothelial cells, which represent the main sources of circulating TF, TFPI, tPA, and PAI-1, 50 ng/ml resistin (we chose the concentration on basis of our preliminary studies with the maximum effect, data not shown) infusion for 48 h significantly up-regulated the expression of ApoC-I, ACE, TNFRSF1A, and CD40 as well as other genes (data not shown). ApoC-I is reported to be associated with glycometabolism and lipid metabolism (33). CD40/CD40L may participate in the development of coronary atherosclerosis and the triggering of acute coronary syndromes (34). So, the significant stimulated genes in the present study are those closely associated with atherothrombosis. The results of our microarray assay supplemented some direct evidences that resistin has a potential role in inducing dyslipidemia and chronic inflammation state, which may, in turn, stimulate TF and PAI-1 expression.

In conclusion, our present study suggests that endogenous increasing level of resistin in patients with metabolic syndrome is closely associated with thrombotic complications in Southern Chinese, which may be due to the cross action with coagulant and fibrinolysis mediating factors. The limitation of the present study is the relatively small samples and lack of follow-up investigations. So large-scale multi-center prospective trials are necessary to determine if resistin level is predictive of thromboembolic events in patients with MetS.

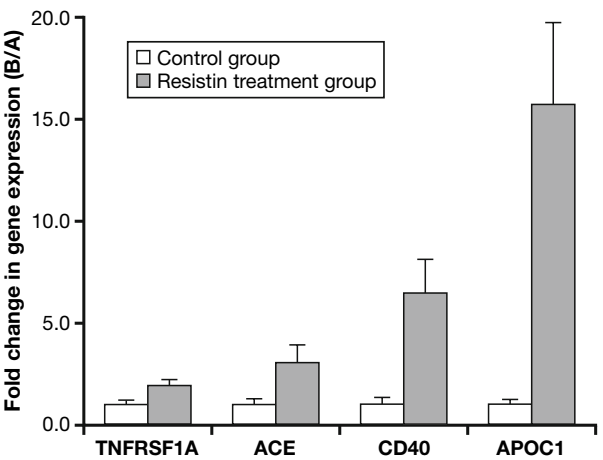

Fig. 4 - *Discrepancy of the expression of cardiovascular disease biomarkers in human umbilical vein endothelial cells treated with resistin. A: control group; B: resistin treatment group. TNFRSF1A: Tumor necrosis factor receptor superfamily, member 1A; CD40: tumor necrosis factor receptor superfamily, member 5; APOC1: apolipoprotein C-I.*

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REFERENCES

1. Cornier MA, Dabelea D, Hernandez TL, et al. The metabolic syndrome. Endocr Rev 2008, 29: 777-822.
2. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet 2005, 365: 1415-28.
3. Bataille V, Perret B, Dallongeville J, et al. Metabolic syndrome and coronary heart disease risk in a population-based study of middle-aged men from France and Northern Ireland. A nested case-control study from the PRIME cohort. Diabetes Metab 2006, 32: 475-9.
4. Simons LA, Simons J, Friedlander Y, McCallum J. Does a diagnosis of the metabolic syndrome provide additional prediction of cardiovascular disease and total mortality in the elderly? The Dubbo Study. Med J Aust 2007,186: 400-3.
5. Wang J, Ruotsalainen S, Moilanen L, Lepistö P, Laakso M, Kuusisto J. The metabolic syndrome predicts cardiovascular mortality: a 13-year follow-up study in elderly non-diabetic Finns. Eur Heart J 2007, 28: 857-64.
6. Jung HS, Park KH, Cho YM, et al. Resistin is secreted from macrophages in atheromas and promotes atherosclerosis. Cardiovasc Res 2006, 69: 76-85.
7. Steppan CM, Bailey ST, Bhat S, et al. The hormone resistin links obesity to diabetes. Nature 2001, 409: 307-12.
8. Norata GD, Ongari M, Garlaschelli K, Raselli S, Grigore L, Catapano AL. Plasma resistin levels correlate with determinants of the metabolic syndrome. Eur J Endocrinol 2007, 156: 279-84.
9 Osawa H, Ochi M, Tabara Y, et al. Serum resistin is positively correlated with the accumulation of metabolic syndrome factors in type 2 diabetes. Clin Endocrinol (Oxf) 2008, 69: 74-80.
10. Takata Y, Osawa H, Kurata M, et al. Hyperresistinemia is associated with coexistence of hypertension and type 2 diabetes. Hypertension 2008, 51: 534-9.
11. Ohmori R, Momiyama Y, Kato R, et al. Associations between serum resistin levels and insulin resistance, inflammation, and coronary artery disease. J Am Coll Cardiol 2005, 46: 379-80.

12. Pischon T, Bamberger CM, Kratzsch J, et al. Association of plasma resistin levels with coronary heart disease in women. Obes Res 2005, 13: 1764-71.
13. Reilly MP, Lehrke M, Wolfe ML, Rohatgi A, Lazar MA, Rader DJ. Resistin is an inflammatory marker of atherosclerosis in humans. Circulation 2005, 111: 932-9.
14. Iqbal N, Seshadri P, Stern L, et al. Serum resistin is not associated with obesity or insulin resistance in humans. Eur Rev Med Pharmacol Sci 2005, 9: 161-5.
15. Filippidis G, Liakopoulos V, Mertens PR, et al. Resistin serum levels are increased but not correlated with insulin resistance in chronic hemodialysis patients. Blood Purif 2005, 23: 421-8.
16. Esmon CT. The regulation of natural anticoagulant pathways. Science 1987, 235: 1348-52.
17. Rapaport SI. The extrinsic pathway inhibitor: a regulator of tissue factor-dependent blood coagulation. Thromb Haemost 1991, 66: 6-15.
18. Gillum RF, Fortmann SP, Prineas RJ, Kottke TE. International diagnostic criteria for acute myocardial infarction and acute stroke. Am Heart J 1984, 108: 150-8.
19. Alberti KG, Zimmet P, Shaw J; IDF Epidemiology Task Force Consensus Group. The metabolic syndrome-a new worldwide definition. Lancet 2005, 366: 1059-62.
20. Jin H, Qiu WB, Mei YF, et al. Testosterone alleviates tumor necrosis factor-alpha-mediated tissue factor pathway inhibitor downregulation via suppression of nuclear factor-kappa B in endothelial cells. Asian J Androl 2009,11: 266-71.
21. Malik S, Wong ND, Franklin SS, et al. Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in United States adults. Circulation 2004, 110: 1245-50.
22. Hong Y, Jin X, Mo J, et al. Metabolic syndrome, its preeminent clusters, incident coronary heart disease and all-cause mortality--results of prospective analysis for the Atherosclerosis Risk in Communities study. J Intern Med 2007, 262: 113-22.
23. Ay C, Tengler T, Vormittag R, et al. Venous thromboembolism--a manifestation of the metabolic syndrome. Haematologica 2007, 92: 374-80.
24. Hivert MF, Sullivan LM, Fox CS, et al. Associations of adiponectin, resistin, and tumor necrosis factor-alpha with insulin resistance. J Clin Endocrinol Metab 2008, 93: 3165-72.
25. Qi Q, Wang J, Li H, et al. Associations of resistin with inflammatory and fibrinolytic markers, insulin resistance, and metabolic syndrome in middle-aged and older Chinese. Eur J Endocrinol 2008, 159: 585-93.
26. Lubos E, Messow CM, Schnabel R, et al. Resistin, acute coronary syndrome and prognosis results from the AtheroGene study. Atherosclerosis 2007,193: 121-8.
27. Weikert C, Westphal S, Berger K, et al. Plasma resistin levels and risk of myocardial infarction and ischemic stroke. J Clin Endocrinol Metab 2008, 93: 2647-53.
28. Diamant M, Nieuwland R, Pablo RF, Sturk A, Smit JW, Radder JK. Elevated numbers of tissue-factor exposing microparticles correlate with components of the metabolic syndrome in uncomplicated type 2 diabetes mellitus. Circulation 2002,106: 2442-7.
29. DelGiudice LA, White GA. The role of tissue factor and tissue factor pathway inhibitor in health and disease states. J Vet Emerg Crit Care (San Antonio) 2009, 19: 23-9.
30. Crawley J, Lupu F, Westmuckett AD, Severs NJ, Kakkar VV, Lupu C. Expression, localization, and activity of tissue factor pathway inhibitor in normal and atherosclerotic human vessels. Arterioscler Thromb Vasc Biol 2000, 20: 1362-73.
31. Meltzer ME, Doggen CJ, de Groot PG, Rosendaal FR, Lisman T. The impact of the fibrinolytic system on the risk of venous and arterial thrombosis. Semin Thromb Hemost 2009, 35: 468-77.
32. Aquilante CL, Kosmiski LA, Knutsen SD, Zineh I. Relationship between plasma resistin concentrations, inflammatory chemokines, and components of the metabolic syndrome in adults. Metabolism 2008, 57: 494-501.
33. de Haan W, Out R, Berbée JF, et al. Apolipoprotein CI inhibits scavenger receptor BI and increases plasma HDL levels in vivo. Biochem Biophys Res Commun 2008, 377: 1294-8.
34. Antoniades C, Bakogiannis C, Tousoulis D, Antonopoulos AS, Stefanadis C. The CD40/CD40 ligand system: linking inflammation with atherothrombosis. J Am Coll Cardiol 2009, 54: 669-77.