Implication of Progranulin and C1q/TNF-Related Protein-3 (CTRP3) on Inflammation and Atherosclerosis in Subjects with or without Metabolic Syndrome

Hye Jin Yoo1, Soon Young Hwang2, Ho Cheol Hong1, Hae Yoon Choi1, Sae Jeong Yang1, Dong Seop Choi3, Sei Hyun Baik1, Matthias Blüher3, Byung-Soo Youn4+*, Kyung Mook Choi1+*  
1 Division of Endocrinology and Metabolism, Department of Medicine, College of Medicine, Korea University, Seoul, Korea, 2 Department of Biostatistics, College of Medicine, Korea University, Seoul, Korea, 3 Department of Medicine, University of Leipzig, Leipzig, Germany, 4 AdipoGen, Inc., Yeonsu-gu, Incheon, Korea

Abstract

Objective: Progranulin and C1q/TNF-related protein-3 (CTRP3) were recently discovered as novel adipokines which may link obesity with altered regulation of glucose metabolism, chronic inflammation and insulin resistance.

Research Design and Methods: We examined circulating progranulin and CTRP3 concentrations in 127 subjects with (n = 44) or without metabolic syndrome (n = 83). Furthermore, we evaluated the relationship of progranulin and CTRP3 levels with inflammatory markers and cardiometabolic risk factors, including high-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), estimated glomerular filtration rate (eGFR), and adiponectin serum concentrations, as well as carotid intima-media thickness (CIMT).

Results: Circulating progranulin levels are significantly related with inflammatory markers, hsCRP (r = 0.30, P = 0.001) and IL-6 (r = 0.30, P = 0.001), whereas CTRP3 concentrations exhibit a significant association with cardiometabolic risk factors, including waist circumference (r = −0.21), diastolic blood pressure (r = −0.21), fasting glucose (r = −0.20), triglyceride (r = −0.34), total cholesterol (r = −0.25), eGFR (r = 0.39) and adiponectin (r = 0.26) levels. Serum progranulin concentrations were higher in patients with metabolic syndrome than those of the control group (199.55 [179.33, 215.53] vs. 185.10 [160.30, 204.90], P = 0.051) and the number of metabolic syndrome components had a significant positive correlation with progranulin levels (r = 0.227, P = 0.010). In multiple regression analysis, IL-6 and triglyceride levels were significant predictors of serum progranulin levels (R² = 0.251). Furthermore, serum progranulin level was an independent predictor for increased CIMT in subjects without metabolic syndrome after adjusting for other cardiovascular risk factors (R² = 0.365).

Conclusions: Serum progranulin levels are significantly associated with systemic inflammatory markers and were an independent predictor for atherosclerosis in subjects without metabolic syndrome.

Trial Registration: ClinicalTrials.gov NCT01668888.

Citation: Yoo HJ, Hwang SY, Hong HC, Choi HY, Yang SJ, et al. (2013) Implication of Progranulin and C1q/TNF-Related Protein-3 (CTRP3) on Inflammation and Atherosclerosis in Subjects with or without Metabolic Syndrome. PLoS ONE 8(2): e55744. doi:10.1371/journal.pone.0055744

Editor: Massimo Federici, University of Tor Vergata, Italy

Received September 4, 2012; Accepted December 30, 2012; Published February 7, 2013

Copyright: © 2013 Yoo et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Funding: Dr. KMC was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2012006363) and Drs. SHB and KMC were supported by the Brain Korea 21 Project of the Ministry of Education and Human Resources Development, Republic of Korea (A102065-1011-1070100). Dr. HJY was also supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2012R1A1A005257). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: BSY is employed by AdipoGen, Inc. This does not alter the authors’ adherence to all the PLOS ONE policies on sharing data and materials.

* E-mail: medica7@gmail.com (KMC); bsyoun@gmail.com (BSY)
† These authors contributed equally to this work.

Introduction

Inflammation is known as a pivotal pathogenic mechanism of obesity-related disorders such as type 2 diabetes, metabolic syndrome, and atherosclerosis. Adipose tissue functions as a major endocrine organ by adipokine-mediated modulation of a number of signaling cascades in target tissues that exhibit pro-inflammatory or anti-inflammatory activity [1]. Therefore, targeting the molecular mechanism that leads to dysregulated production of adipokines may provide a novel therapeutic strategy for the treatment of inflammation-related metabolic disorders and cardiovascular disease (CVD) [2].

Progranulin was first purified as a growth factor from conditioned tissue culture media [3] and is known to play a critical role in multiple physiologic and pathologic conditions, including cell growth, wound healing, tumorigenesis and neurodegenerative disease such as fronto-temporal dementia [4]. Recently, Tang et al. demonstrated that progranulin directly binds to tumor necrosis factor receptors (TNFR) and disturbs the TNF-α-TNFR interaction, suggesting its role as a physiological
Progranulin and CTRP3 in Metabolic Syndrome

Subjects and Methods

Study Design and Participants

Subjects who visited the Health Promotion Center of Korea University Guro Hospital for a routine health check-up were enrolled between October 2009 and March 2011 using predefined inclusion and exclusion criteria. Inclusion criteria were apparently healthy volunteers with age between 20 and 80 years. We exclude the participants who had a history of CVD (myocardial infarction, unstable angina, stroke, or cardiovascular revascularization), type 2 diabetes, stage 2 hypertension (resting blood pressure, ≥160/100 mmHg), malignancy, or severe renal or hepatic disease. This study excluded subjects with a history of chronic inflammatory conditions that may affect the study results, and subjects that had taken medications that might affect inflammatory status within the last 6 months were also excluded. Participants were free of any lipid-lowering therapies for at least a 6-month period prior to enrollment. Finally, one hundred twenty-seven apparently healthy subjects who agreed to participate in the study were enrolled. Forty-four subjects had metabolic syndrome and 83 participants were classified as a normal control group. Metabolic syndrome was defined according to the criteria established by the National Cholesterol Education Program Adult Treatment Panel III using the adjusted waist circumference for Asians [14]. All participants provided written informed consent and the Korea University Institutional Review Board, in accordance with the Declaration of Helsinki of the World Medical Association, approved the study protocol.

Clinical and Laboratory Measurements

Body mass index (BMI) was calculated as weight/height$^2$ (kg/m$^2$) and waist circumference was measured at the midpoint between the lower border of the rib cage and the iliac crest. All blood samples were obtained the morning after a 12-hour overnight fast, and were immediately stored at −80°C for subsequent assays. Serum triglyceride and high density lipoprotein cholesterol (HDLC) levels were determined enzymatically using a chemistry analyzer (Hitachi 747; Hitachi Inc., Tokyo, Japan). Low density lipoprotein cholesterol (LDLC) concentrations were estimated using the Friedewald formula [15]. The glucose oxidase method was used to measure plasma glucose levels, and an electrochemiluminescence immunoassay (Roche Diagnostics, Indianapolis, IN, USA) was used to measure insulin levels. Insulin resistance was calculated with the homeostasis model assessment of insulin resistance (HOMA-IR) [16]. Estimated glomerular filtration rate (eGFR) was calculated from the Modification of Diet in Renal Disease (MDRD) study equation: (ml/min/1.73 m$^2$) = 1.73 × (Scr)$^{-1.154}$ × (Age)$^{-0.203}$ × (1.210 for female) [17]. Serum IL-6 levels were measured by ELISA (R&D Systems, Minneapolis, MN, USA). Latex-enhanced turbidimetric immunoassay (HiSens hsCRP L11A; HBI Co., Ltd., Anyang, Korea) was used for measurement of hsCRP. Adiponectin levels were measured by ELISA (AdipoGen, Incheon, Korea). Newly-developed ELISA was used for measurement of CTRP3-3 (AdipoGen, Incheon, Korea; intra- and inter-assay CVs: 7.2±1.0% and 5.8±2.7%, respectively) and progranulin (AdipoGen, Incheon, Korea; intra- and inter-assay CVs: 5.8±0.6% and 7.0±0.3%, respectively) levels.

Measurement of CIMT

The IMT of the common carotid artery was determined using high-resolution B-mode ultrasonography (EnVisor; Philips Medical Systems, Andover, MA, USA) with a 5–12 MHz transducer. Measurements of CIMT were made using IMT measurement software (Intimascope; Media Cross Co., Tokyo, Japan) at 3 levels of the lateral and medial walls, 1–3 cm proximal to the carotid bifurcation. The mean IMT was the average value of 99 computer-based points in the region. The CIMT level in this study was calculated as the average of the left and right mean IMT values. All measurements were recorded by one trained technician who was blinded to the subjects’ anthropometric and laboratory data.

Statistical Analysis

Each variable was assessed for a normal distribution. Data are expressed as mean ± SD or median (inter-quartile range [25%–75%]). Differences between groups were tested using an independent two-sample t-test or Mann-Whitney U test for continuous variables, and the Chi-square test was used to test for differences in the distribution of categorical variables. Spearman’s correlation test was performed to determine the relationships of serum progranulin and CTRP3 levels with study variables. P-values for
the linear trend of serum progranulin and CTRP3 levels according to the tertiles in the number of metabolic syndrome components were calculated by analysis of variance (ANOVA). Multiple linear stepwise regression analysis with progranulin and CTRP3 levels as dependent variables was performed to identify the risk factors that determine serum progranulin and CTRP3 concentrations in the study subjects. The second multiple linear stepwise regression analysis was performed to determine the risk factors for the CIMT study subjects. Serum progranulin levels had significant positive correlations with various metabolic parameters, including BMI, waist circumference, glucose tolerance, blood pressure, and lipid profiles (Table 2). On the other hand, circulating CTRP3 levels were significantly negatively correlated with waist circumference, diastolic blood pressure, total cholesterol, triglyceride, and fasting glucose levels, and positively correlated with age, eGFR, and serum adiponectin levels. However, serum CTRP3 concentrations had no significant correlation with serum hsCRP or IL-6 levels. Interestingly, the number of metabolic syndrome components had a significant positive relationship with circulating progranulin levels (r = 0.304, P = 0.001 and r = 0.300, P = 0.001, respectively), but had no significant correlations with various metabolic parameters, including BMI, waist circumference, glucose tolerance, blood pressure, and lipid profiles (Table 2). On the other hand, circulating CTRP3 levels were significantly negatively correlated with waist circumference, diastolic blood pressure, total cholesterol, triglyceride, and fasting glucose levels, and positively correlated with age, eGFR, and serum adiponectin levels. However, serum CTRP3 concentrations had no significant correlation with serum hsCRP or IL-6 levels. Interestingly, the number of metabolic syndrome components had a significant positive relationship with circulating progranulin levels (r = 0.227, P = 0.010) and a negative correlation with CTRP3 levels (r = −0.175, P = 0.050). Moreover, serum progranulin levels increased significantly according to the number of metabolic syndrome components (P for linear trend ≤ 0.01).

### Results

#### Baseline Characteristic of the Study Subjects

The clinical and biochemical characteristics of the study subjects are presented in Table 1. The metabolic syndrome group showed a significantly higher mean BMI, waist circumference, blood pressure, triglyceride, total cholesterol, fasting glucose, HOMA-IR, hsCRP, and CIMT values compared to the control group. HDL-cholesterol and adiponectin levels in the metabolic syndrome group were significantly lower than in the control group. Importantly, circulating progranulin concentrations in the metabolic syndrome group were greater than those in the control group, and almost reached a significant level (199.55 [179.33, 215.53] vs. 185.10 [160.30, 204.90], P = 0.051), whereas there was no significant difference in serum CTRP3 levels.

### Correlation of Circulating Progranulin and CTRP3 Concentrations with Cardiometabolic Risk Factors

Serum progranulin levels had significant positive correlations with serum hsCRP and IL-6 levels (r = 0.304, P = 0.001 and r = 0.300, P = 0.001, respectively), but had no significant correlations with various metabolic parameters, including BMI, waist circumference, glucose tolerance, blood pressure, and lipid profiles (Table 2). On the other hand, circulating CTRP3 levels were significantly negatively correlated with waist circumference, diastolic blood pressure, total cholesterol, triglyceride, and fasting glucose levels, and positively correlated with age, eGFR, and serum adiponectin levels. However, serum CTRP3 concentrations had no significant correlation with serum hsCRP or IL-6 levels. Interestingly, the number of metabolic syndrome components had a significant positive relationship with circulating progranulin levels (r = 0.227, P = 0.010) and a negative correlation with CTRP3 levels (r = −0.175, P = 0.050). Moreover, serum progranulin levels increased significantly according to the number of metabolic syndrome components (P for linear trend ≤ 0.01).
whereas CTRP3 serum concentration decreased significantly ($P$ for linear trend = 0.04, Figure 1). In multiple stepwise linear regression analysis, IL-6 ($P$= 0.01) and triglyceride ($P$<0.001) levels were significant determining factors for serum progranulin levels ($R^2 = 0.251$), whereas sex ($P$<0.001), triglyceride levels ($P$<0.001) and LDL-cholesterol levels ($P$= 0.02) were significant decisive factors for circulating CTRP3 concentrations ($R^2 = 0.321$) (Table S1).

Determinant Factors Associated with CIMT Values in Subjects with or without Metabolic Syndrome

Spearman correlation analysis also showed that serum progranulin level was significantly positively correlated with CIMT in subjects without metabolic syndrome ($r$ = 0.236, $P$ = 0.035). Similarly, the results of our multiple stepwise linear regression analysis showed that age, sex, BMI, HDL-cholesterol, and circulating progranulin ($P$= 0.039) levels were significant predictors for CIMT in subjects without metabolic syndrome ($R^2 = 0.365$)(Table 3). On the other hand, age, diastolic blood pressure, and LDL-cholesterol levels were significant determining factors for CIMT in the metabolic syndrome group ($R^2 = 0.433$).

Discussion

The present study showed that circulating progranulin levels mainly have a significant relationship with inflammatory markers, such as hsCRP and IL-6, whereas circulating CTRP3 concentrations exhibit a significant association with cardiometabolic risk factors, including waist circumference, diastolic blood pressure, fasting glucose levels, lipid profiles, eGFR, and adiponectin levels. Furthermore, we found that serum progranulin level is an independent marker for carotid atherosclerosis in subjects without metabolic syndrome, even after adjusting for other cardiovascular risk factors.

Progranulin, also known as proepithelin or acrogranin, is a widely-expressed, 593 amino acid secreted glycoprotein [18]. Reported biological activities of progranulin include growth factor-like activities, modulation of immune responses, and neuronal effects [19]. Recently, Tang et al. found that progranulin is a ligand of TNFR and the anti-inflammatory effects of progranulin are mainly mediated by inhibition of TNF-$\alpha$-activated intracellular signaling. Treatment of bone marrow-derived macrophages with recombinant progranulin inhibited TNF-$\alpha$-induced phosphorylation of p38, c-Jun N-terminal kinase (JNK), and the mitogen-activated protein kinase (MAPK) family, and impaired NF-$\kappa$B nuclear translocation [5]. They have shown that progranulin prevents mice from inflammatory arthritis by blocking

**Table 2.** Spearman Correlation of Serum Progranulin and CTRP3 with Various Metabolic Parameters.

|                      | CTRP3 | Progranulin |
|----------------------|-------|-------------|
|                      | $r$   | $P$         | $r$   | $P$         |
| Sex                  | 0.476 | <0.001      | 0.127 | 0.155       |
| Age                  | 0.240 | 0.007       | 0.016 | 0.861       |
| Body mass index      | $-0.129$ | 0.149     | 0.126 | 0.159       |
| Waist circumference  | $-0.214$ | 0.016     | 0.098 | 0.271       |
| Systolic blood pressure | $-0.076$ | 0.397     | 0.121 | 0.175       |
| Diastolic blood pressure | $-0.207$ | 0.020     | 0.144 | 0.107       |
| AST                  | $-0.126$ | 0.159     | 0.096 | 0.283       |
| ALT                  | $-0.138$ | 0.123     | 0.136 | 0.128       |
| Total cholesterol    | $-0.245$ | 0.006     | 0.041 | 0.648       |
| HDL-cholesterol      | 0.093  | 0.302       | $-0.079$ | 0.378       |
| Triglycerides        | $-0.338$ | <0.001    | 0.041 | 0.648       |
| LDL-cholesterol      | $-0.135$ | 0.131     | $-0.003$ | 0.973       |
| Fasting glucose      | $-0.198$ | 0.026     | 0.134 | 0.134       |
| HOMA-IR              | $-0.108$ | 0.321     | 0.166 | 0.123       |
| eGFR                 | 0.392  | <0.001      | $-0.023$ | 0.800       |
| IL-6                 | 0.125  | 0.162       | 0.300 | 0.001       |
| hsCRP                | $-0.050$ | 0.574     | 0.304 | 0.001       |
| Adiponectin          | 0.260  | 0.003       | $-0.047$ | 0.597       |

CTRP-3, C1q/TNF-related protein-3; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; eGFR, estimated glomerular filtration rate; IL-6, interleukin-6; hsCRP, high-sensitivity C-reactive protein; IMT, intima-media thickness.

doi:10.1371/journal.pone.0055744.t002

Figure 1. Serum C1q/TNF-related Protein-3 (CTRP3) (A) and Progranulin Levels (B) According to Number of Metabolic Syndrome Components.

doi:10.1371/journal.pone.0055744.g001
interaction with TNF-α [5]. However, not all the actions of progranulin on inflammatory cells are inhibitory, and the interactions between progranulin and inflammation were reported to be more complicated in some previous reports. During the inflammatory process, progranulin is digested into smaller peptides, called granulins, that are pro-inflammatory and neutralize the anti-inflammatory effect of intact progranulin [6]. Moreover, Okura et al. reported that progranulin increased the expression of TNF-α and IL-1β in human monocyte-derived macrophages [20]. In a cutaneous wound, progranulin promoted the accumulation of neutrophils and macrophages, suggesting the chemotactic activity of progranulin for inflammatory cells [21]. Furthermore, we previously reported that elevated progranulin serum concentrations were positively associated with omental adipose tissue macrophage infiltration and increased in subjects with type 2 diabetes, suggesting progranulin as a chemotaxant molecule [8]. These results support the hypothesis that progranulin may play dual roles in the inflammatory process and may exert anti-inflammatory or pro-inflammatory functions depending on the target tissue. In this study, which included subjects without diabetes, circulating progranulin levels had a significant positive correlation with serum hsCRP and IL-6 levels, reflecting chronic subclinical inflammation. Very recently, progranulin was identified as a novel adipokine that mediates high fat diet-induced insulin resistance. In that study, insulin resistance induced by progranulin was significantly improved by a neutralizing antibody against IL-6, implicating IL-6 as a mediator of progranulin-induced insulin resistance in adipocytes [7]. Interestingly, multiple regression analysis in this study showed that serum IL-6 level was an independent determining factor for circulating progranulin levels, even after adjusting for other confounding risk factors.

Our study demonstrates that serum progranulin is an independent marker for subclinical atherosclerosis, represented as CIMT. Atherosclerosis is a chronic inflammatory process resulting from the interaction of modified lipoprotein, macrophages, and the normal cellular elements of the arterial wall [22]. Growing evidence suggests that various adipokines are directly involved in the process of atherosclerosis [23]. An immunohistochemical analysis of human carotid endarterectomy specimens indicated that intimal vascular smooth muscle cells and some macrophages in human atherosclerotic plaque express progranulin [24]. Progranulin in the plaque would be cleaved into granulins, which increase IL-6 levels and drive the migration of inflammatory cells to the vessel wall [24]. A recent clinical study reported that serum progranulin levels were significantly higher in subjects with non-alcoholic fatty liver disease (NAFLD), which is now regarded as an independent cardiovascular risk factor, and were associated with adverse lipid profiles [25]. In the present study, an independent association between CIMT and serum progranulin levels, together with age, sex, BMI, and HDL-cholesterol levels, was found in subjects without metabolic syndrome. On the other hand, in subjects with metabolic syndrome, age, diastolic blood pressure, and LDL-C levels were determining risk factors for CIMT. Although the exact explanation for this result is not clear, progranulin may have a major influence on the early stages of atherosclerosis, which may be associated with inflammation rather than the classical cardiovascular risk factors.

CTRP3 is a newly-discovered adipokine whose structure contains a 246 amino acid sequence protein, and is regarded as an adiponectin paralog [26]. Recombinant CTRP3 reduced glucose output in cultured rat hepatoma cells by suppressing gluconeogenic genes [10], significantly inhibited LPS-induced IL-6 and TNF-α secretion in THP-1 cells, and reduced NF-kB p65 activity [12]. These results suggest the biological relevance of CTRP3’s antidiabetic and anti-inflammatory properties. In the present study, we included subjects without diabetes, and circulating CTRP3 showed significant negative correlations with metabolic risk factors, including waist circumference, serum triglyceride, and glucose levels. We also observed a significant positive correlation between serum CTRP3 levels and circulating adiponectin concentrations. However, in our previous study, serum CTRP3 levels were elevated in subjects with type 2 diabetes and showed significant positive correlation with cardiometabolic risk factors such as waist-to-hip ratio, glucose, and hsCRP levels [13]. Although the reason or these discordant results could not be clarified in the present study, we could suggest several hypotheses to explain this result. First, the paradoxical increase of CTRP3 in the subjects of type 2 diabetes might be originated from a compensatory mechanism to overcome the metabolic stress or resistance. Hormone resistance to the effects of insulin, leptin, and fibroblast growth factor 21 (FGF21) has been reported in diabetes and obesity [27,28]. In our previous study, a subgroup analysis that included only subjects without diabetes showed a similar tendency to the results of this study, although the negative relationship between CTRP3 level and cardiometabolic risk factors did not reach a significant level due to the insufficient number of subjects [13]. Secondly, the biological function of CTRP3 can be different according to glucose tolerance status. Kopp et al. showed that CTRP3 reduced the LPS induced release of macrophage migration inhibitor factor in non-diabetic controls, whereas no effects in type 2 diabetic subjects [11]. Lastly, the participants of the previous study included type 2 diabetes, so many people had been taken various kinds of medications which may affect the circulating CTRP3 levels. Further studies to clarify the underlying mechanism for the regulation of CTRP3 should be followed. Interestingly, circulating CTRP3 levels had significant negative correlations with various metabolic risk factors such as waist circumference, diastolic blood pressure, triglycerides, and fasting glucose, whereas serum progranulin levels showed significant positive relationship with inflammatory markers such as hsCRP and IL-6. These results suggest that CTRP3 may be more

| Table 3. Multiple Stepwise Regression Analyses for Determinant Factors Associated With Carotid Intima-Media Thickness in Subjects With or Without Metabolic Syndrome. |
| --- |
| **B** | **SE** | **P** |
| **Subjects without metabolic syndrome (R² = 0.365)** |
| (Constant) | 0.014 | 0.147 | 0.927 |
| Age | 0.008 | 0.001 | 0.000 |
| Sex | −0.045 | 0.026 | 0.085 |
| Body mass index | 0.010 | 0.004 | 0.019 |
| HDL-cholesterol | −0.002 | 0.001 | 0.059 |
| Progranulin | 0.001 | 0.000 | 0.039 |
| **Subjects with metabolic syndrome (R² = 0.433)** |
| (Constant) | −0.268 | 0.268 | 0.324 |
| Age | 0.011 | 0.002 | 0.000 |
| Diastolic blood pressure | 0.004 | 0.002 | 0.122 |
| LDL-cholesterol | 0.001 | 0.001 | 0.142 |

Independent variables for mean IMT: age, sex, body mass index, systolic blood pressure, diastolic blood pressure, HDL-cholesterol, triglycerides, LDL-cholesterol, fasting glucose, hsCRP, adiponectin and progranulin levels. SE, standard error; R², coefficient of determination. doi:10.1371/journal.pone.0055744.t003
closely related with metabolic parameters, whereas progranulin may be more closely associated with inflammatory parameters in humans.

There are some limitations to this study. First, because it was a cross-sectional study, no causality could be defined. It is not clear whether circulating progranulin and CTRP3 levels are causative factors or markers of the pathogenesis of inflammatory diseases and atherosclerosis. Secondly, this study enrolled only Asian subjects without diabetes or CVD, so the relationship of serum progranulin and CTRP3 levels to metabolic risk factors should be further evaluated in other ethnic populations and in the context of different interventions for the treatment of diabetes and CVD. Thirdly, the subjects with renal insufficiency, defined as an eGFR <60 (mL/min/1.73 m²), were very few in this cohort (n = 2). Therefore, to clarify the relationship of renal dysfunction with CTRP3, further studies including the subjects with renal impairment should be followed. Lastly, the data about smoking, alcohol, and exercise were not available in this cohort, so we could not adjust the effect of these lifestyle factors.

In conclusion, this study showed that serum progranulin levels had a significant positive relationship with hsCRP and IL-6 concentrations. Furthermore, serum progranulin level was an independent determining risk factor for carotid atherosclerosis in subjects without metabolic syndrome. On the other hand, circulating CTRP3 concentration had a significant association with cardiometabolic risk factors, such as obesity, glucose levels, lipid parameters, eGFR, and adiponectin levels. Further experimental and prospectively-designed studies should be performed to clarify the influences of these two novel adipokines, progranulin and CTRP3, on the pathogenesis and outcomes of chronic metabolic disorders and cardiovascular disease.

Supporting Information

Table S1 Multiple Stepwise Regression Analyses for Determinant Factors Associated with Serum Progranulin and CTRP3 Levels.

(DOC)

Author Contributions

Conceived and designed the experiments: HJY BSY KMC. Performed the experiments: HCH HYC SJY. Analyzed the data: SYH. Contributed reagents/materials/analysis tools: DSC SHB. Wrote the paper: HJY KMC MB.

References

1. Deng Y, Scherer PE (2010) Adipokines as novel biomarkers and regulators of the metabolic syndrome. Ann N Y Acad Sci 1212: E1–E19.
2. Ouchi N, Parker JL, Lugus JJ, Walsh K (2011) Adipokines in inflammation and metabolic disease. Nat Rev Immunol 11: 85–97.
3. Zhou J, Gao G, Gralla J, Serreze G (1993) Purification of an autocrine growth factor homologous with mouse epithelin precursor from a highly tumorigenic cell line. J Biol Chem 268: 10863–10869.
4. Liu CJ (2011) Progranulin: a promising therapeutic target for rheumatoid arthritis. FEBS Lett 585: 3675–3680.
5. Tang W, Lu Y, Tao QY, Zhang Y, Guo FJ, et al. (2011) The growth factor progranulin binds to TNF receptors and is therapeutic against inflammatory arthritis in mice. Science 332: 478–481.
6. Liu CJ, Boch X (2012) Progranulin: a growth factor, a novel TNFR ligand and a drug target. Pharmacol Ther 133: 124–132.
7. Matsubara T, Mita A, Minami K, Hosooka T, Kitazawa S, et al. (2012) PGRN is a key adipokine mediating high fat diet-induced insulin resistance and obesity through IL-6 in adipose tissue. Cell Metab 15: 39–50.
8. Youn BS, Bang SI, Kloting N, Park JW, Lee N, et al. (2009) Serum progranulin concentrations may be associated with macrophage infiltration into omental adipose tissue. Diabetes 58: 627–636.
9. Wung GW, Wang J, Hug C, Tsao TS, Lodish HF (2004) A family of Acrp30/adiponectin structural and functional paralogs. Proc Natl Acad Sci U S A 101: 10302–10307.
10. Peterson JM, Wei Z, Wong GW (2010) C1q/TNF-related protein-3 (CTRP-3) and Pigment Epithelium-Derived Factor (PEDF) are adipocyte-derived growth factor, acrogranin) mediates tissue repair and tumorigenesis. J Biol Chem 285: 39691–39701.
11. Kopp A, Bala M, Buechler C, Falk W, Gross P, et al. (2010) C1q/TNF-related protein-3 is a novel adipokine that regulates hepatic glucose output. J Biol Chem 285: 39691–39701.
12. Weigert J, Neumeier M, Schaller A, Fleck M, Scholmerich J, et al. (2005) The adipokine paralog CORS-26 has anti-inflammatory properties and is produced by human monocyte cells. FEBS Lett 579: 5965–5970.
13. Choi KM, Hwang SY, Houg HC, Yang SJ, Choi HY, et al. (2012) C1q/TNF-Related Protein-3 (CTRP-3) and Pigment Epithelium-Derived Factor (PEDF) Concentrations in Patients With Type 2 Diabetes and Metabolic Syndrome. Diabetes 61: 2932–2936.
14. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, et al. (2005) Diagnosis and management of the metabolic syndrome. An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Executive summary. Circulation Rev 17: 322–327.
15. Friedewald WT, Levy RI, Fredrickson DS (1972) Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 18: 499–502.
16. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, et al. (1985) Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 28: 412–419.
17. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, et al. (2006) Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 145: 247–254.
18. Wu H, Siegel RM (2011) Medicine: Progranulin resolves inflammation. Science 332: 427–428.
19. Cenik B, Cenik BK, Herz J, Yu G (2012) Progranulin: a prototypically processed protein at the crossroads of inflammation and neurodegeneration. J Biol Chem Aug 2.
20. Okura H, Yamashita S, Ohama T, Saga A, Yamamoto-Kakata A, et al. (2010) HDL/apolipoprotein A1 binds to macrophage-derived progranulin and suppresses its conversion into proinflammatory granulin. J Atheroscler Thromb 17: 567–577.
21. He Z, Bateman A (2003) Progranulin [granulin-epithelin precursor, PC-cell-derived growth factor, acrogranin] mediates tissue repair and tumorigenesis. J Mol Med (Berl) 81: 600–612.
22. Glass CK, Witzum JL (2001) Atherosclerosis: the road ahead. Cell 104: 503–516.
23. Fantuzzi G, Mazzone T (2007) Adipose tissue and atherosclerosis: exploring the connection. Arterioscler Thromb Vase Biol 27: 996–1003.
24. Kojima Y, Ueno K, Inoue K, Takagi Y, Kikuta K, et al. (2009) Progranulin expression in advanced human atherosclerotic plaque. Atherosclerosis 206: 102–109.
25. Ylmaz Y, Eren F, Yonal O, Polat Z, Bacha M, et al. (2011) Serum progranulin as an independent marker of liver fibrosis in patients with biopsy-proven nonalcoholic fatty liver disease. Diab Markers 31: 205–210.
26. Svetak M, Sporova I, Hejlkov P, Laczak B, Stejskal D (2010) Collagenous repeat-containing sequence of 26 kDa protein - a newly discovered adipokine - serum lato - A minireview. Biomed Pap Med Fac Univ Palacky Olomouc Czech Republic 154: 199–202.
27. Fisher FM, Chui PC, Antonellis PJ, Bina HA, Kharitonenkov A, et al. (2010) Obesity is a fibroblast growth factor 21 (FGF21)-resistant state. Diabetes 59: 2781–2789.
28. Caro JF, Kolaczynski JW, Nyce MR, Ohannesian JP, Opentanova I, et al. (1996) Decreased cerebrospinal-fluid/serum leptin ratio in obesity: a possible mechanism for leptin resistance. Lancet 348: 159–161.