A novel adipokine C1q/TNF-related protein-3 decreases in psoriasis patients and ameliorates imiquimod-induced psoriasis-like skin lesions

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INTRODUCTION

Psoriasis is a chronic immune-mediated inflammatory skin disease. Epidemiological investigations suggest patients with psoriasis have a high prevalence of metabolic disorders such as diabetes mellitus, obesity, dyslipidemia or even Metabolic Syndrome (MetS)¹. Recently, It is pointed out that psoriasis is associated with an increased risk of developing cardiovascular disease (CVD) including atherosclerosis, hypertension, ischemic heart disease, myocardial infarction stroke and arrhythmias². However, the precise mechanism of the co-occurrence is still obstacle.

C1q/TNF-related proteins-3 (CTRP3) is an important newly identified adipokine which is mainly expressed by adipocytes, adipose stromal cells and in other tissues³. The biological functions of CTRP3 are defined as a regulator of glucose homeostasis, a cardio-protective factor and anti-inflammatory cytokine⁴. Our research focuses on the CTRP3 variation in psoriasis patients and the correlation between CTRP3 and abnormal inflammatory cytokines. Furthermore, we investigate the function of CTRP3 in the pathogenesis of psoriasis process by *in vivo* and *in vitro* assay.

HYPOTHESIS

We hypothesize that CTRP3 serves as a molecular linker among psoriasis, metabolic disorders and cardiovascular comorbidities.

METHODS

1. Collection of psoriasis vulgaris patients and normal healthy control serum, ELISA assay of serum CTRP3 and psoriatic inflammatory cytokines. Statistical analysis of CTRP3 levels with metabolic parameters.
2. Imiquimod-induced psoriasis mouse model, primary keratinocytes and HaCaT cell line were used for researching the function of CTRP3 in the pathogenesis of the disease.
3. Human pre-adipocyte culture and differentiation system were employed to analysis the decreased reason of CTRP3 in psoriasis patients.

RESULTS

1. Circulating CTRP3 levels in psoriasis vulgaris patients were significantly lower compared to age- and sex-matched healthy controls.

psoriasis group showed significantly higher levels of body mass index, diastolic blood pressure, triglycerides and leptin whereas a statistically lower expression of HDL cholesterol and adiponectin. Serum CTRP3 concentrations were 240.7 ± 139.6 ng/mL in psoriasis group which were lower than those in the control group (380.4 ± 214.9 ng/mL) and reached a significant level ($p < 0.0001$).

Table 1 Baseline characteristics of study subjects

	Control group (n=40)	Psoriasis group (n=77)	p-value
Body Mass Index (Kg/m ²)	22.9±2.31	24.2±3.79	0.0378
Diastolic blood pressure (mm Hg)	71.8±10.2	78.2±9.90	0.0013
Triglycerides (mmol/L)	0.99±0.31	1.82±1.70	0.0029
HDL (mmol/L)	1.34±0.21	1.01±0.24	<0.0001
CTRP3 (ng/mL)	380.4±214.9	240.7±139.6	<0.0001
Leptin (ng/mL)	2.90±2.49	9.83±12.6	0.0006
Adiponectin (μg/mL)	37.2±25.7	27.7±23.4	0.0435

RESULTS

2. Correlations between CTRP3 levels and Metabolic Parameters

Table 2 Association between CTRP3 levels and various metabolic parameters

	Psoriasis group		Control group	
	r	p	r	p
Weight	-0.3595	0.0013	0.1359	0.4031
Body Mass Index	-0.3532	0.0016	0.08608	0.5974
Chest circumference	-0.2498	0.0284	---	---
Waist circumference	-0.2910	0.0103	---	---
Hip circumference	-0.3642	0.0011	---	---
ALT	-0.2817	0.0131	0.1473	0.3645
Fasting glucose	-0.3433	0.0032	-0.03960	0.8083
Total Cholesterol	-0.2410	0.0386	-0.05583	0.7322
Triglycerides	-0.4089	0.0003	-0.2026	0.2100
HDL	0.2831	0.0145	-0.1875	0.2466
Adiponectin	0.6818	<0.0001	0.7244	<0.0001

Fig.1 CTRP3 levels correlated with psoriatic parameters. (A) PASI scores; (B) alcohol consumption; (C) before and after treatment

3. CTRP3 ameliorated the phenotype of imiquimod-induced psoriasis like skin lesions

Fig.2 CTRP3 ameliorated the phenotype of imiquimod-induced psoriasis like skin lesions. (A) animal experiment design; (B) changes of phenotype on ears and back skins (C).

Fig.3 CTRP3 decreased the infiltration of neutrophils in imiquimod-induced psoriasis like lesions. (A) immunohistochemistry detection of Ly6G; (B) real time RT-PCR analysis of CXCL1 and PCNA mRNA expression in mouse epidermis

Fig.4 CTRP3 inhibited the proliferation of keratinocytes stimulated by psoriatic cocktail inflammatory cytokines (IFNγ, TNFα, IL-17A and IL-22). (A) clone formation assay; (B) western blot detection of PCNA and caspase-3

Fig.5 CTRP3 down-regulated the inflammatory cytokines and chemokines induced by psoriatic cocktail cytokines. (A) real time RT-PCR; (B) ELISA analysis

Fig.6 Western blot analysis of signaling pathways involved in CTRP3 intervention

Fig.7 TNFα and IL17A could inhibit the secretion of CTRP3 during the differentiation of human subcutaneous adipocytes. (A) Oil Red for the lipid droplets of adipocytes; (B) CTRP3 levels analyzed by ELISA.

CONCLUSION

This is the first study that explored the concentration of CTRP3 in psoriasis patients. We concluded that CTRP3 levels which correlated with metabolic parameters in psoriasis patients decreased in psoriasis serum and could be recovered after treatment. CTRP3 could alleviate the phenotype in imiquimod-psoriasis mouse and reduced over-activation of psoriasis keratinocytes. Psoriatic inflammatory cytokines could inhibit CTRP3 production in subcutaneous adipocytes. Our scientific results provide a new possible implication for the co-occurrence of psoriasis comorbidities.

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