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ARTICLE

Clinical Research

Serum secreted EMC10 (scEMC10) levels are inversely associated with metabolically active brown adipose tissue in humans

Qing Miao[1,6]✉, Yahao Wang[1,6], Qiongyue Zhang[1,6], Wei Wu[1], Yifei Yu[1], Fangfang Zeng[1], Yehong Yang[1], Chuantao Zuo[2], Yihui Guan[2], Chong Wee Liew[3], Matthias Blüher[4,5], Yiming Li[1] and Xuanchun Wang[1]✉

BACKGROUND/OBJECTIVES: Secreted endoplasmic reticulum membrane complex subunit 10 (scEMC10) has been implicated in obesity in mice and humans. In this study, the associations of serum scEMC10 levels with thermoneutrality-modulated brown adipose tissue (BAT) activity and thyroid hormone (TH)-dependent thermogenesis were investigated in humans.

SUBJECTS/METHODS: Serum scEMC10 levels were measured in participants from multiple cohorts using enzyme-linked immunosorbent assay, including participants with or without active BAT determined by PET-CT scanning, participants with positive BAT before and after thermoneutrality, and patients with hyperthyroidism before and after anti-thyroid drug (ATD) treatment. The difference in serum scEMC10 between participants with positive or negative BAT, and the changes of serum scEMC10 in participants with positive BAT before and after thermoneutrality and in patients with Grave's disease-caused hyperthyroidism before and after ATD treatment were determined.

RESULTS: PET–CT scan with ^{18}F-FDG indicated participants with positive BAT were significantly younger and leaner than ones with negative BAT. There was, however, no significant difference in serum scEMC10 between the two groups. Serum scEMC10 levels in participants with positive BAT were significantly elevated by 2-h thermoneutrality ($p = 0.0017$), concomitant with disappearance of active BAT. No significant association of serum scEMC10 with serum levels of either TSH, FT3, or FT4 was observed in participants from both Chinese and White cohorts. ATD treatment normalized thyroid function and reduced the uptake of ^{18}F-FDG into skeletal muscle of patients with hyperthyroidism. Serum scEMC10 concentration, however, remained unchanged in these patients before and after ATD treatment.

CONCLUSIONS: Serum scEMC10 levels are inversely associated with BAT activity in humans.

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INTRODUCTION

Since identification of metabolically active brown adipose tissue (BAT) in adult humans [1–3], BAT has been pursued as a therapeutic target to combat metabolic diseases. Via dissipating energy to generate heat, BAT activation has been proven to efficiently reduce body weight in rodents. Due to either uncertainty or decrease of BAT mass in subjects with obesity [1, 4, 5], BAT-based therapies have failed to show favorable effect on weight loss in humans [6, 7]. However, BAT activation, via either β3-adrenergic receptor agonist or cold exposure, has been proven with beneficial effects on glucose and lipid metabolism independent of weight loss [6–9]. In addition, the interplay between BAT and other tissues, such as liver, skeletal muscle, gut, and even the central nervous system, has been shown to influence systemic metabolism [10]. Although debated [11, 12], BAT activation still holds a promise for the treatment of metabolic diseases in humans.

Multiple signals have been well documented to regulate BAT activation, among which the sympathetic nervous system (SNS) is a key modulator [13]. Upon binding to β3-adrenergic receptors in brown adipocyte, norepinephrine (NE) released from the nerve terminals of SNS activates cAMP-PKA signaling, which in turn phosphorylates CREB and p38 MAPK, eventually converging on the promotion of UCP1 expression [14]. Thyroid hormone (TH),

[1]Department of Endocrinology, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai, China. [2]PET Center & Department of Nuclear Medicine, Huashan Hospital, Shanghai Medical College, Fudan University, Shanghai, China. [3]Department of Physiology & Biophysics, University of Illinois at Chicago, Chicago, IL, USA. [4]Helmholtz Institute for Metabolic, Obesity and Vascular Research (HI-MAG) of the Helmholtz Zentrum München at the University of Leipzig and University Hospital Leipzig, Leipzig, Germany. [5]Medical Department III—Endocrinology, Nephrology, Rheumatology, University of Leipzig Medical Center, Leipzig, Germany. [6]These authors contributed equally: Qing Miao, Yahao Wang, Qiongyue Zhang. ✉email: miaoqing@huashan.org.cn; wangxch@fudan.edu.cn

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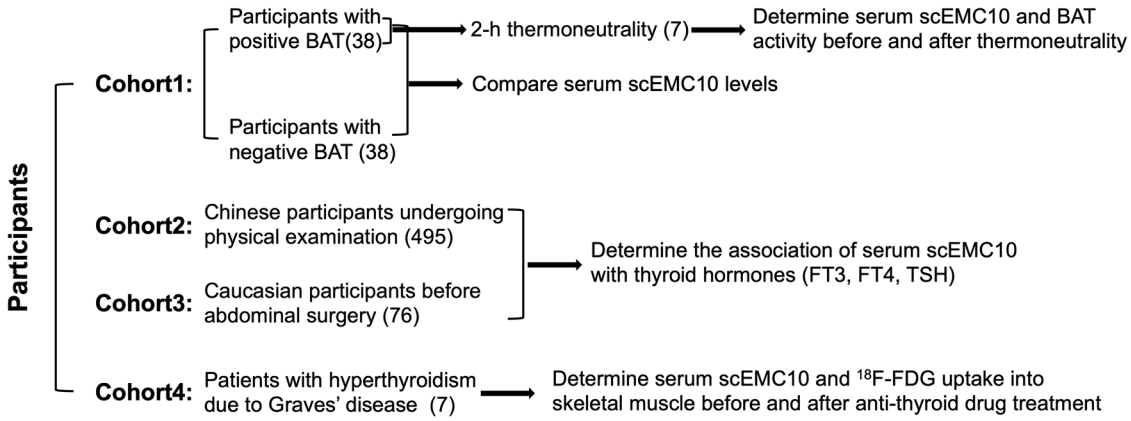

Fig. 1 Overview cartoon of all human cohorts included in this study.

Table 1. Anthropometric parameters and clinical characteristics of participants with positive or negative BAT.

Characteristics	BAT-positive ($N = 38$)	BAT-negative ($N = 38$)	p value
Female (%)	27 (71.05)	20 (52.63)	0.098
Age (year)	38.2 ± 7.0 (20.0–50.0)	43.4 ± 7.8 (27.0–65.0)	**0.003**
BMI (kg/m^2)	21.3 ± 2.3 (17.6–26.6)	23.2 ± 3.2 (17.1–30.5)	**0.005**
FBG (mmol/L)	4.8 ± 0.4 (4.2–5.6)	4.8 ± 0.4 (3.8–6.3)	0.615
SBP (mmHg)	123.6 ± 14.2 (102.0–158.0)	126.1 ± 12.3 (102.0–148.0)	0.410
DBP (mmHg)	79.1 ± 10.3 (60.0–100.0)	80.0 ± 7.6 (65.0–97.0)	0.810
HR (bpm)	73.2 ± 9.8 (57.0–107.0)	71.6 ± 9.3 (53.0–89.0)	0.452

The bold values indicate that the differences between the two group are significant.

another key regulator of BAT thermogenesis, influences BAT activity by modulating the tissue's sensitivity to SNS stimulation and regulating the expression of UCP1. Additionally, SNS stimulation of BAT also triggers the expression of deiodinase type II, an enzyme that increases local TH availability and signaling [15]. These observations provide a rationale that we recruit participants with positive BAT undergoing thermoneutrality and participants with hyperthyroidism receiving ATD treatment in this study, to determine the role of scEMC10 in human BAT thermogenesis. Besides NE and TH, a collection of other hormones, cytokines, and neurotransmitters have been shown to modulate BAT thermogenesis, such as insulin, glucagon, leptin, BMP7 (bone morphogenic protein 7), serotonin, and histamine [13, 15]. Recently we identified a hormone-like circulating factor—scEMC10 (the secreted isoform of endoplasmic reticulum membrane complex subunit 10), as a novel modulator of BAT thermogenesis [16].

Previously, we observed elevated circulatory scEMC10 promoted, while either *Emc10* gene knockout (*Emc10* KO) or antibody neutralization of circulating scEMC10 prevented, diet-induced obesity and its associated metabolic disorders in mice, including impaired glucose tolerance, dyslipidemia, and fatty liver [16]. These metabolic phenotypes have been linked to scEMC10-modulated BAT thermogenesis, since inhibition of scEMC10 promotes BAT thermogenesis via activation of the PKA-CREB/p38 MAPK signaling pathway in BAT [16]. In humans, serum scEMC10 is upregulated in obesity, and positively correlates with insulin resistance, plasma glucose and free fatty acid. In a cohort of participants with obesity, the reduction of body weight evoked by either bariatric surgery or life-style modification is positively associated with a decrease of serum scEMC10, along with an improvement of insulin sensitivity [16]. Moreover, serum scEMC10 has been identified with positive and negative associations with liver fat content and resting metabolic rate, respectively, in humans [17, 18].

Collectively, these findings suggest that scEMC10 plays a critical role in the regulation of BAT activity and could be a potential therapeutic target for metabolic disorders. However, to date, no study has explored the association of serum scEMC10 levels with BAT activity in humans, nor has any data identified the dynamic change of serum scEMC10 in patients with hyperthyroidism or its relationship with TH-modulated thermogenesis. In this study, we attempt to address these issues in multiple cohorts (Fig. 1).

PATIENTS AND METHODS PATIENTS

Cohort 1

By examining images of PET-CT scans, we identified 38 adult participants with active BAT out of about 2400 individuals who underwent PET-CT scan in our hospital who were later recalled to the cohort (Table 1). Each participant with positive (active) BAT was gender and age-matched as seem as possible to a participant with negative BAT (Table 1). In the BAT-positive group, there were 7 participants who volunteered to stay at a climate chamber of thermoneutrality (28 °C) for 2 h. PET-CT scan and blood sampling were performed before and after thermoneutrality (Table 2). All subjects were healthy Chinese adults (aged between 20–50 with BMI < 30), and had no history of diabetes, hypertension, heart disease, severe infection, chronic liver or kidney disease, or cancers, and did not take any regular medications (especially adrenergic receptor blockers, antidepressants, or psychiatric drugs, et al.). Pregnant women and subjects with implantable medical electronic devices were excluded. The ethics committee of Huashan Hospital at Fudan University approved the study, and written informed consent was obtained from all volunteers. The trial was registered at ClinicalTrials.gov (NCT01387438).

Table 2. Anthropometric parameters and clinical characteristics of participants with positive BAT before and after thermoneutrality (TN).

Patients	Sex	Age (year)	BMI(kg/m^2)	FBG(mmol/L)		HR(bpm)		SBP(mmHg)		DBP(mmHg)		AT (°C)	
				T1	T2	T1	T2	T1	T2	T1	T2	T1	T2
1	F	41	17.8	3.4	4.4	70	50	93	98	59	66	36.2	36.2
2	F	42	23.8	4.4	4.4	81	82	130	140	95	90	36.0	36.6
3	F	28	19.5	5.3	4.5	67	68	104	102	69	66	37.2	37.5
4	F	42	19.8	4.3	4.7	67	61	120	92	76	69	36.6	36.2
5	F	45	18.9	5.3	4.4	107	84	134	124	96	75	36.3	36.6
6	M	28	18.5	4.4	5.3	90	90	138	111	90	81	36.7	36.7
7	M	37	21.2	4.7	4.7	81	65	116	122	82	83	36.2	36.2
p value				0.772		0.063		0.310		0.161		0.379	
Mean		37.6	19.9	4.5	4.6	80	71	119	113	81	76	36.5	36.6

T1 before thermoneutrality, *T2* after thermoneutrality, *F* female, *M* male, *BMI* body mass index, *FBG* fasting blood glucose, *HR* heart rate, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *AT* axillary temperature.

Table 3. The association of serum scEMC10 with thyroid hormones in a Chinese physical examination cohort and a White cohort.

Variable		Cohort 1 ($n = 495$)		Cohort 2 ($n = 76$)	
		β	*p* value	β	*p* value
TSH (mU/L)	Model1	−0.634	0.231	0.022	0.881
	Model2	−0.58	0.269	0.092	0.501
FT3 (pmol/L)	Model1	−0.006	0.994	−0.088	0.615
	Model2	0.093	0.905	0.07	0.674
FT4 (pmol/L)	Model1	−0.051	0.821	−0.026	0.635
	Model2	−0.002	0.992	−0.023	0.643

Cohort 1 Chinese physical examination cohort, *Cohort 2* White cohort, *Model1* crude model, *Model2* adjusted for gender, age, and BMI, β regression coefficient.

Cohort 2

A total of 495 Chinese subjects who underwent physical examinations were enrolled in the cross-sectional study (Table 3). Chinese subjects with the following conditions were excluded: diabetes, acute or chronic inflammatory disease, heart, liver or renal failure, cancer, or active use of oral hypotensive, hypolipidemic, anti-diabetic medications. The ethics committee of Huashan Hospital at Fudan University approved the study, and written informed consent was obtained from all subjects.

Cohort 3

We included 76 Caucasian individuals who underwent abdominal surgery for cholecystectomy, weight reduction surgery, abdominal injuries or explorative laparotomy into our cross-sectional study (Table 3). All subjects had a stable weight, defined as the absence of fluctuations of >2% of body weight for at least 3 months before surgery. This study was approved by the ethics committee of the University of Leipzig (approval numbers: 159-12-21052012 and 017-12-23012012) following the principles of the Declaration of Helsinki. All human study participants gave written informed consent before taking part in the study.

Cohort 4

Seven patients with Graves'-caused hyperthyroidism were recruited at Department of Endocrinology, Huashan Hospital affiliated with Fudan University (Table 4). All patients were newly diagnosed with hyperthyroidism, had no history of endocrine diseases, and were not taking any medication. After diagnosed by two independent senior investigators, all patients were subject to the first-round PET-CT scans followed by the treatment with methimazole. When their hyperthyroidic symptoms disappeared and thyroid hormone (i.e., FT3 and FT4) levels returned to the normal range, these patients were given the second-round PET-CT scans. None of the patients received beta-adrenoceptor antagonists. The ethics committee of Huashan Hospital at Fudan University approved the study, and written informed consent was obtained from all patients.

Data collections

Basic information about age, sex, height, body weight, medication utilization, diagnosis, smoking and drinking histories were obtained from all of the subjects. Levels of serum free T3 (FT3), free T4 (FT4), TSH, and anti-thyroid stimulating hormone receptor antibodies (TRAb) were measured by radioimmunoassay with commercially available kits (Roche Diagnostics GmbH, Sandhofer Strasse 116, 68305 Mannheim, Germany). Fasting plasma glucose levels were measured using the glucose oxidase method (7600 automatic biochemical analyzer, Hitachi High-Tech Science Systems Corporation, Japan).

PET-CT scan

In this study, metabolically active BAT was quantified using PET-CT scan. Room temperature in the PET-CT center (31°12′ N, 121°30′ E) was maintained at 21–23 °C. All subjects stayed in the room at least for 1 h before the injection of ^{18}F-FDG at a dose of 5.55–7.40 MBq/kg body weight through the cubital vein. One hour after the injection, whole-body scans were performed with Biograph 64 PET-CT scanner (SIEMENS, Germany). Calculations were completed with Open PACS and PET-CT Viewer software (http://www.med.harvard.edu/JPNM/DisplayFreeware/) [19]. The presence of adipose tissue and the uptake of ^{18}F-FDG were identified by CT (-250 to -50 Hounsfield units) and PET, respectively. Areas of adipose tissue larger than 4 mm in diameter and with the maximum ^{18}F-FDG SUV (SUV max) of ≥2.0 were identified as the active BAT regions [1].

Measurement of scEMC10 in human serum

Serum scEMC10 was measured using a double sandwich ELISA kit (PZ0101, Phrenzer Biotechnology, Shanghai, China). Briefly, add 50 µL of assay buffer, scEMC10 standard or human serum samples, and detecting antibody conjugated with HRP sequentially to each well of 96-well immunoplates from the ELISA kit. Seal the immunoplates with sealer film, and then incubate them at room temperature on a microplate shaker set at 500 rpm for 2 h. Aspirate each well and wash with 300 µL of 1X washing buffer for 4 times. After the last wash, remove any remaining washing buffer by aspirating or decanting. Invert the plates and

Table 4. Anthropometric parameters and clinical characteristics of patients with Graves' disease-caused hyperthyroidism before and after ATD treatment (methimazole).

Patients	Sex	Age (year)	BMI		HR (bpm)		TSH (mIU/L)		FT3 (pmol/L)		FT4 (pmol/L)		TRAb (U/L)
			T1	T2	T1	T2	T1	T2	T1	T2	T1	T2	T1
1	M	42	29.2	29.9	101	79	0.001	0.01	23.03	6.56	67.64	16.53	28.3
2	M	35	22.5	24.8	102	69	0.001	8.927	30.80	3.26	95.28	6.44	14.6
3	M	32	18.5	20.0	96	90	0.002	0.003	21.39	6.21	77.97	21.39	40
4	M	33	19.4	21.1	100	74	0.019	0.008	16.11	4.82	35.15	13.96	4.1
5	F	57	22.7	23.7	85	66	0.124	3.614	19.58	6.66	42.87	17.61	9.6
6	F	33	20.7	21.4	95	65	0.001	0.016	21.88	12.3	62.28	32.84	36.4
7	F	24	18.3	19.3	110	87	0.001	0.002	25.13	4.10	74.25	12.77	39.8
p value			**0.0013**		**0.0005**		0.2175		**0.0004**		**0.002**		
Normal range					60–100	60–100	0.35–5.5	0.35–5.5	3.5–6.5	3.5–6.5	10.2–31	10.2–31	<1

The bold values indicate that the differences between *T1* and *T2* are significant.
T1 before ATD treatment (methimazole), *T2* after ATD treatment (methimazole), *M* male, *F* female.

blot them against clean paper towels. Add 100 µL of TMB substrate to each well and then incubate for 5–30 min at room temperature. Add 100 µL of stop solution to each well. Determine the optical density using a microplate reader set to 450 nm corrected with 570 nm or 630 nm. The ELISA system had an intra- and inter-assay coefficient of variation at 4.9–6.2% and 3.6–7.5%, respectively.

Statistical analysis

All analyses were performed with Statistical Package for Social Sciences (version 26, SPSS, Chicago, IL, USA) and figures were generated with GraphPad prism (version 8.0, GraphPad Software Inc.). Normally distributed data were described as means ± standard deviation (SD). Data that are not normally distributed, as determined using Kolmogorov–Smirnov test, were logarithmically transformed and expressed as median with interquartile range. Student's paired *t* test was used to compare the differences between different groups. A two-tailed *p* value less than 0.05 is considered significant.

RESULTS

Serum scEMC10 levels in participants with positive or negative BAT

A total of 38 healthy participants with detectable BAT by PET-CT scan were enrolled into the BAT-positive group, and 38 well-matched participants without detectable BAT at ambient temperature were served as the BAT-negative control group. Clinical characteristics between the two groups, such as FBG, SBP, DBP, and heart rate were not statistically different. Although age and BMI were matched as much as possible, the overall age and BMI of participants with positive BAT were still significantly younger or lower than those with negative BAT (Table 1). Serum scEMC10 levels were evaluated in participants of the two groups. There was no statistical difference in serum scEMC10 between BAT-positive and negative groups regardless of unadjusted ($p = 0.818$) or adjusted ($p = 0.738$) for age, and BMI (Fig. 2). To further validate the finding, we performed sensitivity analysis using either exclusion of large deviations in age and BMI or stratification of

Fig. 2 Serum scEMC10 levels in participants with positive (+) or negative (−) BAT.

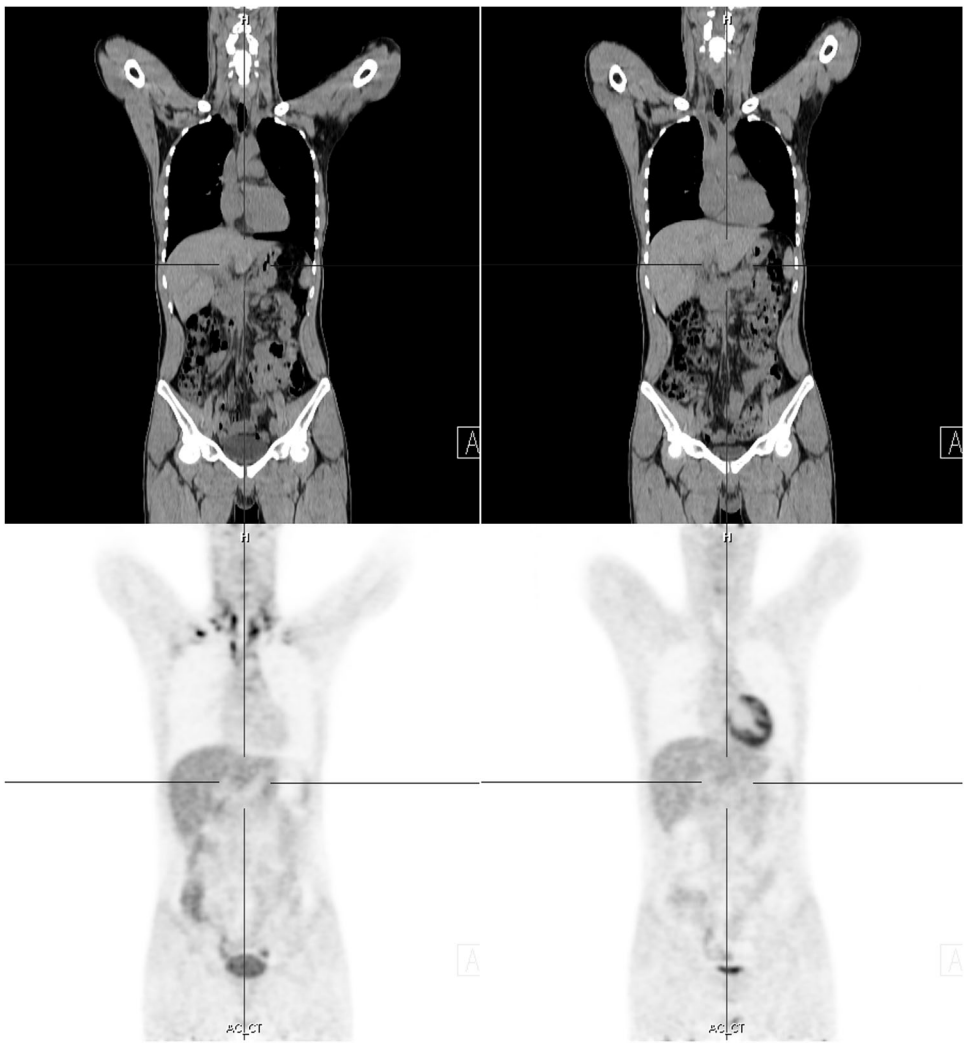

Fig. 3 The images of a participant before (left) and after 2-h thermoneutrality (right) generated by PET-CT scanning with ^{18}F-FDG.

age and BMI into tertiles. The sensitivity analysis showed that there still existed no significant difference in serum scEMC10 levels between the two groups, regardless of which method was used (Supplementary Tables 1–4).

Changes in BAT activity and serum scEMC10 levels of participants with positive BAT before and after thermoneutrality

Seven participants in the BAT-positive cohort were subject to thermoneutrality (TN) (28 °C) for 2 h. Their clinical characteristics were shown in Table 2. Metabolically active BAT, which was identified in cervical and supraclavicular areas by ^{18}F-FDG PET–CT scanning before thermoneutrality, disappeared in all these participants after 2-h thermoneutrality (Fig. 3).

Strikingly, serum scEMC10 levels were robustly elevated by thermoneutrality in all participants, with medians of the cohort at 2.34 and 4.25 ng/mL before and after thermoneutrality, respectively. Statistical analysis revealed the difference significant ($p = 0.0017$) (Fig. 4). These data suggest scEMC10 exerts an inhibitory effect on human BAT thermogenesis, congruent with its role in mouse models [16].

The impact of scEMC10 on thyroid hormone-associated thermogenesis

Thyroid hormones (THs) have been shown an important role in both BAT and whole-body thermogenesis [15]. To determine the

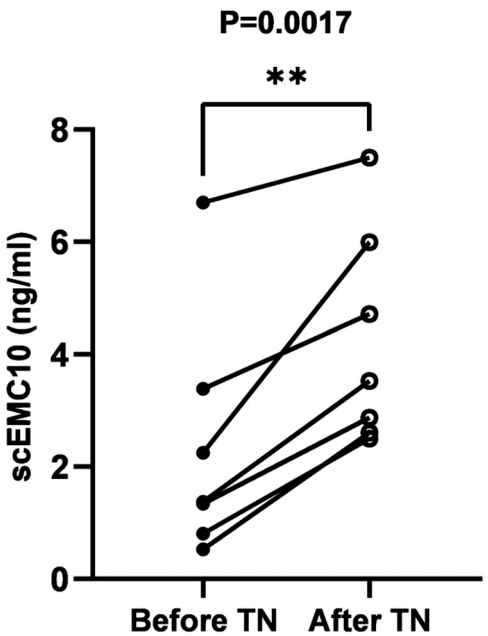

Fig. 4 Serum scEMC10 levels in participants with positive BAT before and after 2-h thermoneutrality (TN).

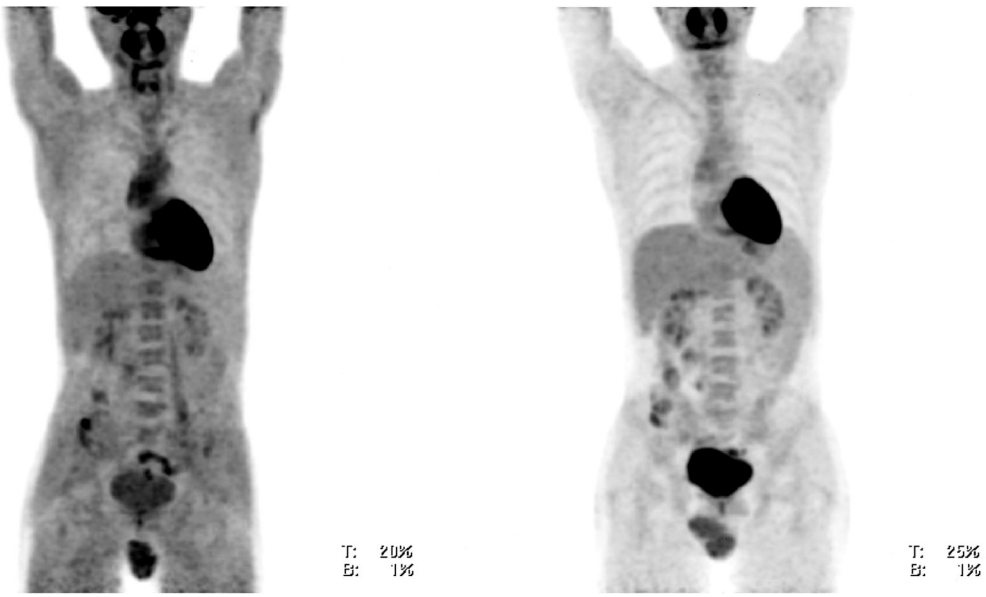

Fig. 5 The images of a patient with Graves' disease-caused hyperthyroidism before (left) and after (right) ATD treatment (methimazole) generated by PET-CT scanning with ^{18}F-FDG.

possible impact of scEMC10 on thyroid hormone-associated thermogenesis, we firstly investigated the association of serum scEMC10 with THs in a Chinese physical examination cohort and a White cohort. There was no significant association of serum scEMC10 levels with either TSH, free T3, or free T4 in both cohorts regardless of unadjusted or adjusted for gender, age, and BMI (Table 3).

We next assessed the change of serum scEMC10 in patients with hyperthyroidism due to Graves' disease who underwent ^{18}F-FDG PET–CT scanning before and after the treatment with methimazole, an anti-thyroid drug (ATD). As shown in Table 4, the ATD treatment normalized thyroid functions, along with amelioration of thyrotoxic symptoms in these patients. No active BAT was detected by ^{18}F-FDG PET–CT scanning in all patients both before and after the ATD treatment, except one who had no active BAT before the treatment, but exhibited active BAT after the treatment (Fig. 5). All patients showed increased ^{18}F-FDG uptake into their skeletal muscle before the ATD treatment followed by almost loss of ^{18}F-FDG deposit after the treatment (Fig. 5). There was no statistical difference in serum scEMC10 levels of these patients between before and after the ATD treatment ($p = 0.927$) (Fig. 6).

Taken together, these observations suggest scEMC10 is not involved in thyroid hormone-modulated thermogenesis.

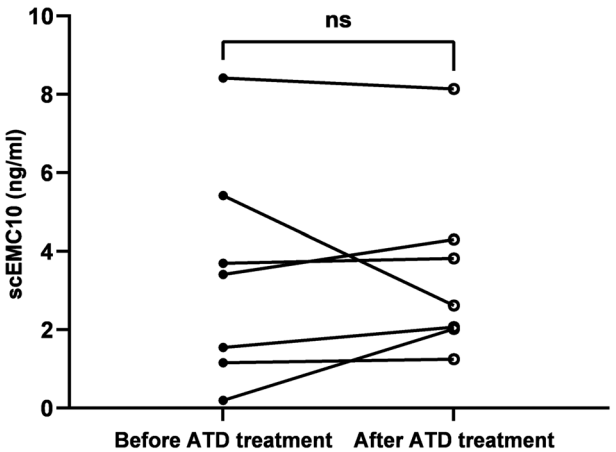

Fig. 6 Serum scEMC10 levels in patients with Graves' disease-caused hyperthyroidism before and after ATD treatment (methimazole).

DISCUSSION

A major advance in the understanding of adipose biology during the past decades is the identification of functionally active BAT in adult humans. The BAT activity in human is determined by multiple factors, including sex, age, BMI, and ambient temperature [1, 2, 20, 21]. In this study, we observed participants with positive BAT are significantly younger and leaner than ones with negative BAT, consistent with other previous studies [1, 22]. However, there was no significant difference in serum scEMC10 between the BAT-negative and positive groups at room temperature. In participants with positive BAT, serum scEMC10 levels were significantly elevated by thermoneutrality, concomitant with suppression of active BAT determined by PET-CT scan, suggesting scEMC10 acts as a suppressor of BAT activity in humans which is congruent with its inhibitory role in BAT thermogenesis in mice [16]. These findings also suggest scEMC10 a regulatory role in facultative thermogenesis, rather than a determinant role in BAT mass in humans. Facultative thermogenesis, which cold exposure activates, while thermoneutrality inactivates, has been linked to human BAT [4, 21, 23]. It has been shown that the regulation of facultative thermogenesis involves the SNS in both rodents and humans [24, 25]. EMC10 has been implicated in the SNS-regulated BAT thermogenesis where *Emc10* KO potentiates β3 adrenoceptor agonist-evoked the PKA-CREB/p38 MAPK signaling and expression of UCP1 and PGC1α in mouse brown adipocytes [16]. Regarding the mechanistic insight into how circulating scEMC10 targets and modulates intracellular PKA signaling, we have identified that extracellular scEMC10 can be transported into cytosol where it binds to the catalytic subunit α of PKA and inhibits the latter's stimulatory action on CREB [16]. We afterwards confirmed the entry of extracellular scEMC10 to another cell—pancreatic β cell via currently unknown receptor-mediated internalization and uncovered the structural basis for the interaction of scEMC10 with PKA catalytic subunit α using AlphaFold 2 prediction model and Co-IP experiment (data not shown). Collectively, these data suggest scEMC10 suppresses facultative thermogenesis via inhibition of SNS-PKA signaling in humans.

It is well established that facultative thermogenesis, a quick-response form of nonshivering thermogenesis emanating from BAT, is blunted in obesity, and even its small increases can significantly affect the long-term energy homeostasis, making BAT a promising therapeutic target to treat metabolic diseases, such as type 2 diabetes [23, 26, 27]. We have proven that a scEMC10-neutralizing antibody is effective in treating diet-induced obesity, impaired glucose tolerance, and fatty liver in mouse, which is mainly attributed to heightened BAT thermogenesis [16]. Consistent with the inhibitory effect of scEMC10 on human BAT activity at thermoneutrality, *Emc10* KO prevents diet-induced obesity in mouse under thermoneutral condition (30 °C) [16]. Taken together, these observations suggest inhibitory modulation of scEMC10, via either neutralizing antibody or antagonist for scEMC10 or its receptor, will be a therapeutic strategy for metabolic diseases via enhancing facultative thermogenesis.

PET-CT scanning analysis did not identify active BAT in patients with hyperthyroidism, which might account for the observation that serum scEMC10 levels remained unchanged before and after ATD treatment. Of note, there was an apparent reduction in the uptake of ^{18}F-FDG into whole body, especially into skeletal muscle, after ATD treatment, which coincides with a previous study showing patients with elevated levels of THs exhibited increased whole-body thermogenesis together with an increase in skeletal muscle mitochondrial uncoupling [28]. This may be accounted for by the fact that deiodinase II, a key enzyme converting cellular T4 to more active T3 which in turn increases thermogenesis, is predominantly expressed in skeletal muscle in adult humans [23, 29]. A larger cohort consisting of patients with hyperthyroidism and positive BAT is needed to investigate whether there is an association between serum scEMC10 and TH-regulated BAT activity.

It has been shown that both BAT and skeletal muscle contribute to nonshivering thermogenesis in humans [30]. The findings of this study that serum scEMC10 is inversely associated with BAT activity, while does not correlate with skeletal muscle thermogenesis, suggest scEMC10-modulated facultative thermogenesis is BAT-specific and independent of skeletal muscle in humans. This may be explained by differential distribution of scEMC10 receptor which plays a permissive role in scEMC10-modualted PKA signaling, rather than subtypes of β adrenergic receptors in BAT and skeletal muscle since both tissues express β2 receptor and human BAT thermogenesis has been linked to activation of β2 adrenergic receptor [14, 31, 32]. We have shown that scEMC10 is involved in β3 adrenoceptor-modulated thermogenesis in mouse BAT [16]. Further experiments are needed to determine whether scEMC10 regulates β2-adrenoceptor signaling and whether scEMC10 receptor is present in skeletal muscle.

We acknowledge that there are several limitations in this study. Firstly, the sample size in both BAT-positive and hyperthyroidic cohorts are relatively small. Actually these 38 participants with positive BAT were sieved out of about 2400 subjects who underwent PET-CT scans, demonstrating a prevalence of 1.58% for detectable BAT in adult humans which is consistent with our previous finding [33]. Secondly, these 7 participants with hyperthyroidism are BAT negative before ATD treatment, making it impossible to exhibit an expected reduction of BAT activity after ATD-induced resolution of hyperthyroidism. Thirdly, we do not include a cohort with cold exposure which together with thermoneutrality will solidify the role of scEMC10 in modulation of BAT facultative thermogenesis. The association of serum scEMC10 with BAT activity in participants exposed to cold warrants further exploration.

In conclusion, our data link scEMC10 to BAT facultative thermogenesis, but not to thyroid hormone-associated skeletal muscle thermogenesis in humans.

DATA AVAILABILITY

The data that support the findings of this study are available upon request from the corresponding authors.

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AUTHOR CONTRIBUTIONS

QM and XW conceived the research idea, designed the study, and wrote the manuscript. YW measured serum scEMC10 in humans. QZ, WW, FZ, YYa and MB collected the data. QM, YYu and MB analyzed data and performed the statistical analysis. CZ and YG performed PET-CT scans and analyzed the data. CWL and YL proofread the manuscript for clarity and correctness. All authors have agreed to submit the manuscription.

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Correspondence and requests for materials should be addressed to Qing Miao or Xuanchun Wang.