Upregulation of cluster of differentiation 36 mRNA expression in peripheral blood mononuclear cells correlates with frailty severity in older adults

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Abstract

Background Aging-associated frailty has been connected to low-grade chronic inflammation and also to progressive monocytic activation. CD36 (cluster of differentiation 36, platelet glycoprotein 4 or fatty acid translocase) has been shown to induce the expression of pro-inflammatory cytokines and to activate macrophage connected inflammation. This study aims to examine whether the expression of CD36 is up-regulated among frail older adults.

Methods The demographic data, Fried Frailty Index, metabolic and inflammatory parameters of our observational study were obtained from the comprehensive geriatric assessment programme of a hospital-based outpatient department. The mRNA isolated from the peripheral blood mononuclear cells (PBMCs) was used to determine the levels of CD36, tumour necrosis factor alpha (TNF-α), and CXC chemokine ligand-10 (CXCL10) mRNAs with real-time polymerase chain reaction (PCR).

Results A total of 189 older adults (58% female) were included in the analysis, and the mean age was 77.19 ± 6.12 years. The numbers of participants who fitted in the groups of robust, pre-frail, and frail were 46, 106, and 37, respectively. Our data showed that CD36 mRNA expression levels in PBMCs were the highest in the frail group (1.25 ± 0.53 in robust, 2.13 ± 1.02 in pre-frail, and 2.78 ± 1.15 in frail group, P < 0.001). Further regression analyses revealed that CD36 mRNA levels were positively correlated with both the pre-frail and frailty status in the univariate analysis (both P’s < 0.001). What might suggest something worthy of further investigation is that, with potential confounders being adjusted for, CD36 remained as an independent factor that positively correlated with the pre-frail and frailty status in the multivariable analysis (P < 0.001).

Conclusions CD36 mRNA levels in PBMCs in robust older adults are significantly lower than in pre-frail and in frail. Our findings suggest that CD36 mRNA levels in PBMCs may be considered a potential biomarker for frailty severity.

Keywords Frailty severity; Cluster of differentiation 36; Peripheral blood mononuclear cells; Biomarker; Cytokines

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Introduction

Frailty is considered an aging-related geriatric syndrome characterized by progressive reduction in physical, socio-psycho functions, and its ensued incapacity in coping acute external and internal stressors, consequently resulting in malnutrition, protracted illnesses, hospitalization, and, ultimately, disabilities and mortality.1–4

The pathophysiology of frailty has been connected to an abnormal, low-grade chronic inflammation, and several monocyte–macrophage cytokines have been shown independently associated with frailty, including interleukin 6 (IL-6), tumour necrosis factor alpha (TNF-α), and monocytic expressed CXC chemokine ligand-10 (CXCL10).1,5 Moreover, age-related dysregulation of senescent immune system results in increased inflamm-aging associated responses and oxidative stress, leading to metabolic disorders, such as cardiovascular diseases (CVDs) and diabetes mellitus (DM).6,7 As monocytes and macrophages are both necessary players in inflammatory responses for signalling downstream expression of immuno-linked chemokines, such as tumour necrosis factor and interleukin family.8 Also, for efficient clinical interventions, blood work coupled indicators would be desirable for quantitative frailty measurement.9 Hence, it is evident to use peripheral blood mononuclear cells (PBMCs) as a model to investigate the correlation between frailty and its persistent pro-inflammatory activation.

CD36 (cluster of differentiation 36) is multifunctional and is commonly expressed on the surface of many cell types with specific ligands for corresponding cellular regulations.10,11 As a glycosylated receptor protein, it functions in modulating lipid metabolism, regulating inflammatory cascade, and maintaining energy stability.11,12 Significantly, among its many ligands, the binding and uptake of oxidized LDL (oxLDL) are often considered in terms of activation of macrophage inflammation and foam cell formation,13 which in turn induces downstream pathway for cytokine expression, such as pro-inflammatory TNF-α and IL-6.14 In addition, CD36 also appears to be able to form a heterodimer complex with toll-like receptor 4 (TLR4) to regulate sterile inflammatory response.15 Importantly, it has been proposed that CD36 participates in the pathogenesis of CVDs and DM,16,17 and a number of studies suggested that patients with frailty are susceptible to CVDs and DM.6,7,18 Because the up-regulation of peripheral blood monocyte CD36 level also occurs in these metabolic co-morbidities19,20 and, to the best of our knowledge, no research has been carried out on CD36 in the context of frailty, we would like to test our hypothesis that CD36 mRNA levels in PBMCs are up-regulated in frail older adults.

Methods

Ethics statement

Prior to our study, all written informed consents were gathered from all enrolled participants, and the ethics approval of our protocol was obtained from the Ethics Committee of National Taiwan University Hospital (registration number: 200701017R). The articles of the consent form included the study aim, procedures, inclusion and exclusion criteria, medical care, harm and benefit, privacy, the rights of the participants, and the right for disclamation. All procedures in this work were in compliance with the Declaration of Helsinki. Crucially, those who declined to join or otherwise did not participate remained with their family physicians and were not disfavoured in any way.

Subjects

Over the period from January 2007 to June 2008, under a hospital-based programme, those older patients with chronic diseases visiting the outpatient department for follow-ups were enrolled for a comprehensive geriatric and frailty assessment.21 Our study was an observational one, and the geriatric indications for the inclusion criteria were described in our prior studies.22,23 For those elderly qualified for enrolment were with one of the following indications: (i) functional decline of newly gained daily living disabilities; (ii) geriatric conditions such as multiple co-morbidities, incontinence, and fall; (iii) depression or dementia associated disorders; (iv) anticipated heavy dependence on healthcare; or (v) age 80 and above, whereas the exclusion criteria included bedridden, residing in nursing homes, life expectancy of 6 months or less, or with severe hearing or communication disorders.

Data collection

Using a structured questionnaire, the information of participants was collected by trained research nurses, and these gathered anthropometric data, medical record, and medication history were reviewed by their primary care physicians. The information included the history on demographics, smoking and drinking habits, body mass index (BMI), geriatric syndromes, diseases, blood pressure readings, and current medication. The Frailty Index was evaluated by a modified version of Fried’s criteria.2 The definition of ‘weight loss’ is a self-referred, unplanned weight loss of more than 3 kg, or greater than 5% of the previous year’s body weight. Statements for appraising the conditions of ‘Exhaustion’ and ‘Low physical activity’ were adapted based on the Depression Scale of the Cen-
ter for Epidemiological Studies and the Taiwan International Physical Activity Questionnaire-Short Form as described in our previous studies. The criteria for ‘Slow walking speed’ and ‘Weakness’ were as described in Fried et al. The subjects were considered ‘robust’, if the number of positive components screened was 0, ‘pre-frail’ if 1 or 2, and ‘frail’ if equal to or greater than 3 by Fried’s criteria.2

A bio-electrical impedance analysis (BIA) was implemented to all subjects for examining their body composition. Under the characteristics of the BIA model (Tanita BC-418, Tanita Corp., Tokyo, Japan) and in combination with an eight-contact electrode, a constant high frequency current (50 KHz, 500 μA) was applied to segmentally measure the body composition by parts, including arms, legs, and the trunk region. Dressed in light clothing, in a fasted and after voiding state, the participants were instructed to stand on the analysers according to the user’s manual without any footwear and with both hands firmly gripping on holders/sensor electrodes. Excluding the trunk region, the sum of measured segmental body composition can be used, as verified previously in extrapolating the approximated values of fat mass (FM), fat-free mass (FFM), the predicted muscle mass of the appendicular fractions, and appendicular skeletal muscle mass (ASM); for the estimated value of appendicular skeletal muscle mass index (ASMI), the formula of \( ASMI = ASM/(height \times meters)^2 \) was employed. With subjects on medical devices excluded for safety concerns, all described examinations were performed in accordance with the standard procedure.24,25

### Biochemical assay

Blood samples for complete blood count (CBC) and biochemical analyses were taken via the antecubital vein of the study participants with a prior 8 h fasting. In a common lab centre of our hospital, which is officially recognized by the College of American Pathologists and by ISO15189, the obtained blood samples were processed and then kept in −70°C for further analysis. For CBC, the samples were analysed on the XE5000 analyser of Sysmex (Kakogawa, Japan). Biochemical analysis was carried out by the AU5800 series clinical chemistry analyser of Beckman Coulter (Shizuoka-Ken, Japan).

### Isolation of human peripheral blood mononuclear cells and quantitative real-time polymerase chain reaction analysis

By centrifugation, participants’ PBMCs were separated and enriched through a Ficoll-sodium metrizoate density gradient (Amersham Biosciences, Uppsala, Sweden). The total RNA of isolated PBMCs was extracted by REzol (PROtech Technology, Sparks, NV) following the instructions of manufacturer. A RNA-to-cDNA kit (Applied Biosystem, Carlsbad, CA) was used for synthesizing samples of single-strand cDNA and for qPCR reactions, and the synthesized cDNAs were then amplified by TaqMan gene expression master mix kit (Applied Biosystem, Carlsbad, CA) in a final 20 μL reaction mix with ABI 7000 real-time PCR system. The following gene-specific primers of CD36, CXCL10, and TNF-α were used in the qPCR analysis: CD36 (forward: 5'-GGCCA AAGAA ATGGTA ACCCA GG-3', reverse: 5'-GCCCT TGGTC CAACT GATAG TGA-3'), CXCL10 (forward: 5'-GAAAT TATTC CTGGA AGCCCA ATT-3', reverse: 5'-TCACCT TTATT TTTTG AGCCCA ATTT-3'), CD36 (forward: 5'-GCCTG TGATG AGCCC ATCTA TC-3', reverse: 5'-AAAGT AGACC TGCCC AGACT CG-3'), and TNF-α (forward: 5'-CCCTG GTATG AGCCCA ATCTA TC-3', reverse: 5'-AAAGT AGACC TGCCC AGACT CG-3'), whereas primers of GAPDH (forward: 5'-GAAGG TGAAG GTCGG AGTC-3', reverse: 5'-GAAGA TGGTG ATGGG ATTC-3') were used for the purpose of RNA transcript normalization.

### Statistical analyses

In the descriptive statistical analysis, frequencies and percentages were used to describe the categorical variables, while for continuous variables, means, and standard deviations were employed. We used ANOVA (analysis of variance) to test the significant differences in continuous variables of the three frailty subgroups; \( \chi^2 \) test or Fisher exact test was performed to test differences in percentages. To analyse the association between the status of frailty and the covariates of interests, univariate and multivariable linear regression models were used. The pairwise correlation of biomarkers was estimated using Pearson correlation method. A probability of \( <0.05 \) was considered significant. The statistical analyses in this study were executed using SAS version 9.4 (SAS Institute, Cary, NC).

### Results

A total of 189 participants were enrolled in the present study. The participants who fit in the category of robust, pre-frail, and frail groups numbered 46, 106, and 37, respectively. The demographic data among the overall participants and the three groups of frailty status were listed in Table 1. The participants in the frail group were notably older than those in the groups of robust and pre-frail and had lower educational level (64.9% with <6 years of education) than that in robust (28.3%) and pre-frail (56.6%) groups. Importantly, when factored in common co-morbidities, there were significantly higher percentages of participants with diabetes (54.1%) and stroke (43.2%) in the frail group, therefore with higher percentage of thiazolidinediones prescription (13.5%). On the other hand, the participants in the robust group were with considerable higher percentage of hyperlipidaemia (76.1%), hence the notable higher percentage of statin use (50%).

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The physical examination and laboratory test results for the three groups are shown in Table 2. There were no significant differences of anthropometric measurements such as weight, waist circumference, blood pressure, and appendicular skeletal mass index (ASMI) among these three groups. With regard to laboratory test, the levels of haemoglobin and ALT were significantly lower in the frail group than that in the robust group (\(P = 0.001\) for haemoglobin and \(P = 0.0365\) for ALT). When comparing mRNA expression of TNF-\(\alpha\), CD36, and CXCL10 in PBMCs among these three groups, remarkably, CD36 mRNA expression levels in PBMCs were 2.78 ± 1.15 in the frail group, considerably higher than that in the robust group (1.25 ± 0.53) and in the pre-frail group (2.13 ± 1.02) (\(P < 0.001\)), whereas the mRNA expression levels of TNF-\(\alpha\) in PBMCs were not significantly different among these three groups. At the same time, the mRNA expression levels of CXCL10 were slightly higher in the frail group; however, with no statistical significances among these three groups (\(P = 0.0555\)).

Prompted by the findings that PBMCs expressed TNF-\(\alpha\) and CXCL10 have been shown elevated with frailty in previous research,1,5 and PBMCs expressed CD36 mRNA levels were higher in the frailty group in Table 2, we further evaluated the correlation between TNF-\(\alpha\), CD36, and CXCL10 mRNA expression in PBMCs of all participants. Interestingly, as shown in Figure 1, CD36 was significantly correlated with CXCL10 (\(P < 0.001\)). However, in analysing the relationship between the mRNA expression of the various study biomarkers and ASMI, CD 36 and CXCL10 mRNA levels were not associated with ASMI except for TNF-\(\alpha\) mRNA levels (\(P = 0.006\)).

Lastly, the univariate and multivariable regression analyses were used to explore the correlation among mRNA expression of CD36, TNF-\(\alpha\), CXCL10 in PBMCs and the frailty status (Table 3). When comparing the pre-frail with the robust
group, CD36 (P < 0.001) and CXCL10 (P = 0.034) were both positively correlated with pre-frail status in univariate analysis. Also, when comparing the frailty with the robust group, both CD36 (P < 0.001) and CXCL10 (P = 0.0346) were still positively correlated with the frailty status. Crucially, when age, sex, and other related variables were adjusted for, only CD36 remained as an independent factor that positively correlated with frailty status (Table 3) (P < 0.001).

### Discussion

If our literature survey serves us well, this study appears to be the first one that correlates the PBMCs expressed CD36 and CXCL10 mRNAs to the different levels of frail severity in older adults. We began with demonstrating that the frail older adults were expressing much higher CD36 mRNA, together with some increases in CXCL10 mRNA in PBMCs when compared with the robust older adults. Next, of all older participants, we demonstrated that CD36 was significantly correlated with CXCL10. Finally, using the regression model, we identified that in our older adults, CD36 and CXCL10 were both positively correlated with frailty severity. Most importantly, in addition to its pre-frail detectable characteristics, we further confirmed that CD36 alone, with related covariants adjusted for, remained an independent factor that positively correlated with different levels of frail severity. These distinct features impart CD36 a potential biomarker for keeping track of pathological development of aged-related frailty.

Studies have revealed that monocytes gradually become more activated as frailty advances, and certain inflammatory markers are more elevated in frail individuals than in age-matched controls. Notably, apart from TNF-α and IL-6, it has also been shown that monocyteic expression of CXCL10 mRNA in PBMCs had considerably elevated in frail aged adults, compared with their corresponding non-frail aged counterparts. Interestingly, with a larger sample size, we observed a resembling CXCL10 mRNA up-regulation in PBMCs.
Nevertheless, amid the same older cohort, we were the first to establish that CD36 not only correlates positively with frail severity but in a stronger association than CXCL10 does. We concluded that CD36 mRNA in PBMCs is a promising biomarker for frailty.

Being a scavenger receptor, CD36 operates in moderating inflammatory status by interacting with ligands coupled to processes for managing oxidized lipoprotein. Deletion of CD36 in mice alleviates immuno-induced liver injury by down-regulating CXCL10-mediated hepatic cellular apoptosis. Furthermore, work from kidneys of mice with diet-induced hypercholesterolemia suggests that the expression of CXCL10 bridges the positive connection between CD36 activity and renal fibrosis severity.

Our findings demonstrated that mRNA expressions of CD36 and CXCL10 were positively associated among our participating pre-frail and frail adults. Nevertheless, amid the same older cohort, we were the first to establish that CD36 not only correlates positively with frail severity but in a stronger association than CXCL10 does. We concluded that CD36 mRNA in PBMCs is a promising biomarker for frailty.

Table 3 Linear regression models for frailty status

| Variable | Pre-frail (n = 106) | Frail (n = 37) |
|----------|---------------------|---------------|
|          | Estimate  | SE   | P-value | Estimate  | SE   | P-value |
| Univariate |          |      |         |          |      |         |
| TNF-α    | -0.0904  | 0.1285 | 0.4829  | -0.0542  | 0.1597 | 0.7346  |
| CD36     | 0.8793   | 0.1763 | < 0.0001 | 1.5311   | 0.2191 | < 0.0001 |
| CXCL10   | 0.6717   | 0.3142 | 0.0340  | 0.8317   | 0.3903 | 0.0346  |
| Multivariable |          |      |         |          |      |         |
| TNF-α    | 0.0537   | 0.1579 | 0.7341  | 0.1010   | 0.2005 | 0.6153  |
| CD36     | 1.0542   | 0.2170 | < 0.0001 | 1.8343   | 0.2755 | < 0.0001 |
| CXCL10   | 0.6627   | 0.3698 | 0.0754  | 0.6972   | 0.4695 | 0.1400  |

Multivariable linear regression models were adjusted by age, sex, hyperlipidaemia, diabetes mellitus, stroke, thiazolidinediones, statins, haemoglobin, and aspartate aminotransferase (ALT). CD36, cluster of differentiation 36; CXCL10, CXC chemokine ligand-10; TNF-α, tumour necrosis factor-α.
older adults. However, after adjusting for co-morbid confounders, our findings indicated that only mRNA level of CD36 expressed in PBMCs was independently and positively correlated with frail severity. Therefore, our results suggest that the expression of CD36 in PBMCs may reflect the extent of frail severity in the older adults. Additionally, several studies had provided evidence arguing that CD36 engages in the pathological progression of CVDs and DM. As a consequence, we would like to introduce CD36 mRNA level in PBMCs as a novel frail biomarker for jointly monitoring conditions of frailty and its ensued co-morbidities.

It is well-known that the contributors of frailty are cumulative effects of multiple deficits, and hence, on top of our major finding of a new frail biomarker, we also observed a higher incident of frailty amidst participants with lower educational level as well as with conditions of stroke and DM (Table 1). Intriguingly, it has been proposed that the DM mediates the inverse association between education and CVDs incidence. Also, it has been shown that educational level correlates with the odds of being frail. These support the effects of education on chronic disease control and, hence, on frailty. Thus, it would be rewarding to further explore the correlation between frailty, the level of education, and its co-morbidities. Moreover, in a clinical setting, such as in Rockwood clinical frailty scale, the onset of cognitive deficits is often considered a major determining factor to frailty; dementia and Alzheimer’s disease (AD), for instance, have been strongly and independently linked to frailty. Remarkably, in mice, CD36 has been recently proposed as an AD therapeutic target for being a scavenger receptor to interact with amyloid fibrils during the pathological progression of amyloid plaque formation, and in AD patients, CD36 was also reported to be highly expressed in the cerebral cortex. Together, these findings may not only connect the expression of CD36 to the condition of cognitive deteriorations but also to frailty. Strikingly, although our Frailty Index was based on a modified version of Fried’s criteria without factoring in the cognitive impairment, CD36 mRNA level in PBMCs still displayed a strong positive association with frailty among older adults. Therefore, further longitudinal studies are required to confirm our postulation that CD36 in PBMCs is a promising biomarker in tracking the frail progression under different frameworks of Frailty Index.

Sarcopenia has been recognized as an important risk factor for geriatric frailty, and it is conceivable that the muscle mass/function is their overlapping theme. Noticeably, a recent study has immunochemically linked CD36 to muscle atrophy in vitro. However, in our study, the levels of CD36 and CXCL10 mRNA in PBMCs did not correlate with ASMI as the mRNA level of TNF-α in PBMCs negatively did (Figure 1). The possible reason may be that it is owing to our small number of frail participants and the somewhat different pathophysiologic nature of frailty and sarcopenia. Clearly, the role that CD36 plays in these compound ailments warrants further observation and examination.

The first limitation of this study is that our analysis was based on the transcriptional expression of PBMCs rather than the translational levels, and for this reason, our data cannot reflect the actual level of CD36 proteins, as PBMCs are a mixture of many cell types ranging from lymphocytes and monocytes to a small percentage of dendritic cells. The second limitation is that we were unable to pinpoint the up-regulated CD36 mRNA to its corresponding mature, receptor-carrying cell type. The third limitation is that our results were measured in a fixed point in time. In other words, this observation was cross-sectional, and the casual directionality between CD36 mRNA level and frailty cannot be determined. Lastly, the number of participants in the study was small, especially the number in the frail group. It calls for further scaled-up cohort studies to confirm the causality between CD36 and frailty. Also, it is compelling to investigate the fundamental cells and molecular biology of our findings.

Because frailty develops from senescence-induced cellular changes resulting in tissue dysregulation and then organ impairment, a marker at the cellular level would be of great value in filling the gap in the pathophysiological knowledge for medical interventions. Analysing PBMCs cellular gene expression provides an edge in detection and a window for continuous inspection in the pathogenesis of frail condition. In essence, here, we established that the CD36 mRNA level, under pre-frail and frail circumstances, is attuned upwardly in PBMCs of older adults and is a promising candidate for monocyte-linked frail biomarker.

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Conflict of interest

The authors declare that they have no conflict of interest. The authors confirm that they complied with the ethical guidelines for authorship and publishing for the Journal of Cachexia, Sarcopenia and Muscle.
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