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Review

Nutritional regulation of coupling factor 6, a novel vasoactive and proatherogenic peptide

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ABSTRACT

High sodium, high glucose, and obesity are important risk factors for age-related diseases such as cardiovascular disease (CVDs), stroke, and cancer. Coupling factor 6 (CF6) is released from vascular endothelial cells and functions as a circulating peptide that inhibits prostacyclin and nitric oxide generation by intracellular acidosis. High glucose elevates CF6 by activation of protein kinase C and p38 mitogen-activated protein kinase, whereas CF6 causes type 2 diabetes mellitus, resulting in a high glucose vicious cycle. Low glucose increases inhibitory factor peptide 1, an endogenous inhibitor of CF6. High salt intake increases CF6 through nuclear factor κB signaling, whereas CF6 induces salt-sensitive hypertension and salt-induced congestive heart failure. Oral administration of vitamin C cancels salt-induced increase in CF6, and estrogen replacement leads to the delayed onset of CF6-induced salt-sensitive hypertension and the rescue from cardiac systolic dysfunction. Because CF6 contributes to the onset of CVDs, nutritional regulation of CF6 will shed light on the understanding of preventive strategy and mechanisms for CVDs and a target for therapy.

Introduction

High salt, high glucose, and obesity are important risk factors for age-related diseases such as cardiovascular diseases (CVDs) and malignant tumors. Increasing evidence shows that there is a close relationship between high salt intake and inflammation in humans [1,2] and obesity is associated with salt sensitivity [3]. Furthermore, high salt and obesity promote the aging process synergistically in adolescents [4]. In experimental models, high salt accelerates the development of autoimmunity by T-cell differentiation and exacerbates autoimmune disease [5,6].

We identified a circulating peptide that inhibits prostacyclin and nitric oxide (NO) by intracellular acidosis [7]. It is a component of adenosine triphosphate (ATP) synthase, and called as coupling factor 6 (CF6). Interestingly, this peptide binds to the cell surface ATP synthase like other ligands [8–17] and accelerates proton import [18]. Because endothelial dysfunction emerges as an important pathogenic mechanism for atherosclerosis and is an early manifestation of CVD, CF6 exerts a number of profound effects [19–22]. As a result, CF6 contributes to the pathogenesis of CVDs such as hypertension, acute myocardial infarction, end-stage renal disease, and stroke [23–27]. In this review, we focus on the nutritional regulation of CF6 and clinical implications.

Structure and binding regulation of CF6

As shown in Figure 1 (left side), CF6 peptide is derived from genomic DNA as an immature form (1–108 amino acids), and transferred to the mitochondria through upstream-located import signal peptide (1–32) [28]. After deletion of the signal peptide, it becomes a mature form (33–108) in the peripheral stalk of ATP synthase [29–31], and mature CF6 is transferred to the plasma membrane by undetermined mechanism [17]. One of

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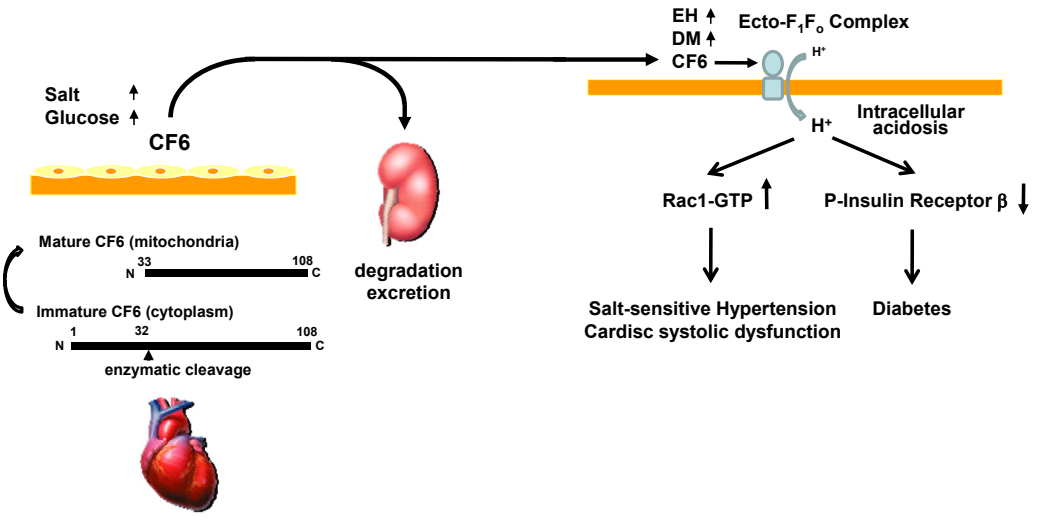

Fig. 1. Overview of the release, degradation, intracellular signaling, and biological functions of coupling factor 6 (CF6). DM, diabetes mellitus; EH, essential hypertension.

the most CF6-expressing organs is the heart [7], whereas one of the most CF6-releasing organs or tissues is the vascular endothelium [21,32]. The circulating structure of CF6 is highly flexible, and is reminiscent of a molten globule state [33]. The fashion of CF6 binding to the β-subunit of cell-surface ATP synthase is suppressed by adenosine diphosphate (ADP), and it is similar to that of high-density lipoprotein (HDL) in hepatocytes; ADP suppresses the binding of apo-E–rich HDL to β-subunit of ATP synthase and HDL endocytosis [10]. This negative feedback is related to the duration of the biological effects of CF6.

Nutritional regulation of CF6

Glucose regulates CF6 generation

Exposure to high glucose enhances CF6 expression and secretion in vascular endothelial cells [34]. It is dependent of increased osmolarity, protein kinase C (PKC), and p38 mitogen-activated protein (MAP) kinase because inhibition of PKC and p38 MAP kinase suppresses high glucose-induced increase in CF6 release. In clinical settings, the plasma concentration of CF6 is higher in patients with diabetes than in those without it [25]. By a multiple stepwise regression analysis, the level of CF6 is independently correlated with those of glucose and cholesterol positively, and with that of 6-keto-$PGF_{1\alpha}$ negatively. It is of importance that high glucose increases CF6 release [34], whereas CF6 increases glucose level as described later, thereby generating a vicious cycle.

CF6 regulates glucose metabolism

Diabetes is a serious global public health issue that has been described as the most challenging health problem. Diabetes is a significant cause of blindness, nontraumatic lower limb amputations, and end-stage renal disease resulting in transplantation and dialysis. Diabetes also increases the mortality secondary to heart failure, and diabetic cardiomyopathy is characterized by high blood glucose and lipids levels which generate oxidative stress, defective calcium handling, and fibrosis.

In these contexts, CF6 contributes to the development of insulin resistance (Fig. 1, right side). Chronic stimulation of ecto-F_1 F_o complex by CF6 enhances proton import in tissues expressing the CF6 receptor. Proton regulates cellular function by modulating the charge and structure of macromolecules related to insulin signaling. CF6-overexpressing transgenic mice (TG) manifest the decrease in phospho-insulin receptor β, insulin receptor substrate (IRS)-1, phosphoinositide 3-kinase, and phospho-Akt1 in skeletal muscle, resulting in a decrease of plasma membrane-bound glucose transporter 4 [35]. In the liver, TG manifest the decrease in phospho-insulin receptor β, IRS-2 instead of IRS-1, and phospho-Akt1, resulting in an increase in hepatic glucose production. In patients with diabetes, circulating CF6 is elevated [36].

Glucose regulates inhibitory factor peptide 1, an endogenous inhibitor of CF6

Two nano-motors of F_1 and F_o constitute the F_1 F_o complex, ATP synthase. The molecular rotary motor F_1-ATPase rotates in a counterclockwise direction as it hydrolyses ATP [37], whereas its partner motor F_o, which is present in an inner membrane, rotates in a clockwise direction via a proton flux. In mitochondria, F_o forces the backward (clockwise) rotation of F_1, resulting in ATP synthesis [38], whereas in the plasma membrane, F_1 forcefully hydrolyzes ATP and rotates F_o inversely to pump protons in the opposite direction, resulting in intracellular acidosis [18]. CF6 potentiates a counterclockwise rotation by the hydrolysis of ATP to ADP. Inhibitory factor (IF)1 peptide inhibits unidirectional rotation of counterclockwise [39], thereby being capable of blocking CF6 effect without affecting ATP synthesis. We recently identified that IF1 inhibits CF6-induced decrease in intracellular pH in human embryonic kidney 293 cells and attenuates CF6-induced apoptosis [40].

IF1 is encoded in the *ATPIF1* gene that is located in chromosome 1 of human genome. Despite little influence of environmental factors such as smoking, physical activity, and inflammation status on IF1 concentration [41], low glucose triggers IF1 transcription by nuclear factor (NF)-κB binding to the proximal promoter [42,43]. Exposure of primary neurons to glucose deprivation increases the IF1 level [44], and the