Available online at www.sciencedirect.com

Metabolism

www.metabolismjournal.com

Review

Kinase-SUMO networks in diabetes-mediated cardiovascular disease

Eugene Chang [a], *Jun-ichi Abe* [b,*]

[a] *Department of Medicine, Case Cardiovascular Research Institute, Case Western Reserve University, Cleveland, OH, USA*
[b] *Department of Cardiology — Research, Division of Internal Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA*

ARTICLE INFO

Article history:
Received 28 August 2015
Accepted 12 January 2016

Keywords:
Type II diabetes mellitus
SUMOylation
cardiovascular disease

ABSTRACT

Type II diabetes mellitus (DM) is a common comorbidity in patients with cardiovascular disease (CVD). Epidemiological studies including the Framingham, UKPDS, and MRFIT studies have shown diabetes to be an independent risk factor for cardiovascular disease associated with increased incidence of morbidity and mortality. However, major randomized controlled clinical trials including ADVANCE, VAD, and ACCORD have failed to demonstrate a significant reduction in CVD complications from longstanding DM with strict glycemic control. This suggests that despite the strong clinical correlation between DM and CVD, the precise mechanisms of DM-mediated CVD pathogenesis remain unclear. Signal transduction investigations have shed some light on this question with numerous studies demonstrating the role of kinase pathways in facilitating DM and CVD pathology. Abnormalities in endothelial, vascular smooth muscle, and myocardial function from the pathological insults of hyperglycemia and oxidative stress in diabetes are thought to accelerate the development of cardiovascular disease. Extensive interplay between kinase pathways that regulate the complex pathology of DM-mediated CVD is heavily regulated by a number of post-translational modifications (PTMs). In this review, we focus on the role of a dynamic PTM known as SUMOylation and its role in regulating these kinase networks to provide a mechanistic link between DM and CVD.

1. Introduction

Type II diabetes mellitus (DM) is a known cardiovascular disease (CVD) risk factor as shown in numerous epidemiological studies including the landmark Framingham Heart Study [1,2], United Kingdom Prospective Diabetes Study [3] (UKPDS), and Multiple Risk Factor Intervention Trial [4] (MRFIT). Compared to individuals without diabetes, type II diabetics are at greater risk of developing CVD including atherosclerosis, diabetic cardiomyopathy, stroke, renal disease, and myocardial

Abbreviations: AGE, advanced glycation end-products; CVD, cardiovascular disease; DM, type II diabetes mellitus; EC, endothelial cell; ERK5, extracellular-signal regulated kinase 5; KLF, Krüppel-like factor; KO, knock-out; ICER, inducible cAMP early repressor; NEMO, NF-κB Essential MOdulator; NF-κB, nuclear factor kappa B; p90RSK, p90 ribosomal S6 kinase; PDE3A, phosphodiesterase 3 A; PKC, protein kinase C; PIAS, protein inhibitor of activated STAT; PPAR, peroxisome proliferator-activated receptor; PTM, post-translational modification; ROS, reactive oxygen species; SENP, sentrin-specific protease; STZ, streptozotocin; SUMO, small ubiquitin-related modifier; TAC, transverse aortic constriction; VE-cadherin, vascular endothelial cadherin.

* *Corresponding author at:* The University of Texas MD Anderson Cancer Center, Room Number: IBT8.803E, 2121 W. Holcombe Blvd, Unit Number: 1101, Houston, TX, 77030, USA. Tel.: +1 713 745 2803; fax: +1 713 745 2816.
E-mail addresses: jabe@mdanderson.org, junichiabe2000@gmail.com (J. Abe).

http://dx.doi.org/10.1016/j.metabol.2016.01.007
0026-0495/

infarction [5]. Type II diabetics often have multiple CVD risk factors including dyslipidemia, hypertension, and obesity.

Surprisingly, despite this epidemiological correlation as well as clinical evidence that strict glycemic control is beneficial for microvascular disease, such evidence is lacking for macrovascular disease. Three major randomized controlled clinical trials (ADVANCE [6], VADT [7], and ACCORD [8]) that examined near-normal glycemic control (A1C 6.4–6.9%) over a 3.5–6 year time period failed to demonstrate a significant reduction in CVD complications from longstanding DM. In contrast, post-trial observations from the UKPDS showed that there was a CVD risk reduction benefit with strict glycemic control in patients with newly diagnosed diabetes [9]. According to these results together with the epidemiological data from the Framingham, UKPDS, and MRFIT studies, we may suggest that although there is an association between DM and CVD, the precise mechanisms through which DM increases CVD risk remain unclear.

Signal transduction investigations have shed some light on this question with numerous studies demonstrating the role of kinase pathways in facilitating DM and CVD pathology [10]. Abnormalities in the endothelial, vascular smooth muscle, and myocardial functions caused by the pathological insults of hyperglycemia and oxidative stress in diabetes are thought to accelerate the development of cardiovascular diseases [11]. Numerous kinase signaling pathways are shared in DM and CVD pathology, several of which are heavily regulated by post-translational modifications (PTMs) [12]. In this review, we focus on the role of a dynamic PTM known as SUMOylation and its role in regulating certain kinase networks to provide a mechanistic link between DM and CVD.

2. SUMOylation — Dynamic Post-Translational Modification

Small Ubiquitin-related Modifier (SUMO) is a 10-kDa post-translational protein modifier [13,14]. SUMO covalently attaches to lysine (K) residues at a specific consensus motif Ψ-K-x-D/E in which Ψ is a hydrophobic residue, x is any amino acid, and D/E represent negatively charged aspartic acid and glutamic acid residues. Modification of target proteins can result in conformational changes or alteration of interaction surfaces allowing for regulation of protein functions including intracellular trafficking, cell cycle progression, DNA repair and replication, RNA metabolism, transcriptional regulation, apoptosis, protein stability, and kinase activity [13,15,16]. Four SUMO proteins are expressed in humans; SUMO1–SUMO3 are ubiquitously expressed whereas SUMO4 is limited to the kidney, lymph node, and spleen [14,15].

SUMO conjugation (SUMOylation) is a dynamic and reversible modification that allows for transient changes in signal transduction (Fig. 1). It utilizes an enzymatic machinery similar to that of ubiquitination [15]. This cascade begins with the E1 activating enzyme and ends with the E3 ligating enzyme that leads to the conjugation of SUMO to lysine residues on target proteins [14]. Several SUMO E3 ligases have been identified including protein inhibitor of activated STAT (PIAS) family (PIAS1, PIAS2(x), PIAS3, PIAS4(y)), polycomb-2 protein (Pc2), and RanBP2/Nup358 [12].

Substrates are deconjugated by SUMO proteases sentrin/SUMO-specific proteases (SENP) and ubiquitin-like protein specific proteases (Ulp) [17,18]. This process is further discussed in the de-SUMOylation section.

3. Endothelial Dysfunction and Diabetes

Endothelial dysfunction is one of the hallmarks of DM and even found in diabetic patients without CVD risk factors [19,20]. Impaired endothelial function can be defined as a loss of vascular homeostasis leading to pathologic inflammation, apoptosis, permeability, and coagulation of the endothelium. Hyperglycemia induces pathologic changes in the endothelium through the production of AGEs (advanced glycation end-products) and ROS (reactive oxygen species) [10]. *In vivo* studies of the streptozotocin (STZ) induced diabetic rat model show an increase in leukocyte adhesion and rolling with increased expression of inflammatory cytokines and adhesion molecules under high glucose conditions [21]. Furthermore, hyperglycemia induces corresponding epigenetic changes of key inflammation regulators like NF-κB in endothelial cells leading to long-term upregulation of inflammatory gene expression [22,23]. Together these data suggest that hyperglycemia-induced endothelial dysfunction predisposes the vascular wall to atherogenesis. Below we review a few of the regulatory pathways of kinases and SUMO that link DM to CVD.

3.1. *NF-κB and IKK*

NF-κB is a master regulator of endothelial inflammation and plays an important role in DM and CVD pathogenesis. Hyperglycemia induces numerous epigenetic changes in the endothelium including the upregulation of NF-κB through its downstream mediators AGEs and ROS [22,23]. Similarly, atherogenesis occurs through NF-κB induced leukocyte recruitment, cytokine release, and adhesion molecule expression [24]. Overlap between the two mechanisms highlights the central role of inflammation in linking DM to CVD progression.

Under resting conditions, NF-κB exists in an inactivated state within the cytoplasm bound to IκB (inhibitor of κB). Stimulants like TNF trigger the activation of IKK (IκB kinase) to phosphorylated IκB, leading to IκB's degradation *via* ubiquitination and unmasking of NF-κB's nuclear localization signal. This then frees NF-κB to translocate into the nucleus and transactivate pro-inflammatory genes including TNF, IL-1, IL-8, E-selectin, VCAM1, and ICAM1 [25]. SUMOylation has been reported to be involved at different levels of NF-κB regulation. The NF-κB protein precursor p100 can be modified by SUMO to activate the non-canonical pathway [26]. IκBα can be modified by SUMO1 to protect it from ubiquitination and degradation, limiting NF-κB activation [27]. In contrast, modification of IκBα by SUMO2/3 confers the opposite effect and dissociates IκBα from NF-κB leading to NF-κB activation [28]. Under high glucose conditions, IκBα SUMOylation is increased leading to further activation of NF-κB [29].

IκB kinase (IKK) is an important regulatory kinase in NF-κB activation that is activated during hyperglycemia [30,31]. Composed of two kinases (IKKα and IKKβ) and a regulator subunit NEMO/IKKγ (NF-κB Essential MOdulator), IKK has three total