

Review Article

Sumoylation modulates oxidative stress relevant to the viability and functionality of pancreatic beta cells

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Abstract: Sumoylation is an evolutionarily conserved regulatory mechanism to play an important role in various cellular processes through modulation of protein localization, stability and functionality. Recent studies including ours have consistently demonstrated that sumoylation provides protection for cells against oxidative stress. Given that pancreatic beta cells are a vulnerable target of oxidative stress, we thus in this minireview, updated the advancement of sumoylation in the regulation of ROS generation, and discussed its impact on several critical signaling pathways relevant to beta cells against oxidative stress and maintenance of functionality. Specifically, we bring together how sumoylation represses intracellular ROS formation, and protects beta cells against oxidative stress through regulating I κ B/NF κ B, JNK/c-Jun, and Maf/Nrf2 pathways. The tight implication of sumoylation in oxidative stress reflects that it could be an essential mechanism for beta cells to adapt to the detrimental cellular microenvironment.

Keywords: Sumoylation, beta cell, oxidative stress, ROS, diabetes

Introduction

Oxidative stress is now known to be associated with nearly all pathological states, especially those involving inflammatory processes [1]. It refers to a persistent imbalance between the excessive productions of reactive oxygen species (ROS) and the limited capacity to detoxify those reactive intermediates. ROS, defined as highly reactive molecules including charged species such as superoxide anion (O²⁻), hydroxyl radicals (HO \bullet), and uncharged species such as hydrogen peroxide (H₂O₂) [2, 3]. In mammalian cells, ROS are formed continuously under physiological condition as a consequence of metabolic reactions, and these cellular oxidants have recently been recognized as signaling molecules essential for the regulation of cellular processes and functionalities [4]. In contrast, ROS accumulation along with oxidative stress is a common feature under diseased condition. For example, under diabetic condi-

tion, increased glucose flux not only enhances oxidant production but also impairs antioxidant defenses, thereby leading to ROS accumulation and oxidative stress [5, 6]. Extensive studies for the past few decades have clearly demonstrated the enzymes implicated in ROS detoxification, while the molecular mechanisms underlying the regulation of ROS production and detoxification are remained to be fully elucidated.

In type 1 diabetes (T1D), autoimmune responses against beta cell self antigens lead to the production of copious amounts of inflammatory cytokines, which then induce excessive ROS generation and oxidative stress to mediate beta cell destruction. Indeed, animals with beta cell specific expression of antioxidant enzymes are resistant to developing type 1 diabetes, and beta cells deficient in Nox2, the main intracellular ROS producer, are protected from cytokine- or alloxan-induced apoptosis [7-9]. As

such, oxidative stress resulted from autoimmune responses is believed to be the leading cause for beta mass loss in the pathogenesis of type 1 diabetes [10]. Unlike type 1 diabetes, beta mass loss in type 2 diabetes, however, is first manifested by a period of beta cell dysfunction [11]. Sustained exposure of isolated islets to high glucose induces increases of intracellular ROS [12, 13], which renders beta cells undergoing apoptosis. It has now become evident that oxidative stress caused by chronic exposure to elevated glucose or fatty acid contributes to beta cell death in type 2 diabetes [14, 15]. Collectively, beta cell death caused by oxidative stress is likely a major mechanism for beta mass loss shared by both type 1 and type 2 diabetes.

Post-translational attachment of a small ubiquitin-like modifier (SUMO) to the lysine (K) residue(s) of a target protein (defined as sumoylation) is an evolutionarily conserved regulatory mechanism [16, 17]. To be functionally active, SUMO needs to be hydrolyzed by a SUMO-specific protease (SEN1) to expose its C-terminal diglycine motif, a prerequisite for its covalent conjugation to the substrate proteins. The sumoylation process involves a SUMO-activating enzyme (E1, Uba2/Aos1), a single SUMO-conjugating enzyme (E2, Ubc9), and a SUMO-E3 ligase (such as the PIAS family or RanBP2) [18]. Sumoylation is a reversible process and, in some cases, dynamic cycles of sumoylation/desumoylation of target proteins are required for cellular processes [18, 19]. Over the past few years, sumoylation is not only found to be an important regulatory mechanism for the functionality of many vital cellular proteins, but also found to be a major player in the pathogenesis of human diseases such as Huntington's disease, Parkinson's disease, Alzheimer's disease, cancer and cardiovascular diseases [20]. Particularly, studies including ours have consistently demonstrated that sumoylation regulates the capacity of cells against oxidative stress [16]. Our recent studies further revealed that sumoylation regulates cell viability through repressing intracellular ROS generation [21, 22]. While these results are important and exciting, its impact on pancreatic beta cells, a ROS vulnerable target, is yet to be fully elucidated. Therefore, in this mini-review we intend to summarize the advancement for the impact of sumoylation on ROS gen-

eration and the related signaling pathways for beta cells against oxidative stress.

Sumoylation regulates ROS generation

The NADPH oxidases (Nox) have been recognized to be the major source of reactive oxygen species (ROS) relevant to oxidative stress in mammalian cells [23]. The Nox family is consisted of 7 members (Nox1 to 5, and Duox 1 and 2) implicated in diverse pathophysiological processes such as host defense, cellular signaling, thyroid hormone synthesis and otosclerosis formation [24]. The Nox enzymes are oxidoreductases characterized by 6 transmembrane domains and two centrally coordinated heme residues and C-terminal regions for binding of FAD and NADPH [25]. The production of superoxide is featured by the donation of electrons from NADPH along with reduction of oxygen.

Of note, the Nox enzymes responsible for ROS formation was originally characterized in phagocytes such as dendritic cells and macrophages [26, 27]. However, it was recently found that other types of cells also express isoforms of certain Nox enzymes [28, 29]. For example, NOX2 is a complex consisting of membrane-bound elements (gp91phox/Nox2 and p22phox) and cytosolic components (p47phox, p67phox, and GTPases Rac1/2), while studies in mice revealed that pancreatic beta cells also express the NOX2 related elements such as gp91phox (Nox2), p22phox and p47phox, suggesting that NOX2 is also employed by pancreatic beta cells during physiological or pathological processes. Indeed, combination of cytokines (e.g., IL-1 β , IFN- γ and TNF- α) induced excessive ROS production along with pancreatic beta cells undergoing apoptosis through up-regulation of Fas and Fas ligand [30]. As a result, animals with ectopic expression of antioxidant enzymes in the pancreatic beta cells are resistant to developing type 1 diabetes [31, 32], and beta cells deficient in Nox2, a major ROS producer, are protected from cytokine- or alloxan-induced apoptosis [33].

Interestingly, previous studies including ours have consistently demonstrated that sumoylation regulates intracellular stress [34, 35]. Particularly, SUMO1 and the SUMO-specific conjugating enzyme, Ubc9, are found to dose-dependently suppress the activity of NADPH oxidase 5 (Nox5). Given that SUMO1 did not

show a perceptible impact on Nox5 expression and calcium levels, the suppressive effect is likely caused by its direct sumoylation. Indeed, sumoylated form of Nox5 was detected and ectopic expression of SUMO1 prevented Nox5 from ubiquitin mediated degradation [36]. More importantly, SUMO1 is also found with the capability to suppress ROS generation from Nox1 and Nox4, and inhibition of sumoylation function by anacardic acid attenuated ROS production. Collectively, these results suggest that sumoylation may function as a regulatory mechanism to limit ROS generation for cells against oxidative stress. It is worthy of note, a significant protein sumoylation turnover in NIT-1 cells, a nonobese diabetic (NOD) mouse derived beta cell line, upon a combination of cytokine stimulation was noted, and furthermore, ectopic SUMO1 expression provided protection for NIT-1 cells against cytokine induced apoptosis (unpublished data). Taken together, there is feasible evidence suggesting that sumoylation of Nox enzymes may protect beta cells against oxidative stress through limiting ROS generation.

Sumoylation wrestles with the I κ B/NF κ B pathway

The nuclear factor κ B (NF κ B) is a family of transcription factors including RelA (p65), RelB, c-Rel, NF κ B1 (p105/p50) and NF κ B2 (p100/p52) with implications in immune response and cell survival or death. They can be either formed as homo or heterodimers to regulate the expression of downstream genes. Among which, the p50/RelA and p52/RelA heterodimers are the most commonly studied [37]. In most cases NF κ B maintains inactive in the cytoplasm by non-covalent interaction with the I κ B proteins such as I κ B α , β or γ . Upon a variety of stimuli such as cytokines, bacterial or viral infections, I κ B is phosphorylated by the I κ B kinase (IKK) complex, which then leads to the degradation of I κ B, and NF κ B is thus released from I κ B and translocated into the nucleus for transcription of genes relevant to immune response or intracellular stress [38-40].

Of note, sumoylation has been recognized to actively regulate the I κ B/NF κ B pathway through modulation of their activation and functionality. For example, studies revealed that H₂O₂ induces NF κ B activation through sumoylation of NF κ B essential modulator (NEMO), the regula-

tory subunit of the I κ B kinase [41, 42], in which H₂O₂ increases PIASy-NEMO interaction and NEMO sumoylation. Indeed, PIASy is found to be a SUMO ligase for NEMO whose substrate specificity seems to be controlled by IKK interaction and oxidative stress conditions [43]. Therefore, NEMO sumoylation provides protection for cells against apoptosis [44]. There is also evidence that SUMO directly sumoylates I κ B α , by which it blocks the translocation of NF κ B p65 subunit into the nucleus to prevent IL-12 secretion, which renders naive CD4 T cells preferentially differentiate into Th2 cells [45]. Recent data demonstrate a reciprocal interaction between SUMO and NF κ B. RelA sumoylation mediated by PIAS3 is induced by NF κ B activation, which in turn represses NF κ B transcriptional activity, this could serve as a negative regulatory mechanism for the NF κ B signaling [46]. In general, sumoylation stabilizes I κ B α from signal induced degradation, and by which it suppresses NF κ B transcriptional activity associated with anti-inflammatory or anti-apoptosis effect.

Sumoylation regulates the JNK/c-Jun signaling

The c-Jun N-terminal kinase (JNK) is a kinase strongly associated with many different stress stimuli and cell death [47, 48]. Interestingly, sumoylation acts on this signaling pathway through various mechanisms. In a model with H₂O₂ induced oxidative stress, ectopic SUMO1 expression increased JNK phosphorylation and exacerbated cell death. In contrast, inhibition of sumoylation by transfection of SENP1 down-regulated JNK activity, which protected cells from H₂O₂ induced death [49]. The transcription factor c-Jun, part of the activator protein 1 (AP-1) complex, is a major downstream target in the JNK pathway. Oxidative stress induced a marked increase in protein sumoylation including c-Jun, which is a part of hypersumoylation response upon JNK activation in a ROS-dependent manner [50]. JNK activates the c-Jun transcription factor, while sumoylation attenuates its transcriptional activity [51]. As a result, knockdown of PIAS1, a SUMO E3 ligase, not only inhibited hypersumoylation induced by ROS, but also enhanced JNK signaling [52]. Of note, sumoylation possesses a double-edged function in modulating JNK-dependent oxidative stress, in which PIAS1, a SUMO E3 ligase, is a direct downstream target of JNK pathway

[52], while sumoylation inhibits the apoptosis signal-regulating kinase 1 (ASK1) activation, which is an upstream activator of JNK [53].

Sumoylation of homeodomain-interacting protein kinase (HIPK) is actively participated in the regulation of JNK signaling. HIPK is involved in a variety of biological processes, some of which are in common with the JNK pathway such as apoptosis and morphogenesis [54-57]. For example, knockdown of *Drosophila* SUMO gene (*Smt3*) upregulates the JNK signaling pathway, while this enhanced JNK activity can be attenuated by suppression of HIPK expression. Sumoylation sequesters HIPK in the nucleus, while desumoylation renders HIPK cytoplasmic translocation, leading to JNK activation [58].

Sumoylation modulates the Maf/Nrf2 activity

The Maf proteins, including c-Maf, MafA and MafB, are transcriptional activators of tissue-specific genes and regulators of cell differentiation. MafA expression is primarily limited to the insulin-producing beta cells and relates to the insulin gene, as well as other genes relevant to the function of pancreatic beta cells [59]. Recent studies revealed that sumoylation of MafA serves as a post-translational regulatory mechanism to negatively regulate its transcriptional and transforming activities [60]. Incubation of beta cells in low glucose (2 mM) or under oxidative stress condition induced by H₂O₂ increases the sumoylation of endogenous MafA. The mutant MafA (K32R), which lacks the SUMO1 acceptor site, is not able to repress reporter gene expression, whereas wild-type MafA sumoylated by SUMO1 elicits statistically significant repression. Given that the functionality of MafA is required for the development and maintenance of mature insulin-producing beta cells [61], sumoylation of MafA may play an essential role in the regulation of insulin secretion and beta cell viability.

c-Maf, another member of Maf families, transactivates the IL-4 gene to induce Th2 cell development. Therefore, abnormalities in c-Maf may contribute to the reduced IL-4 production by CD4 T cells from NOD mice. Interestingly, sumoylation of c-Maf represses its binding to the IL-4 promoter, leading to less amount of IL-4 production, and by which it limits the protective Th2 responses [62]. As a result, enhanced c-Maf sumoylation is considered

contributing to immune deviation in type 1 diabetes by reducing c-Maf access to and transactivation of the IL-4 gene [63]. However, it remained unclear whether sumoylation of c-Maf also promotes T cell apoptotic sensitivity other than inhibiting IL-4 secretion during the development of type 1 diabetes [64].

Nrf2, a key transcriptional activator of the antioxidant response pathway, usually forms a heterodimer with small Maf (sMaf) proteins and binds to the antioxidant response elements (AREs), through which it activates a battery of genes involved in various aspects of cytoprotective and metabolic functions under oxidative stress conditions [65]. For example, upon forming the heterodimer with small Maf proteins it transcribes antioxidant and detoxificant genes implicated in cell survival [66]. Interestingly, sumoylation was recognized to enhance Nrf2 and small Maf protein (MafG) heterodimerization, and to increase their binding activity to the antioxidant response element (ARE). Therefore, sumoylation of Nrf2 and MafG is associated with more GSH synthesis, which renders cells with higher capacity against oxidative stress [67]. Indeed, genes that regulate glucose metabolism and several amino acid transporters are identified as Nrf2-MafG targets, demonstrating diverse roles for the Nrf2-MafG heterodimer in stress response [65]. There is also evidence suggesting that Nrf2 serves as a PPAR γ agonist to increase insulin sensitivity relevant to enhanced antioxidant activity [68]. Furthermore, the Keap1-Nrf2 signaling pathway has been found to down-regulate NF κ B transcriptional activity and attenuate cytokine-induced expression of proinflammatory genes [69]. Taken all these results together, sumoylation of Maf and/or Nrf2 provides protection for beta cells against oxidative stress during the course of diabetes development.

Perspectives

Sumoylation has been consistently recognized to function as a revolutionarily conserved regulatory mechanism involved in different cellular processes against oxidative stress. Given the critical role of pancreatic beta cells played in the regulation of blood glucose homeostasis, sumoylation of substrate proteins in beta cells has now been realized essential for beta cells against oxidative stress and maintenance of functionality. However, the overall impact of

sumoylation on beta cells is a homeostatic effect of multiple substrates in a manner of temporal sumoylation turnover. On the one hand, sumoylation of some particular targets is beneficial, by which it selectively activates or inhibits key proteins in different signal pathways to protect beta cells from oxidative stress. On the other hand, sumoylation of certain targets may exhibit a disadvantageous effect; for example, sumoylation of Keratin reduces its solubility, thereby limiting its cytoprotective function. It is worthy of note, the mechanisms underlying temporal and spatial regulation of sumoylation turnover during oxidative stress are yet to be fully addressed. Also, the functional heterogeneity of different SUMO forms along with various target proteins and corresponding consequences in beta cells remained to be elucidated. Therefore, future investigations aimed to dissect those challenging questions would be necessary.

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Disclosure of conflict of interest

The authors declare no competing financial interests.

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