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Potential Role of SUMO and SUMOylation in the Pathogenesis of Diabetes Mellitus

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Abstract

Diabetes mellitus is a group of metabolic disorders characterized by hyperglycemia and associated with multiple organ systems complications. The incidence and prevalence of diabetes are increasing in an epidemic proportion worldwide. In addition to environmental factors, some epigenetic and post-translational modifications have critical roles in the pathogenesis of diabetes and its complications. Reversible covalent modification such as SUMOylation by SUMO (Small Ubiquitin-like Modifier) has emerged as a new mechanism that affects the dynamic regulation of proteins. In this review, we initially focus on the function of SUMO and SUMOylation. Subsequently, we assess the potential effects of this process in the pathogenesis of type 1 and 2 diabetes mellitus.

Keywords: Diabetes mellitus; Small Ubiquitin-like modifier; SUMO; SUMOylation.

1. Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by hyperglycemia due to an absolute or relative insulin deficiency. Based on pathogenesis, there are two main types of diabetes. In type 1 diabetes (T1DM), there is autoimmune destruction of insulin-producing beta-cells in islets of the pancreas resulting in absolute loss of endogenous insulin. In contrast, type 2 diabetes (T2DM) is a heterogeneous metabolic disorder characterized mainly by hyperglycemia, insulin resistance, and impairment in insulin secretion in various degrees (1-5).

The incidence of diabetes and its associated complications increases worldwide and is projected to double by 2030. The American Diabetes Association estimated that 1.7 million diagnoses of diabetes occur in America annually, and it is the fifth leading cause of death (3). In addition to the environmental factors such as obesity, age, sedentary lifestyle, and lack of exercise that are associated with diabetes (6, 7), genome-wide associated studies (GWAS) have shown that immune responses genes are associated with susceptibility to diabetes; however, the effector mechanisms are unknown (8). Mutations and sequence alterations in DNA are not sufficient to explain the variable manifestations of this disease.

There is growing evidence of epigenetic changes which can affect the severity of diabetes (9). Epigenetics is the study of heritable changes in gene function without any changes in nucleotides sequences (10). This includes dynamic addition or removal of functional groups or proteins by specific enzymes, which can cause changes in the structure and function of various targets. Post Translational Modifications (PTMs) are a diverse mechanism used by cells to control and regulate their biological functions (11). Small Ubiquitin-like Modifier (SUMO) is an essential PTM that modulates many protein functions and plays essential roles in various cellular processes (12).

SUMO with approximately 12KDa is a highly conserved protein produced as an inactive precursor and needs to be cleaved by SUMO-specific protease 1 (SENP1) to become the active form (13). A schematic presentation of the SUMO cycle is shown in **Figure 2.** SUMOylation and deSUMOylation are covalent conjugation and de-conjugation of SUMO family members (14). There are more than one SUMO isoforms in the SUMO system, including SUMO1, SUMO2/3, and recently described SUMO4 and SUMO5 (15, 16). It is worth noting that SUMO4 was identified while studying the association of single nucleotide polymorphisms (SNPs) with type I diabetes; however, it is currently considered an intron-less pseudogene (12).

Moreover, there is abundant evidence to show that the aberrance of SUMO regulation is highly associated with various diseases, including cardiac disease (17), autoimmune diseases (18), neurodegenerative disease (19), and cancers (20). Therefore, we discuss the role of SUMO and SUMOyaltion in different types of diabetes mellitus, including T1DM and T2DM.

2. SUMO and diabetes mellitus

Unlike differences in the pathogenesis of T1DM and T2DM, epidemiologic data shows that both of these disorders manifest in familial clusters. This suggests a common genetic basis for them, and SUMO is one of the common susceptibility genes in both types (21-23).

2.1. SUMO and regulation of insulin secretion

Several studies have shown that SUMOylation has critical roles in the maintenance of pancreatic beta-cell functions through regulating transcriptional activities (24), ion channel activities (25), oxidative stress (26), and insulin exocytosis (27). Moreover, the incretin pathway has important pancreatic and extra-pancreatic roles, and this pathway is impaired in patients with T2DM (28-32). Increased SUMO expression is associated with glucose- and incretin hormone-stimulated insulin secretion. Other proteins in beta cells can be regulated via the same pathway. For example, it has been shown that SUMO protein can inhibit the Kv2.1 voltage-dependent K channel and widening the action potential and reducing the firing frequency of beta-cells, but Kv2.1 inhibition can promote insulin secretion in mice beta cells (33).

SUMO1 can inhibit glucose-dependent insulin secretion via attachment to synaptotagmin VII and exocytosis impedance (34). SUMO1 could also cause intracellular retention of GLP-1R that is associated with a decrease in receptor density in the cell membrane. Although the role of SUMO in nucleoplasmic trafficking is established (35), how SUMO can help forward trafficking in the plasma membrane is not well recognized. One presumption is that SUMO can inhibit GLP-1R oligomerization. Receptor oligomerization is a crucial mechanism for forwarding trafficking of BG protein-coupled class of secretion receptors family, and GLP-1R is one of them. Hence increased SUMO modifications can increase the solubility of proteins such as vaccinia virus protein (36), and oligomerization of GLP-1R, which is regulated by SUMO modification, can change its solubility binding capacity (29).

One of the pathological features of T2DM is normal glucose-stimulated insulin secretion (GSIS) from pancreatic beta cells. Numerous studies showed that SUMOylation regulates vesicle trafficking, such as insulin secretion. Therefore, it has been suggested that SUMOylation may play an inhibitory role in regulating insulin exocytosis. Recently, it has been shown that inhibition of syntaxin1A (a member of the syntaxin superfamily and an essential protein in synaptic exocytosis) significantly promotes the GSIS (37).

Hepatocyte nuclear factor-1α (HNF-1A) is a crucial transcription factor in normal pancreas/liver development and function (38). HNF-1A, along with other transcription factors including pancreatic duodenal homeobox-1 (PDX-1), the hepatocyte nuclear factor-4 alpha (HNF-4A), and-1 beta (HNF-1B), participate in the regulation of glucose-induced insulin secretion (38, 39). Rare variants in the HNF-1A gene contribute to the development of monogenic diabetes, and common HNF-1A variants increase susceptibility to T2DM (40-42). A recent study demonstrated that SUMO3 mediated the HNF-1A SUMOylation in two lysine (K) residues (K) (K205 and K273). In addition, overexpression of PIASγ suppressed the transcriptional activity of HNF-1A. Thus, the

interaction of HNF-1A with SUMO3 and PIASγ revealed potential new targets for drug development in HNF-1A-associated diabetes (43).

Proinsulin disulfide maturation requires protein disulfide isomerase family members (PDIs) in the endoplasmic reticulum (ER) lumen (44). On the other hand, accumulation of misfolded proinsulin has been detected in patients with diabetes, implying that impaired proinsulin disulfide maturation could play an essential role in the pathogenesis of diabetes (45-47). Recently, SUMOylation of protein disulfide isomerase a3 (Pdia3) has exacerbated the proinsulin misfolding and ER stress in pancreatic beta cells (48).

Protein inhibitor of activated STAT (PIASy) is a member of the PIAS family of SUMO E3 ligases, affecting insulin gene transcription, but its mechanism is not well understood. In one study, Onishi et al. demonstrated that PIASy negatively regulates the promoter of the insulin gene via a SUMOylation-independent mechanism (49).

Protein-tyrosine phosphatase 1B (PTP1B) is a negative regulator of growth factor signaling and cell proliferation by dephosphorylating receptor tyrosine kinases, such as the insulin receptor. SUMOylation of PTP1B by PIAS1 reduced its activity and suppressed PTP1B adverse effects on insulin receptor signaling (50).

2.2. SUMO and diabetic nephropathy

Fifteen-thirty years after the onset of diabetes, 30-40% of patients with T1DM and 20-30% of patients with T2DM develop diabetic nephropathy (DN) (51, 52). This is one of the most severe microvascular complications in diabetes, leading to end-stage renal disease and renal failure in the Western population. Recent studies showed that inflammation is a critical link in DN development (53). Defects in glucose metabolism and abnormal hemodynamics trigger inflammation, macrophage infiltration, and secretion of excessive inflammatory factors that are detectable in renal tissue during early stages, which leads to accelerated renal fibrosis. NFκB is the critical pathway in DN inflammation, and SUMO-1 modification on inhibitor of nuclear factor kappa B (IκBα) is the most important regulator of canonical NFκB dimers, which suppresses the inflammation (54, 55). NFκB activation via cytokines in the hyperglycemic condition is a potential mechanism for developing diabetes complications. Renal expression of tumor necrosis factor-alpha (TNF-α), NFκB (p65), IκBα, and SUMO-4 were significantly increased in GK diabetic rats, and SUMO-4 has a crucial role in the regulation of the NFκB pathway in the glomerular cells. Studies showed that SUMO-1 and SUMO-2/3 expressions were significantly upregulated by glucose. High levels of glucose are associated with IκBα destruction and NFκB activation. IκBα modification by SUMO-2/3 occurs in high glucose conditions (56).

Glomerular sclerosis and interstitial fibrosis are the significant pathologic changes in progressive diabetes nephropathy, and TGF-β is a critical factor in DN renal fibrosis (57). High glucose, angiostatin II (Ang II), and other pro-fibrotic factors are essential in the TGF-β activation pathway. This cytokine plays an essential role in DN fibrosis and induces tubular and glomerular cells

hypertrophy, extracellular accumulation, glomerular sclerosis progression, and renal interstitial fibrosis (56). Smad is an essential signaling molecule that negatively regulates TGF-β downstream pathway. Recently studies report that SUMO can affect TGF-β signaling, and Smad SUMOylation suppresses its transcription activity where TGF receptor SUMOylation leads to increasing affinity to its ligand. Smad3 and Smad4 have a critical role in TGF-β signaling and are associated with different cell proliferation and differentiation responses. PIASγ can interact with Smad3 SUMOylation and inhibits TGF-β signaling. In addition, Smad4 SUMOylation is the regulator of its stability and co-expression with PIASγ and SUMO-1 export nuclease stimulate Smad3. Mutation in SUMOylation sides of Smad4 or co-transfection with SuPr-1 significantly increases its transcriptional activity. Also, a direct fusion of SUMO-1 to mutant Smad4 potentially inhibits its transcriptional activity (58, 59). These results proposed that PIASγ can regulate TGF-β/Smad3-mediated signaling via stimulating SUMOylation and Smad3 nuclease export (56). Also, Zhou et al. identified that Smad4 SUMOylation by SUMO2/3 activated the TGF-β/Smad signaling in mesangial cell culture in high glucose conditions (60).

2.3. SUMO and insulin resistance (IR)

Insulin resistance (IR) is characterized by an inability of insulin to activate its signaling pathway and induce subsequent cellular metabolic processes. IR is widely recognized in peripheral tissues, including the liver, fat, skeletal muscle, and vascular endothelium. In addition, IR has a significant effect on the cardiovascular system and results in vascular dysfunction and atherosclerosis. (61).

Peroxisome proliferator‐activated receptor γ (PPARγ) is a superfamily member of nuclear transcription factors. Both activation and overexpression of PPARγ improve the endothelium IR through transrepression of the NFκB pathway (62-64). Also, it is well known that SUMOylation of PPARγ in two sites (lysine 77 (K77) and K365 (murine), or K367 (human)) contributes to the transpressive effect on NFκB (65). In one study, Lan et al. investigated the effect of high glucose and palmitic acid (PA) on PPARγ sumoylation and ROS generation in human umbilical vascular endothelial cells (HUVECs). The assay results revealed that the PPARγ SUMOylation and ROS level was notably increased compared to control. Other results also demonstrated that the PIAS1-reactive oxygen species (ROS)-IκB kinase (IKK) pathway play a crucial role in SUMOylation of PPARγ and results in IR in vascular endothelium via PPARγ-NcoR (nuclear corepressors) complex stabilization. Moreover, downregulation of PIAS1 with PIAS1-specific shRNA significantly resulted in the reversal of endothelium IR induced by high glucose and PA (66).

Endothelium IR is also characterized by reducing endothelium-derived nitric oxide (NO) as well as elevating angiotensin II (AngII), which subsequently leads to dysregulation of vascular integrity (67). The hypothesis is that hyperglycemia induces ROS generation. Eventually, these processes interfere with the interaction of IRS1 to PI3K and prevent eNOS-NO pathway signaling, therefore leading to the endothelial IR induction (68). One study demonstrated that over-SUMOylation of PPARγ induces an endogenous SUMOylation cascade and results in IR and vascular endothelium dysfunction through negative regulation of eNOS-NO signaling in rat's aorta (69).

2.4. SUMO and regulation of GLUT4 in muscles

Most of the insulin-stimulated glucose uptake in humans is by skeletal muscles. Glucose primarily enters the muscle cells via diffusion and glucose transporter carrier proteins. GLUT4 protein is the most important glucose transporter protein in muscles. Glucose uptake via GLUT4 is regulated by insulin (70). When insulin binds to the receptor, it stimulates an intracellular signaling cascade, leading to phosphorylation of TBC1D1 and AS160 (TBC1D1) as Rab-GTPase-activating proteins. Phosphorylation in key residues of TBC1D1 and AS160 results in GLUT4 translocation to the cell surface. Then GLUT4 recycles to intracellular vesicles or becomes targets for lysosomal destruction (71, 72).

Ubiquitin-conjugating enzyme E2 (Ubc9) can regulate this process by controlling SUMO attachment and destroying GLUT4 in L6 muscle cells (73). Similar results were discovered in 3T3-L1 adipocytes where Ubc9 overexpression accelerates GLUT4 accumulation, while depletion of Ubc9 with specific RNAi leads to GLUT4 selective loss (74). Furthermore, Kampmann et al. evaluated the expression of UBC9 and GLUT4 in type 2 diabetic patients with severe IR compared to age-matched type 2 diabetic patients who did not become dependent on insulin administration and with an age-matched healthy group. In skeletal muscles, the expression of GLUT4 was significantly reduced, which was related to reduced levels of UBC9 protein. Nevertheless, the protein expression of GLUT1, AS160, and TBC1D1 was not notably altered between groups. Collectively, downregulation of GLUT4 may partially describe the severe IR and poor control of blood glucose in subjects with type 2 diabetes mellitus who suffered from IR.(70).

Recently, Carmichael et al. manipulated the rate of cellular SUMOylation in L6 myocytes using a lentiviral transduction system and evaluated the effect on insulin-dependent surface expression of GLUT4. Treatment of L6 myocytes with insulin substantially reduced whole cellular SUMO1-ylation rate but not other types of SUMO, including SUMO2/3. Surprisingly, no evidence has been identified that changes in SUMOylation rate had any potential effect on GLUT4 expression in L6 rat myocytes. Although SUMOylation plays a vital role in the insulin signaling pathway, based on these results, SUMOylation is not a suitable target for the treatment of IR (75).

2.5.SUMO and regulation of inflammatory mediators

It has been reported that NFκB is one of the main targets of SUMOylation and SUMOylated IκBα inhibits the NFκB transcriptional activity. Subsequently, NFκB activation triggers the transcription of three groups of genes, including auto-regulatory genes (p50 and p65), immune response genes, and activators (e.g., IL-1, IL-2, IL-6, IL-12, TNFα, and IL-2Rα), and negative feedback regulators (e.g., IκBα) (76-78). A study revealed that overexpression of mice SUMO2 (mSUMO2) significantly reduced IL-12 and NFκB activity in DCs. Although, SUMO2 overexpression did not alter the expression of MHC-II, B7, IL-1, IL-6, and IL-7. Therefore, NFκB and SUMOylation may contribute to the development of autoimmune diabetes (79).

Adipocyte dysfunction promotes the pathogenesis of autoimmune-mediated diabetes. SUMO-dependent deletion of SENP-1 protease resulted in more severe T1DM-related complications such as glucose intolerance, insufficient insulin secretion, and hyperglycemia. In a SENP1-deficient experimental model, increased expression of NFκB and CCL5 chemokine by peri-pancreatic adipocytes resulted in more significant inflammation and destruction of pancreatic islets. SENP-1 deletion in adipocytes induced hyper-SUMOylation of the nuclear factor-κB essential modulator (NEMO), an NFκB activating factor. NFκB suppression in SENP1-deficient mice impairs the development of T1DM. This suggests that reduced inflammation of pancreatic islets and T1DM-mediated pathology results from SENP1-dependent deSUMOylation of NEMO (80)

2.6. The other roles of SUMO in diabetes

Cardiovascular disease (CVD) is a life-threatening complication in patients with diabetes (81, 82). In addition, the underlying mechanisms of CVD may be partially distinct in T1DM versus T2DM (83). Several studies revealed that ER stress plays a vital role in developing and progression of diabetic cardiomyopathy (DCM) (84, 85). Recently, it was demonstrated that SUMOylation was enhanced by chronic diabetic milieu and therefore disrupted nuclear translocation of X-box-binding proteins (XBP1s) in diabetic mice (86). XBP1 is one of the essential factors in unfolded protein response (UPR) signaling during ER stress and plays an essential role in maintaining ER homeostasis (87). Moreover, treatment with U0126 (ERK1/2 inhibitor) significantly suppressed the XBP1's phosphorylation on serine residue S348 and SUMOylation on lysine residue K276, leading to accelerating nuclear translocation of XBP1. Thus, U0126 could be a suitable target for ameliorating the DCM complications (86).

Diabetic cataract (DC) is considered a significant cause of visual impairment in patients with T1DM. High glucose concentration in blood can promote the development and progression of age-related cataracts in patients with T2DM (88, 89). Previously, it was identified that oxidative stress could provoke various PTM, such as SUMOylation (90, 91) and deacetylation (92, 93). Also, NFκB plays a crucial role in regulating oxidative stress, which contributes to DC (94-96). Han et al. showed that IκB SUMOylation and NFκB p65 deacetylation could enhance NFκB p65 activity in human lens epithelial cells (HLECs) in high glucose media. Therefore, it would play an essential role in controlling DC (97).

Immune-mediated islet inflammation (insulitis), the pathologic hallmark of T1DM, is characterized by infiltration of the immune cell around and within the islets, resulting in progressive destruction of islet beta cells and eventually lifelong insulin requirement (98). Recently, it has been demonstrated that M2 macrophages are involved in insulitis and T1DM (99), and subsequently, adoptive transfer of these macrophages attenuates insulitis progression (100, 101). In addition, dysregulation of Ubc9-mediated Nrf2 SUMOylation in beta cells is associated with oxidative stress and beta cells apoptosis (26). Wang et al. revealed that impaired SUMOylation in Ubc9 knockout (KO) mice resulted in higher diabetes incidence than WT controls and a higher insulitis severity. Mechanistically, SUMOylation of IRF4 promotes its stability,

thereby transcribing IL-4 and arginase 1 (Arg1) to induce the polarization of M2 macrophages (102).

Another clinical concern in patients with diabetes is the management of the wound. Several studies revealed delayed or impaired wound healing in diabetes (103). In a recent study, Astragaloside IV (the main active ingredient in astragalus) promoted angiogenesis and improved wound healing *in vitro* and *in vivo* in diabetic rats through SUMOthe -dependent pathway (104).

In nonobese diabetic mice (NOD mice), the SUMO1 protein induces immune deviation and suppresses Th2 cells by inhibiting the IL-4 promoter in a C-maf-dependent manner. C-maf is a critical transcription factor necessary for effective IL-4 transcriptional activity and a normal Th2 response. However, due to unknown reasons, Th2 activity is impaired during T1DM. One study showed that SUMO1 modification in the C-maf protein might exacerbate the inflammatory response associated with T1DM due to an imbalance in Th1/Th2 response (105).

Another study demonstrated that age-dependent attenuation of C-maf SUMOylation could positively regulate IL-21-dependent diabetogenesis. Also, this study identified that C-maf SUMOylation has more significant effects on the pathogenesis of T1DM than it does on the expression of C-maf (106).

2.7. SUMO genes polymorphisms in the pathogenesis of diabetes

Recent studies showed that the NFκB signaling pathway is associated with the pathogenesis of T1DM and T2DM (107-110). SUMO4 can act as an antioxidant agent by inhibiting the NFκB pathway, which results in the induction of survival and inhibition of beta-cell destruction (110). Although in Chinese populations and Japanese patients, this SUMO4 M55V SNP is associated with susceptibility to T2DM (4, 21, 107), the exact relation is under debate. It seems to be due to differences in the genetic background of racial groups (111). It has been shown that SUMO c.163 G>A polymorphism is associated with susceptibility to diabetic nephropathy in north Indian T2DM patients (112), and this polymorphism is associated with the severity of diabetic nephropathy (70). In contrast, Fallah et al. identified no association between the SUMO4 M55V variants and susceptibility to T2DM in Iranian subjects (113).

In addition, SUMO4 is associated with the pathogenesis of T1DM, mainly due to its increased renal expression (110, 114, 115). Cells derived from liver carcinoma (HepG2 cells) transfected with SUMO4M-containing vectors express heat shock protein transcription factors (HSFs) and NFκB to a much greater extent than cells transfected with SUMO4V-containing vectors. SUMO4M (the methionine-containing variant) may be more closely related to the inflammatory responses known to occur in the pathogenesis of T1DM (116). It has been shown that NFκB activity can be enhanced via SUMO4 M55V polymorphism by inhibiting the binding of IκBα to SUMO4 and subsequently increasing the expression of NFκB and IL-1β (110).

According to various case/control studies on SUMO4 M55V SNP, the G allele (valine 55) prevalence is higher in American patients with T1DM (110, 114). A similar study in the United Kingdom showed that the prevalence of the A allele (methionine 55) is more significant (117, 118). SUMO4 M55V SNP and T1DM association have also been confirmed in Korean and Asian patients (119, 120). Consequently, SUMO4 M55V SNP is directly involved in the pathogenesis of T1DM in Chinese infants (121). In addition, a meta-analysis confirmed the association between SUMO4 M55V SNP and the development of T1DM in Asians and Europeans (122). In contrast, It was found that SUMO4 M55V SNP had no significant correlation with the risk of T1DM in Swedish and Latvian patients (123, 124). In a study by Caputo et al. in Argentina, there was no significant association between SUMO4 163A/G SNP and autoimmune diabetes in patients with T1DM, and patients with latent autoimmune diabetes in adults (LADA), and healthy controls (125). Also, in Indians, there was no association between SUMO4 A163G SNP and the risk of T1DM diabetes (126).

Autoimmune-based diabetes mellitus is highly associated with microvascular complications such as retinopathy, nephropathy, and neuropathy. Furthermore, it has been reported that in Swedish patients, the SUMO4 M55V functional polymorphism (both in homozygote and heterozygote genotypes) and diabetes-modulated retinopathy are directly dependent. Thus, it may be that post-translational modification by SUMO4 in diabetes causes ocular damage like retinopathy (127).

Conclusions

In recent years, *in vitro* and *in vivo* studies on the SUMO system provide new insights into the mechanisms which lead to the regulation of several factors involved in the pathogenesis of diabetes mellitus. SUMOylation, directly and indirectly, affects insulin secretion, diabetes nephropathy, regulation of GLUT4 in muscles, and genes involved in inflammation (Table 1). Therefore, dysregulation of SUMO function could potentially contribute to the progression of diabetes and its associated complications. With the development of the latest research tools, it is now possible to improve our understanding of SUMOylation in these processes. Potential novel therapeutic strategies could be developed for diabetes since SUMO has a crucial role in modulating the immune system, protein modification, and biological pathways. As an essential modulator in the pathogenesis of diabetes, SUMO will provide us with potential targets for the design of novel therapeutic agents in the future.

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Table 1. Characteristics of studies on SUMO and SUMOylation effects on Diabetes Mellitus.

SUMO finding/pattern	Species	Results	Ref.
SUMO4 M55V polymorphism	Latvian Autoimmune diabetes patients	No significant association between SUMO4 M55V and T1D susceptibility	(124)
SUMO4 M55V polymorphism	Asian-Indians autoimmune T1D patients	No significant association between SUMO4 M55V and T1D susceptibility	(126)
SUMO4 M55V polymorphism	Chinese children with T1D	Significantly association between the SNP and susceptibility to T1D SUMO4 163G allele and 163GG genotype were significantly increased in T1D patients.	(121)
SUMO4 M55V polymorphism	Experimental model and diabetic patients	An M55V Polymorphism in SUMO-4 differentially activates heat shock transcription factors and increases susceptibility to T1D. HepG2 cell line transfected with SUMO4-expressing vectors showed suppression of NF-κB and activation of heat shock factor transcription factors.	(116)
SUMO1 and Ubc9	Non-obese diabetic mice model (NOD)	SUMO1/Ubc9 conjugation with c-Maf leads to IL4 promoter down-regulation and reduced Th2 response in the NOD mice model	(105)
Not mentioned	SENP1-deficient mice	SENP1-mediated NEMO deSUMOylation in adipocytes limits inflammatory responses and T1D progression.	(80)

SUMO3 and PIASγ	Mouse MIN6 cells	SUMOylation of HNF-1A by SUMO3 and its interaction with PIASγ leads to HNF1α repression and Pancreatic dysfunction/diabetes progression	(43)
PIASγ and MafA	Mouse insulinoma-derived MIN6 cell line	PIASy negatively regulates the promoter of insulin gene via the SUMOylation-independent mechanism	(49)
PIAS1 and PPARγ	HUVECs	PIAS1-ROS- IKK pathway plays a crucial role in SUMOylation of PPARγ and results in IR	(66)
SUMO1	HUVECs and diabetic rats	Astragaloside IV promoted the angiogenesis and improved the wound healing *in vitro* and *in vivo* in diabetic rats through a SUMO-dependent pathway	(104)
Not mentioned	Diabetic model of C57/BL6 mice	treatment with U0126 significantly suppressed the XBP1's phosphorylation and SUMOylation, leading to accelerating nuclear translocation of XBP1	(86)
SUMO1	HLECs	IκB SUMOylation and NFκB p65 deacetylation could enhance NFκB p65 activity in high glucose media	(97)
SUMO1	Isolated islets from NOD/ShiltJ and C57BL/6J mic	SUMOylation of Pdia3 exacerbates the proinsulin misfolding and ER stress in pancreatic beta cells	(48)
SUMO1 and SUMO2/3	Diabetic mice and BMDMs	SUMOylation of IRF4 promotes its stability, thereby transcribing IL-4 and arginase 1 (Arg1) to induce the polarization of M2 macrophages	(102)
SUMO1	INS-1E cell line	SUMOylation may play an inhibitory role in the regulation of insulin exocytosis	(37)
SUMO1	Myc-GLUT4 expressing L6 myocytes	Identified no evidence that changes in SUMOylation levels had any effect on GLUT4 trafficking to the cell surface in L6 myocytes	(75)
SUMO1	Endothelial IR model and adenovirus infection in rats	Over-SUMOylation of PPARγ induces an endogenous SUMOylation cascade and leading to IR and dysfunction of vascular endothelium through negative regulation of eNOS-NO signaling	(69)
Not mentioned	CD4+ T-cells of NOD mice	Attenuation of c-Maf SUMOylation in CD4+ T-cells is positively correlated with the IL-21–mediated diabetogenesis in NOD mice.	(106)
SUMO4 M55V polymorphism	TID patients and HEK293, COS7, and 3T3 cell lines	The SNP resulted in 5.5 times more significant NFκB transcriptional activity and ∼2 times greater expression of IL-12B as an NFκB-dependent gene.	(110)
SUMO4 M55V polymorphism	Latent autoimmune diabetes in adults (LADA) and T1D	No association between SUMO4 163 AG polymorphism with autoimmune diabetes	(125)
SUMO4 M55V polymorphism	Asian T1D patients	Significantly association between the SNP and susceptibility	(120)

SUMO4	Asian T1D patients	Association between the SUMO4 gene with susceptibility to T1D	(115)
SUMO4 M55V polymorphism	Patients with T1D	No effect of the polymorphism on diabetic neuropathy or diabetic nephropathy Markedly reduced prevalence of diabetic retinopathy in heterozygous or homozygous patients for the SNP	(127)
SUMO4 M55V polymorphism	Iranian T2D patients	No association between the SUMO4 M55V variants and susceptibility to T2D	(113)
SUMO4 c.163 G>A polymorphism	North Indian subjects with T2D	Association between the polymorphism and susceptibility to diabetic nephropathy	(112)
SUMO4 M55V polymorphism	Patients with T2D	Association between the polymorphism and severity of diabetic nephropathy	(70)
SUMO4 M55V polymorphism	Japanese T2D	Association between the SUMO4 gene with susceptibility to T2D	(4)

Abbreviation: SUMO, Small Ubiquitin Modifier; **Ubc9**, SUMO-conjugating enzyme; **PIAS3**, Protein Inhibitor of Activated STAT 3; **T1D**, Type-1 Diabetes; **T2D**, T2D; **SNP**, Single Nucleotide Polymorphism; **NOD**, Non-Obese Diabetic mouse; **NEMO**, NF-kappa-B Essential Modulator; **HNF-1A**, Hepatocyte Nuclear Factor-1alpha; **HUVECs,** Human Umbilical Vascular Endothelial Cells; **HLECs**, Human Lens epithelial cells; **Pdia3**, Protein Disulfide Isomerase a3; **BMDMs**, Bone Marrow-Derived Macrophages; **PPARγ**, Peroxisome Proliferator-Activated Receptor γ; **IR**, Insulin Resistant; **XBP1,** X-box- Binding Proteins

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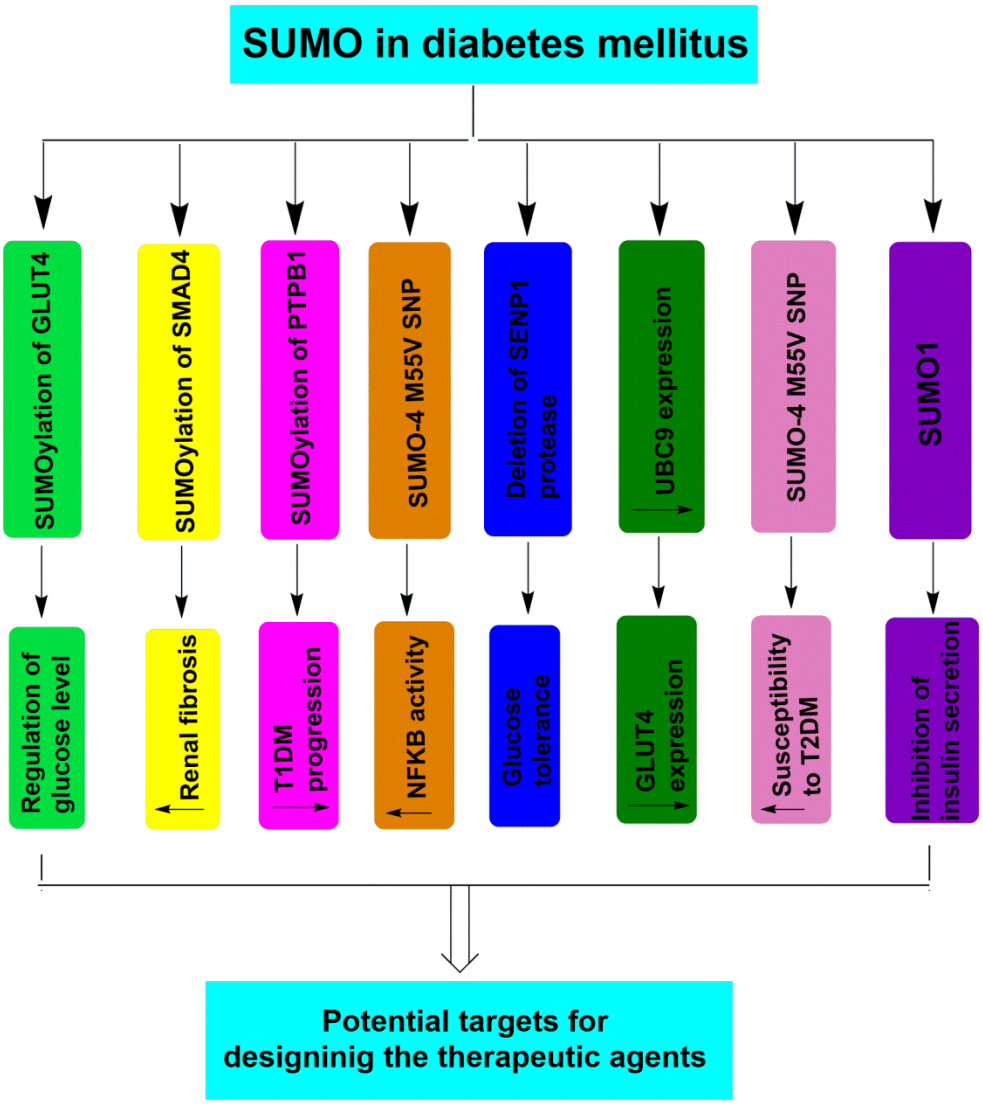
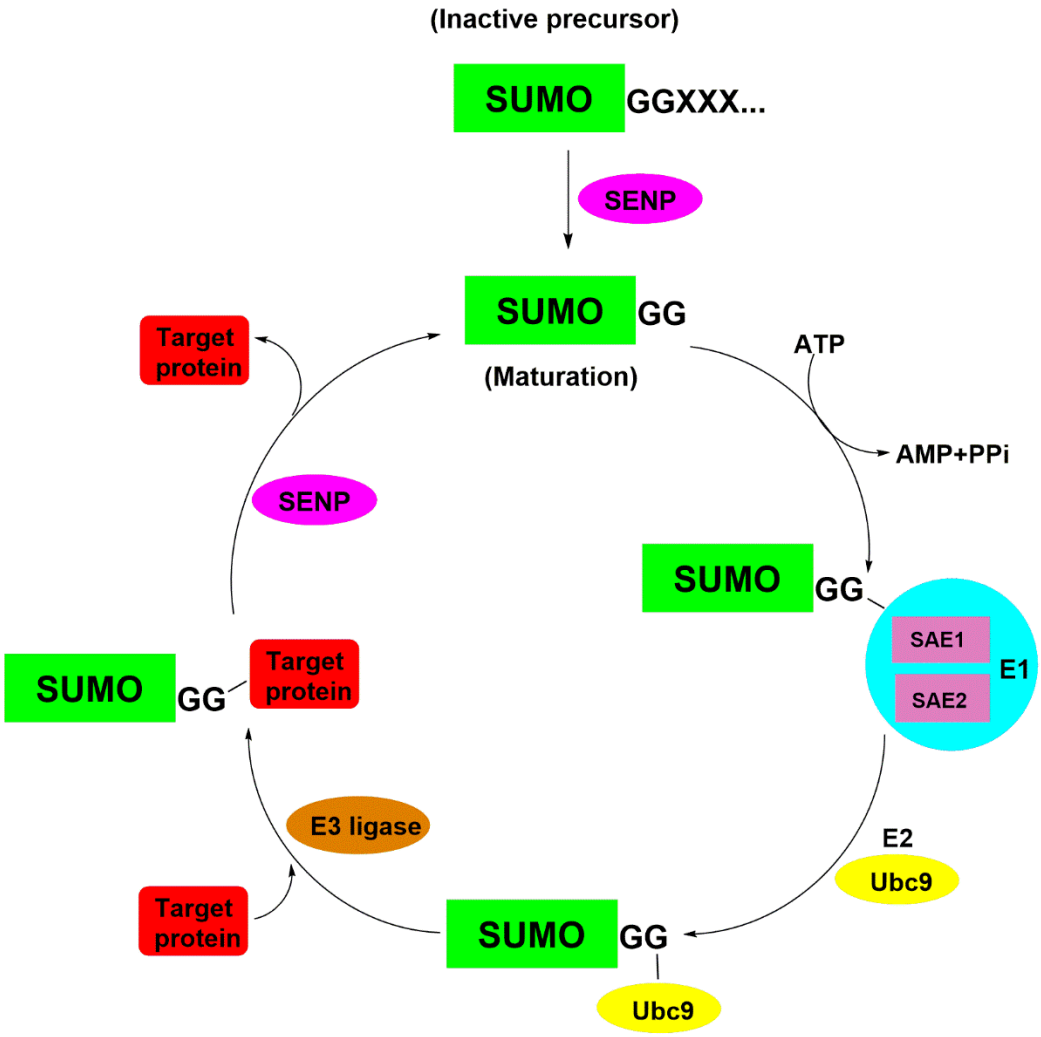


686

687 **Figure 1.** A graphical abstract of SUMO/SUMOylation in diabetes mellitus which provides us
688 potential targets for designing the novel therapeutic agents in the future**.**



689

690 **Figure 2. Schematic presentation of SUMO cycle.** SUMO proteases, SENPs, maturate inactive
691 precursors of SUMO to expose their di-glycine C-terminus motif and then activate by E1 activating
692 enzyme that is a heterodimer of SAE1/SAE2 subunits. Activated SUMO binds to E2 Ubc9 via
693 trans-strification for facilitating SUMO protein binding to a lysine residue of the target protein by
694 E3 ligating enzyme. SUMO E3 ligase is an adaptor between SUMO-Ubc9 and the substrate. It
695 plays a key role in the efficient and targeted SUMO modification of the substrate. SENP proteases
696 cause DeSUMOylation of the substrate to use SUMO for another SUMOylation pathway (128).