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COMMENTARY

A post-translational balancing act: the good and the bad of SUMOylation in pancreatic islets

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Abstract

Post-translational modification of proteins contributes to the control of cell function and survival. The balance of these in insulin-producing pancreatic beta cells is important for the maintenance of glucose homeostasis. Protection from the damaging effects of reactive oxygen species is required for beta cell survival, but if this happens at the expense of insulin secretory function then the ability of islets to respond to changing metabolic conditions may be compromised. In this issue of *Diabetologia*, He et al (https://doi.org/10.1007/s00125-017-4523-9) show that post-translational attachment of small ubiquitin-like modifier (SUMO) to target lysine residues (SUMOylation) strikes an important balance between the protection of beta cells from oxidative stress and the maintenance of insulin secretory function. They show that SUMOylation is required to stabilise nuclear factor erythroid 2-related factor 2 (NRF2) and increase antioxidant gene expression. Decreasing SUMOylation in beta cells impairs their antioxidant capacity, causes cell death, hyperglycaemia, and increased sensitivity to streptozotocin-induced diabetes, while increasing SUMOylation is protective. However, this protection from overt diabetes occurs in concert with glucose intolerance due to impaired beta cell function. A possible role for SUMOylation as a key factor balancing beta cell protection vs beta cell responsiveness to metabolic cues is discussed in this Commentary.

Keywords Apoptosis · Diabetes · Insulin · Islets · Oxidative stress · Redox · Secretion · SENP1 · SUMOylation · UBC9

Abbreviations

GRX1	Glutaredoxin 1
GSH	Glutathione
NRF2	Nuclear factor erythroid 2-related factor 2
PTM	Post-translational modification
ROS	Reactive oxygen species
SENP	Sentrin-specific protease
STZ	Streptozotocin
SUMO	Small ubiquitin-like modifier

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Introduction

Appreciation is growing for the complex role that protein post-translational modifications (PTMs) play in the regulation of cellular signalling [1]. Few, if any, cell functions are not impacted by some form of regulatory PTM, and within pancreatic islets, a diverse array of PTM pathways impact islet biology, including hormone secretion [2], gene transcription [3] and survival [4]. Protein phosphorylation is the best studied, and is a long-known regulator of islet function [5]. Recent phospho-proteomics approaches have begun to identify novel signalling pathways involved in the physiology, diabetes pathophysiology and drug responses of islets [6–8]. These have shed important light on the regulation of beta cell function and survival. However, we have only scratched the surface in our understanding of PTM pathways that play important roles in pancreatic islets, and many other post-translational mechanisms remain to be more fully examined.

The small ubiquitin-like modifier (SUMO) peptides are covalently attached to target proteins and modify target localisation, function and protein–protein interaction. This

post-translational process, called SUMOylation, requires the E2 SUMO-conjugating enzyme UBC9 and is reversed by sentrin-specific proteases (SENPs) [9]. SUMOylation, and, in particular, the SUMO1 protein, was identified by multiple laboratories [10] and initially studied extensively as a regulator of transcription [11]. SUMOylation is now known to have well-defined roles outside the nucleus; for example in the regulation of glucokinase activity [12], mitochondrial dynamics [13] and exocytosis [14]. Knockout of *Ubc9* or key SENP genes results in embryonic lethality [15]. However, in their new study, He et al [16] examine the impact of either upregulating or knocking out *Ubc9* in pancreatic beta cells using inducible and tissue-selective approaches; work that highlights both negative and positive roles for SUMOylation in beta cell function and survival.

SUMOylation and the islet

He et al generated mice with either an inducible overexpression or ablation of *Ubc9* in pancreatic beta cells to either up- or downregulate SUMOylation, respectively. In both lines, manipulation of *Ubc9* has deleterious consequences for beta cell function. However, the aetiology and severity of beta cell dysfunction in each model is distinct, and the longer term metabolic outcomes are different (Fig. 1). Induction of *Ubc9* knockout reduces SUMOylation, initially impairs glucose tolerance, and ultimately causes fasting hyperglycaemia and overt diabetes. This results from early reductions in islet insulin content and granule number, but not an impairment in glucose-stimulated insulin secretion per se (since fractional insulin release was unaffected), followed later by an induction of apoptosis and near-complete loss of beta cell mass. Thus, the main phenotype of the beta cell *Ubc9* knockout mice is the gradual destruction of beta cells. This is consistent with one of the first roles ascribed to SUMOylation: cell protection [17]. Indeed, these mice are highly sensitive to streptozotocin (STZ)-induced diabetes.

Induction of *Ubc9* expression in beta cells increases SUMOylation, but this also results in glucose intolerance. However, the phenotype of these mice is distinct from the knockouts in that the *Ubc9* overexpressers do not develop fasting hyperglycaemia and show a complete preservation of beta cell mass, insulin content and granule content. Impaired insulin secretion from the *Ubc9* overexpressing beta cells seems to represent a true secretory defect, since fractional insulin secretion is decreased in this case. Despite being glucose intolerant, these mice are protected from STZ-induced beta cell loss, hyperglycaemia and diabetes. In short, He et al show that decreasing SUMOylation causes diabetes by inducing (and sensitising) beta cell apoptosis, while increasing SUMOylation protects against beta cell loss while reducing beta cell function.

These observations are in line with what my laboratory [14, 18, 19] and others [12, 20] have shown using complementary models, including in human islets. We know, for example, that increasing SUMOylation blunts glucose-stimulated insulin secretion by directly inhibiting insulin exocytosis [14, 21], and that islet *Senp1* knockout results in glucose intolerance without affecting islet mass or insulin content [18]. Conversely, upregulating *Senp1* causes impaired insulin secretion while inducing beta cell apoptosis and sensitising to IL-1β-induced islet dysfunction and death [19]. In this study, increasing SUMOylation either by SENP1 knockdown or *Sumo1* overexpression protected islets from IL-1β-induced apoptosis [19]. Thus, the overall level of SUMOylation in beta cells is important for determining the balance between cell survival and secretory function (Fig. 1).

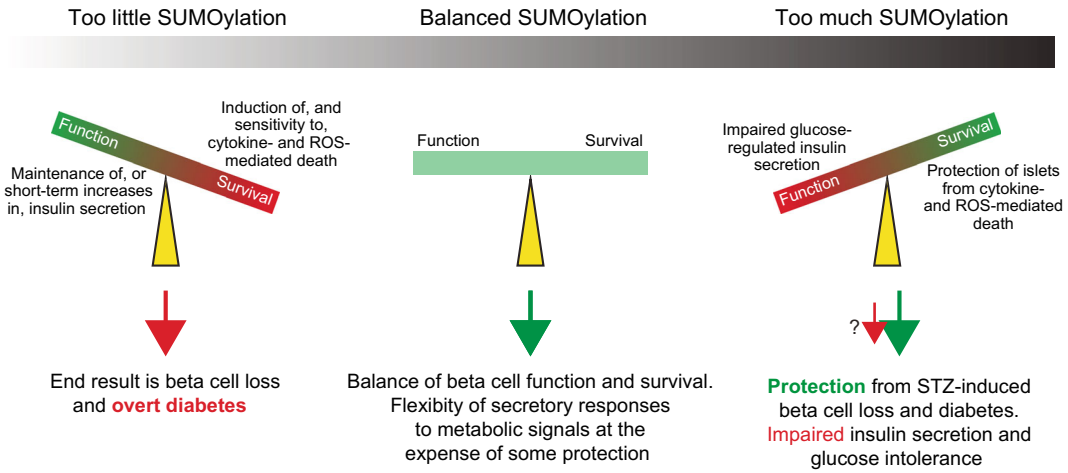

Fig. 1 SUMOylation balances beta cell survival vs function. Loss of SUMOylation leaves beta cells vulnerable to damage and loss due to a deficient antioxidant capacity, which is already notoriously low under normal circumstances. This can lead to hyperglycaemia and diabetes. Upregulation of SUMOylation is protective and can prevent overt hyperglycaemia, but impairs the physiological regulation of insulin secretion and causes glucose intolerance

In the context of STZ-induced beta cell damage (and presumably in type 1 diabetes), increased SUMOylation will protect beta cells from death at the expense of impaired glucose-stimulated insulin secretion, thus preventing fasting hyperglycaemia. This illustrates the importance of beta cell mass in protecting against fasting hyperglycaemia even when islet function is poor. So, why not simply maintain a high level of SUMOylation to increase beta cell protection? In models of high metabolic demand and insulin resistance, such as high-fat-fed mice or human obesity, beta cells must increase their secretory capacity [22]. In the short term at least, metabolic signalling to the plasma membrane via SENP1 amplifies the secretory capacity of beta cells in response to increasing glucose [18]. Perhaps the ability to downregulate SUMOylation via this pathway contributes to the flexibility of beta cell secretory capacity in response to metabolic status. In this sense, it will be interesting to see whether upregulation of islet SUMOylation is protective in high-fat-fed mice, or whether the impaired secretory function prevents islet adaptation, which ultimately could outweigh the beneficial effects of beta cell protection alone.

Downstream SUMO-dependent mechanisms in islets

SUMOylation at the plasma membrane is now reasonably well-appreciated as a mechanism regulating ion channels and receptors, including the glucagon-like peptide-1 receptor in beta cells [20]. My group and others have also shown that SUMOylation regulates exocytotic membrane fusion [14, 23], and this appears to be mediated by direct SUMOylation of exocytotic proteins and consequent regulation of protein–protein interactions amongst members of the secretory machinery [21]. Intriguingly, SUMOylation is suggested to both increase and decrease exocytosis (for a review, see [24]). This may be cell-type specific (perhaps depending on the complement of exocytotic proteins), including amongst islet cell types where SUMOylation enhances glucagon exocytosis [25] but acts as a brake on beta cell exocytosis [14]. In order for a robust insulin secretory response to occur, this brake must be released by one (or more) deSUMOylation events that occur far down the secretory pathway [18], as evidenced by the build-up of 'unreleasable' insulin granules at the plasma membrane of beta cells when SUMOylation is upregulated [14].

One of the initial studies that identified the SUMO1 peptide (called sentrin by that group) demonstrated a role for the protein in protection from Fas- and TNF-induced cell death [17]. Indeed, consistent with the findings of He et al, many studies suggest that SUMOylation is protective [26], although this also may be cell-type or context specific [27]. In islets, SUMOylation protects against IL-1β-induced death and dysfunction by preventing IL-1β-induced caspase 3 cleavage, NFκB translocation and induction of inducible nitric oxide synthase (iNOS) [19]. The capacity of beta cells to handle nitrosative and oxidative stress is regulated in part by nuclear factor erythroid 2-related factor 2 (NRF2) [28], a transcription factor that controls the expression of antioxidant genes (particularly those related to the glutathione pathway). Similar to beta cell UBC9, NRF2 expression in beta cells protects against iNOS-induced islet dysfunction and glucose intolerance [28], and against palmitate-induced oxidative stress [29]. He et al nicely link UBC9 and NRF2 by showing that SUMOylation regulates the nuclear localisation and stability of NRF2, likely by preventing its ubiquitin-mediated proteasomal degradation. Loss of *Ubc9* leads to reduced NRF2 stability and impaired expression of antioxidant genes, which predisposes beta cells to STZ-induced damage, while *Ubc9* upregulation stabilises NRF2 to promote protection from STZ-induced diabetes.

Redox and oxidative stress interactions with islet SUMOylation

He et al demonstrate that loss of NRF2 SUMOylation impairs the antioxidant capacity of beta cells. Indeed, this is likely to account for the increased susceptibility of these mice to STZ-induced diabetes. Importantly, oxidative stress itself is well documented to control SUMOylation [30]. The effects of reactive oxygen species (ROS) on SUMOylation are complex, and may directly activate or inhibit the activity of both the SUMO-conjugating or SUMO-protease enzymes. Thus, while loss of SUMOylation sensitises ROS-mediated beta cell loss, the degree to which metabolic stress or immune attack influence SUMOylation per se is unclear. The ability of high glucose culture, presumably a state of oxidative stress, to upregulate SUMO transcripts and UBC9 protein hints that this could be a feed-forward mechanism [20]. Also, recent work has suggested that palmitate-induced oxidative stress transiently increases NRF2 protein levels [29], although it is not yet known whether this results from a SUMO-dependent stabilisation.

While pathophysiological oxidative stress impacts cellular SUMO pathways (and vice versa), so too do physiological metabolism-driven redox signalling pathways [24]. My group has proposed that insulin secretion is amplified in part by the mitochondrial export of reducing equivalents which act via a classical glutathione–glutaredoxin 1 (GSH–GRX1) signalling pathway to reduce SENP1 thiol groups, increasing its catalytic activity [18]. This deSUMOylates exocytotic proteins to release the SUMO brake on insulin exocytosis [14, 21]. Effectively, this metabolism-driven redox-SENP1 pathway plays an important role controlling the magnitude of insulin secretory responses, depending on the metabolic state of the beta cell. Oxidative stress may interfere with this redox-

dependent signalling mechanism, essentially by co-opting the GSH–GRX1 pathway into a protective role at the expense of islet function.

Perspective

Much remains to be understood about the role(s) for SUMOylation in islet function and survival, and potential contributions of this in diabetes. Interactions between SUMOylation and cellular redox-dependent pathways contribute both to beta cell survival [31] and insulin secretion [24]. The extent to which these pathways overlap is unclear, and the possibility that the metabolic control of deSUMOylation-facilitated insulin secretion is itself directly disrupted by oxidative stress is an intriguing one. Likewise, an impact of metabolism-induced oxidative stress on SUMO pathways that control cell survival, like the UBC–-NRF2 axis identified by He et al, seems possible. Most approaches to study SUMOylation in beta cells have been indiscriminate, via the modulation of global (de)SUMOylation in the cell rather than specific SUMO-targets or pathways. We clearly need to look more closely at specific pathways by dissecting roles of various E3 ligases, SENP isoforms or subcellular compartments. This may be aided by approaches to better elucidate the SUMO-modified proteome in islets, and to determine how this is regulated by redox signalling and in diabetes. In this way we might better understand how beta cells regulate the important balance between maintaining cell function and promoting cell survival, and how we might tip that balance in one direction or another in the treatment of type 1 and type 2 diabetes.

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Contribution statement PEM drafted and revised this article and is responsible for approval of the final published version.

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