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The Roles of SUMO in Metabolic Regulation

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Abstract

Protein modification with the small ubiquitin-related modifier (SUMO) can affect protein function, enzyme activity, protein-protein interactions, protein stability, protein targeting and cellular localization. SUMO influences the function and regulation of metabolic enzymes within pathways, and in some cases targets entire metabolic pathways by affecting the activity of transcription factors or by facilitating the translocation of entire metabolic pathways to subcellular compartments. SUMO modification is also a key component of nutrient- and metabolic-sensing mechanisms that regulate cellular metabolism. In addition to its established roles in maintaining metabolic homeostasis, there is increasing evidence that SUMO is a key factor in facilitating cellular stress responses through the regulation and/or adaptation of the most fundamental metabolic processes, including energy and nucleotide metabolism. This review focuses on the role of SUMO in cellular metabolism and metabolic disease.

Keywords

SUMO; Metabolism; Metabolic disease; One-carbon metabolism; Lipids

9.1 Introduction: Functions of SUMO in Metabolism

Protein modification with the small ubiquitin-related modifier SUMO can affect protein function, enzyme activity, protein-protein interactions, protein stability, protein targeting and cellular localization. The number of identified Sumoylated proteins, and proteins that interact with SUMO through SUMO interacting motifs (SIM), continues to grow (Becker et al. 2013; Bruderer et al. 2011; Eifler and Vertegaal 2015; Hendriks et al. 2014; Impens et al. 2014; Jardin et al. 2015; Jentsch and Psakhye 2013; Kaminsky et al. 2009; Kroetz and Hochstrasser 2009; Lamoliatte et al. 2014; Makhnevych et al. 2009; Subramonian et al. 2014; Tammsalu et al. 2014, 2015; Yang and Paschen 2015; Yang et al. 2012). Like other forms of post-translational modification, sumoylation is now known to be involved in most, if not all cellular processes (Flotho and Melchior 2013; Gareau and Lima 2010; Hecker et al. 2006; Makhnevych et al. 2009; Stehmeier and Muller 2009; Wilkinson and Henley 2010). Sumoylation is a reversible modification: SUMO/sentrin-specific proteases (SENPs) are capable of removing SUMOs from target proteins, contributing to a dynamic control of sumoylation (Flotho and Melchior 2013; Hay 2007; Hickey et al. 2012; Mukhopadhyay and Dasso 2007; Yeh 2009).

Not surprisingly, SUMO is now known to modify and affect the function and/or regulation of specific metabolic enzymes within pathways, and in some cases regulates entire metabolic pathways by affecting the activity of master control proteins or facilitating the translocation of entire metabolic pathways to subcellular compartments (Gareau and Lima 2010). In addition to its established roles in maintaining metabolic homeostasis, there is increasing evidence that SUMO is a key factor in facilitating cellular stress responses. This occurs through the regulation of some of the most fundamental metabolic processes, including energy and nucleotide metabolism, and permits physiological adaptation in response to cellular and environmental queues (Enserink 2015; Makhnevych et al. 2009). SUMO has been implicated in complex human diseases and developmental anomalies that are also associated with nutritional and/or metabolic perturbations including Alzheimer's disease (Dorval and Fraser 2007; Hoppe et al. 2015; Lee et al. 2013, 2014b; Martins et al. 2016; McMillan et al. 2011; Sarge and Park-Sarge 2009), Parkinson's disease (Guerra de Souza et al. 2016) (Eckermann 2013; Krumova et al. 2011), type I diabetes (Li et al. 2005; Wang and She 2008), familial partial lipodystrophy (Simon et al. 2013), diabetes-mediated cardiovascular disease (Chang and Abe 2016), congenital heart disease (Wang et al. 2011), cardiomyopathy (Kim et al. 2015c; Zhang and Sarge 2008), arthritis (Yan et al. 2010), amyotrophic lateral sclerosis (Dangoumau et al. 2016; Foran et al. 2013; Niikura et al. 2014), and cleft lip and/or palate (Alkuraya et al. 2006; Song et al. 2008; Tang et al. 2014).

9.2 SUMO and Transcriptional Regulation of Metabolic Pathways

9.2.1 SUMO and Master Regulation of Lipid Biosynthesis

Cholesterol and fatty acids, which are essential for cellular membrane and lipoprotein particle biosynthesis, can be acquired through diet and/or through cellular biosynthesis (Brown and Goldstein 2009; Goldstein and Brown 2015; Goldstein et al. 2006; Soyal et al. 2015; Weber et al. 2004). Changes in their availability at the cellular level, both deficiencies and excesses, can affect membrane fluidity, the function of membrane-associated proteins, and the maintenance of cellular homeostasis and risk of chronic disease. Many of the enzymes that comprise the cholesterol and fatty acid biosynthesis pathway, as well as proteins required for low density lipoprotein uptake, are regulated at the level of transcription through common feedback loops that involve the sterol regulatory element binding proteins (SREBPs) (Brown and Goldstein 2009; Goldstein and Brown 2015; Goldstein et al. 2006; Jeon and Osborne 2012; Soyal et al. 2015; Weber et al. 2004). SREBPs are members of the family of basic helix-loop-helix leucine zipper (bHLH-Zip) transcription factors and are master regulators that govern the expression of over 30 genes that encode enzymes required for lipid biosynthesis and accumulation. There are three mammalian SREBP isoforms (SREBP-1a, SREBP-1c and SREBP-2) encoded by two genes (SREBP-1 and SREBP-2). SREBP-1a is a master regulator of genes necessary for fatty acid, triacylglyceride and phospholipid biosynthesis, as well as the generation of NADPH and acetyl-CoA cofactors that are required for fatty acid synthesis. SREBP-1a is expressed in proliferating tissues, whereas SREBP-1c is expressed in liver and adipose tissue (Brown and Goldstein 2009; Goldstein et al. 2006; Weber et al. 2004; Yokoyama et al. 1993). SREBP-2 exhibits more ubiquitous expression, but targets cholesterol biosynthesis almost exclusively (Hua et al. 1993; Weber et al. 2004). SREBPs are present in the endoplasmic reticulum as

precursor resident transmembrane proteins in a complex with the lipid-sensing SREBP cleavage-activating protein (SCAP) and the insulin-inducing gene (INSIG), which sequester SREBPs and confine them to the endoplasmic reticulum when membrane cholesterol levels are elevated. SCAP contains a sterol sensing domain, and escorts SREBPs to the Golgi when membrane sterol concentrations are depleted. In the Golgi, SREBPs are processed by two proteolytic cleavage events that liberate the mature protein from the membrane. SREBPs translocate to the nucleus, bind to sterol response elements (SREs) and function to upregulate the expression of genes required for fatty acid and cholesterol biosynthesis (Hirano et al. 2003). Whereas the genes involved in cholesterol biosynthesis are almost exclusively regulated by SREBPs, transcriptional regulation of the genes encoding enzymes required for lipid biosynthesis is complex and responds to many intra- and extracellular signaling pathways (Goldstein and Brown 2015; Weber et al. 2004).

SREBPs that have been liberated from the Golgi by proteolysis are subject to an additional level of regulation in the nucleus by an antagonistic interplay between two posttranslational modifications, sumoylation and phosphorylation (Arito et al. 2008). The SREBPs are targets for the growth-hormone-induced mitogen-activated protein kinases (MAPKs) ERK1 and ERK2. ERK-dependent phosphorylation occurs in close proximity to the site of SUMO modification but elicits very different functional effects on SREBP activity (Arito et al. 2008). Phosphorylation of SREBP-2 at S455 increases its transcriptional activity, whereas SUMO modification at K464 inhibits its activity (Arito et al. 2008). SREBP-2 phosphorylation and sumoylation were shown to be competitive modifications; mutation of S455 to an alanine residue enhances sumoylation whereas the S455G mutant SREBP-2, a phosphorylated SREBP-2 mimic, exhibited impaired sumoylation (Arito et al. 2008). As no direct effects of S455 phosphorylation on SREBP structure or function have been reported, the physiological function of S455 phosphorylation may be to prevent SREBP sumoylation (Fig. 9.1).

SREBP modification with SUMO elicits functional consequences. SREBP sumoylation inhibits SREBP transcriptional activity indirectly through the recruitment of a co-repressor complex that includes histone deacetylase 3 (HDAC3). Following recruitment and establishment of the repressor complex, the SREBP-2 SUMO moiety is likely not essential as most SREBP present in the repressor complex lacks the SUMO modification. HDAC3 activity directly affects lipid homeostasis, as both LDL uptake and expression of the LDL receptor were elevated in HepG2 cells when HDAC3 expression was repressed (Arito et al. 2008). Growth-hormone induced ERK-dependent phosphorylation of SREBPs ensures that lipid synthesis occurs for membrane biosynthesis during periods of growth, whereas sumoylation can repress lipid biosynthesis and attenuate lipid-sensing signals that originate in the endoplasmic reticulum and generate SREBP protein.

There is also evidence that sumoylation of SREBP-1 plays a role in glucagon secretion by the alpha-cells of pancreas. Glucagon reduces hepatic lipid synthesis, and it's been known that SREBP-1c is downregulated by fasting. The metabolic effects of glucagon are mediated through the cAMP-dependent protein kinase A (PKA). It has been recently demonstrated that SREBP-1 is one of the substrates for PKA phosphorylation (Dong et al., 2014). During nutritional deprivation, PKA is activated, resulting in induction of SREBP-1c sumoylation

by PIASy. This cascade results in increased sumoylation of SREBP-1, repression its transcriptional activity, and turning off of hepatic lipogenesis (Lee et al. 2014a). This pathway represents a dynamic fine-tuning of SREBP-1 transcriptional activity in response to various nutritional and hormonal changes to turn off lipid synthesis during fasting or nutritional deprivation. Thus, sumoylation of SREBPs plays an important role in the suppression of the hepatic lipogenic program upon fasting-induced signals.

9.2.2 SUMO and Metabolic Nuclear Receptors

Many metabolic pathways are regulated by the orchestrated action of nuclear receptors (NRs) that exert crucial functions by regulating gene expression, both positively and negatively, in response to changes in metabolite levels (Treuter and Venteclef 2011). Nuclear receptors are a class of cellular proteins that have the ability to sense and respond to the changes in concentration of various small molecules that specifically bind to the receptor and serve as receptor ligands. NRs are generally divided into 3 classes based on the nature of their ligands: **(1)** The first group consists of nuclear receptors that bind steroid hormones, such as the glucocorticoid receptor (GR), receptor (GR), the mineralocorticoid receptor (MR) and the estrogen receptor (ER); receptor (ER); **(2)** The second group consists of orphan nuclear receptors for which ligands has not been yet identified, such as the estrogen-related receptors alpha (ERR α) and gamma (ERR β); upon identification of the ligand, the orphan NRs usually are reclassified and leave this subgroup; **(3)** The third group is comprised of ligand-dependent NRs that are regulated by a diverse group of endogenous and exogenous small molecules, such as PPARs, which bind fatty acids and fatty acid metabolites, liver X receptors (LXRs), which bind oxysterols, Farnesoid X receptor (FXR), which binds bile acid, and retinoic acid receptors (RXR), which bind retinoic acid but can also respond to other ligands by forming heterodimers with other NRs. Several of the NRs are targeted by synthetic ligands in therapy: RXR and its fusion product RXR-PML are targeted by retinoic acid administration in acute promyelocytic leukemia, ER α (NR3A1) is targeted in breast cancer by the synthetic antagonist tamoxifen, GR is targeted in inflammatory diseases by dexamethasone, peroxisome proliferator-activated receptor gamma (PPAR γ) is targeted in type II diabetes by administration of thiazolidinediones (Germain et al. 2006). Sumoylation modulates the transcriptional activities of many NRs, thus affecting metabolism (summarized in Table 8.1). More than 20 nuclear receptors have been reported to be reversibly sumoylated (Treuter and Venteclef 2011). Other modifications of nuclear receptors can inhibit their sumoylation. Acetylated FRX cannot be sumoylated, leading to activation of inflammatory genes (Kim et al. 2015b). In fact, acetylation of SUMO protein itself prevents SUMO binding to proteins containing SIMs.

9.3 SUMO in Familial Partial Lipodystrophy

Familial partial lipodystrophy (FPLD) is a metabolic disorder characterized by abnormal regional and progressive adipose tissue loss after puberty due to adipocyte degeneration. FPLD is often associated with insulin-resistant diabetes with acanthosis nigricans and hypertriglyceridemia. A subset of FPLD cases, also called Dunnigan-type familial partial lipodystrophy, or familial partial lipodystrophy type 2 (FPLD2), is caused by mutations in LMNA gene encoding structural nuclear proteins Lamin A and C (Cao and Hegele 2000;

Speckman et al. 2000). Lamin A/C is sumoylated (Boudreau et al. 2012; Zhang and Sarge 2008) and also binds SUMO through a SUMO-interacting motif (SIM) (Moriuchi et al. 2016). Lamin A mutations linked to familial partial lipodystrophy alter lamin A sumoylation (Simon et al. 2013). The FPLD-causing mutations decrease lamin A binding to SREBP1 and upregulate a large number of SREBP1 target genes (Lloyd et al. 2002; Vadrot et al. 2015). Thus, a model has been proposed where lamin A K486 modification by SUMO blocks binding of interacting proteins, including SREBP1 (Simon et al. 2013). These studies implicate altered lamin A sumoylation in familial partial lipodystrophy; however, the molecular mechanisms of FPLD and the metabolic consequences of altered lamin A sumoylation remain to be elucidated.

9.4 Metabolic Adaptation to Cellular and Oxidative Stress

Metabolic response to cellular stress is essential to maintain cell viability and reestablish homeostasis, and several observations indicate a key role for SUMO as a component of the metabolic stress response (Enserink 2015; Guo and Henley 2014; Nunez-O'Mara and Berra 2013; Yang et al. 2014; Zhou et al. 2004). Hibernation torpor has been used as a model system for studying reduction in blood flow to various organs and thus oxygen and glucose starvation in those tissues. During torpor of ground squirrels, a substantial increase in global sumoylation was observed within brain, liver, and kidney tissues which occurred coincident with increased Ubc9 expression in these tissues (Lee et al. 2007). Likewise, Ubc9 over-expression was shown to protect SH-SY5Y neuroblastoma cells in response to oxygen and glucose starvation, and mice subjected to transient ischemia also showed an increase in SUMO2/3 conjugates in the hippocampus and cerebral cortex (Cimarosti et al. 2008; Yang et al. 2008a, b, c). Hippocampal HT22 cells exposed to arsenite, an inducer of oxidative stress and inhibitor of pyruvate dehydrogenase also increased global protein sumoylation (Yang et al. 2008c). In primary cortical neuronal cultures from rodents and in SH-SY5Y human neuroblastoma cells, sumoylation participates in induction of ischemic tolerance (Lee et al. 2009b). Transgenic mouse lines that overexpress Ubc9 up to 5-fold higher than the wild type mice exhibit resistance to brain ischemia (Lee et al. 2011). These data support a role of sumoylation in cytoprotection responses elicited by cellular stresses (Lee et al. 2014c, 2016b; Tong et al. 2015; Lee and Hallenbeck 2013; Yang et al. 2012).

Although not thoroughly characterized, SUMO-2/3 may play a role in response to cellular stresses such as protein damage (Seifert et al. 2015). In adult differentiated cells, a very small pool of unconjugated SUMO-1 is present in the cell whereas a much larger pool of free SUMO-2/3 is available (Saitoh and Hinchey 2000). Upon exposure to protein-damaging insults such as heat shock, oxidative stress, ethanol, osmotic stress, or replicative stress, an increase in the amounts of SUMO-2/3 conjugated proteins occurs (Bursomanno et al. 2015; Manza et al. 2004; Saitoh and Hinchey 2000). It has been suggested that the activation of SUMO-2/3 conjugation under these conditions stabilizes and thereby increases protein half-lives to enable cell survival. Some debate surrounds the role of reactive oxygen species (ROS) in the SUMO-mediated cell survival. Studies demonstrating an increase in SUMO-2/3 conjugates in response to stress is in contrast to reports that ROS negatively regulates Ubc9 catalyzed sumoylation (Bossis and Melchior 2006). Under physiologically relevant concentrations of H₂O₂, it has been observed that nearly all SUMO conjugation is

inhibited as a result of the formation of a disulfide linkage between the catalytic cysteines of Uba2 and Ubc9 (Bossis and Melchior 2006). Sumoylation is a reversible post-translational modification and sentrin specific proteases (SENP) can efficiently and rapidly desumoylate proteins (Flotho and Melchior 2013). Because the activity of SENPs is unaffected by H₂O₂, ROS exposure is anticipated to result in the rapid deconjugation of sumoylated proteins. Indeed, the regulation of sumoylation by ROS may function to control the redox state of the cell during oxidative stress. In support of this concept, sumoylation represses the transcriptional activity of c-Fos and c-Jun which are potent regulators of oxidative stress responsive genes (Bossis et al. 2005; Tempe et al. 2014).

The promyelocytic leukemia (PML) protein is the main constituent and a scaffold of PML nuclear bodies (NBs), which assemble in response to stress. During oxidative stress, PML protein is oxidized and forms disulfide-mediated spherical meshes that recruit UBC9, which enhances PML sumoylation (Sahin et al. 2014). Sumoylated PML recruits SUMO-binding proteins that become sequestered within the NB inner core. In response to oxidative stress, NBs promote sumoylation of these so-called partner proteins (Sahin et al. 2014).

9.5 SUMO and Energy Metabolism

9.5.1 SUMO in Muscle Metabolism

Perturbations of energy metabolism in skeletal muscle are associated with metabolic syndromes, and contribute to the mechanisms leading to obesity and obesity related disorders. Peroxisome proliferator-activated receptors (PPARs) are a family of nuclear receptor proteins that function as ligand-activated transcription factors which play essential roles in regulating cellular lipid, protein and carbohydrate metabolism (Desvergne and Wahli 1999; Grygiel-Gorniak 2014). The cellular ligands that activate PPARs include fatty acids, and eicosanoids. The nuclear receptor PPAR β/δ plays a major role in cardiac lipid metabolism, and mice with cardiac-specific deletion of this receptor develop myocardial lipid accumulation and cardiomyopathy (Cheng et al. 2004; Vazquez-Carrera 2016). PPAR β/δ is expressed highly in skeletal muscle, and is a determinant of the oxidative capacity of the cell. PPAR β/δ forms an obligate heterodimer with retinoic acid receptor (RXR or NR2B) (DiRenzo et al. 1997). It initiates transcription of target genes by binding to peroxisome proliferator response elements (PPREs). Selective disruption of PPAR β/δ expression in mouse skeletal muscle myocytes has been shown to lead to the onset of obesity and diabetes (Schuler et al. 2006). Similarly, in other mouse models, selective over-expression of PPAR β/δ in skeletal muscle has been shown to rescue mice from diet-induced obesity by enhancing the expression of genes that encode enzymes in the fatty acid oxidation pathway. Thus, PPAR β/δ is a key regulator of fat accumulation (Wang et al. 2004). Another key regulator of lipid metabolism, Krüppel-like transcription factor 5 (KLF5) is present in nuclear protein complexes with PPAR β/δ and these two proteins interact in mammalian two-hybrid and co-immunoprecipitation experiments (Oishi et al. 2008). KLF5^{+/-} mice are resistant to diet-induced obesity, hypercholesterolemia, and glucose intolerant phenotypes despite consuming more food than control mice (Oishi et al. 2008).

Sumoylated KLF5 is found in transcriptionally-repressive regulatory complexes with unliganded PPAR β/δ and co-repressors (Table 9.1). This complex represses

carnitine-palmitoyl transferase-1b (Cpt1b), and uncoupling proteins 2 and 3 (Ucp2 and Ucp3) expression, which are regulators of lipid oxidation and energy uncoupling respectively. Cpt1b catalyzes the rate-limiting step in mitochondrial fatty acid import into mitochondria for β -oxidation. Ucp2 and Ucp3 uncouple oxidative phosphorylation from ATP generation and thereby generate heat, but also function to regulate mitochondria-derived ROS. Upon PPAR β/δ ligand binding, KLF5 is desumoylated and becomes associated with transcriptionally active complexes, leading to the enhancement of Cpt1b, Ucp2, and Ucp3 expression (Fig. 9.2). In this regard, KLF5 desumoylation is a component of nutrient signaling within PPAR β/δ containing transcription factor complexes, and acts as a regulatory switch mediating the transcriptional activation of energy consumption (Oishi et al. 2008).

The nuclear receptor peroxisome proliferator-activated receptor α (PPAR α) is highly expressed in tissues with high fatty acid catabolic activity such as skeletal muscle, liver and brown adipose tissue, small intestine, heart, and kidney. It regulates the anti-inflammatory response and energy homeostasis in response to endogenous ligands such as arachidonic acid as well as other polyunsaturated fatty acids (Kersten 2014). It is activated under conditions of energy deprivation and fasting and promotes expression of genes involved in adipose tissue lipolysis. In addition to directly binding DNA and regulating the expression of metabolic genes, PPARs can also regulate expression of inflammation related genes by inhibiting the activity of other transcription factors via direct protein-protein interactions. This action of PPARs is referred to as transrepression. PPAR α is sumoylated by SUMO-1 on lysine 185 in the hinge region by the activity of the E2-conjugating enzyme Ubc9 and the SUMO E3-ligase PIASy (Table 9.1). SUMO-1 modification of PPAR α leads to the specific recruitment of corepressor NCoR, which results in a decrease of PPAR α trans-activity and down-regulation of a subset of PPAR α target genes (Kim et al. 2015c; Pourcet et al. 2010).

9.5.2 SUMO in Insulin Synthesis and Secretion

The insulin signaling pathway plays an essential role in whole-body glucose homeostasis and in downstream metabolic pathways of energy metabolism. Nutrients and growth hormones promote the production of insulin and lead to the propagation of β -cells in the pancreas. Insulin is secreted from secretory granules within β -cells in response to hyperglycemia. However, the mechanisms whereby β -cells maintain near constant secretory granule stores remain to be fully understood (Mziaut et al. 2006; Trajkovski et al. 2004). Islet cell autoantigen 512 (ICA512) is a key enhancer of insulin gene expression and is an intrinsic granule membrane protein. ICA512 knockout mice have elevated blood glucose levels and impaired insulin secretion, whereas over expression of ICA512 enhances insulin secretion and levels of secretory granules within β -cells. ICA512 is a member of the receptor protein tyrosine phosphatase family but is catalytically inactive. Following granule exocytosis, the cytosolic domain of ICA512 is cleaved generating a soluble cytoplasmic fragment ICA512-CCF, which translocates to the nucleus and, in conjunction with phosphorylated signal transducer and activator of transcription 5 (STAT5), enhances the transcription of genes required for granule synthesis including insulin and ICA512 (Trajkovski et al. 2004). Upon sumoylation of ICA512, the interaction between ICA512 and

STAT5 is weakened, suggesting that ICA512 sumoylation represses the activity of STAT5 and thus regulates insulin production and secretory granule formation (Mziaut et al. 2006).

In pancreatic β -cells, glucose stimulates insulin secretion by a process that involves cell depolarization followed by opening of voltage-dependent Ca^{2+} channels, which leads to insulin granule exocytosis. SUMO1 impairs glucose-stimulated insulin secretion by inhibiting the β -cell exocytotic response to Ca^{2+} . Sumoylation negatively regulates insulin secretion by β -cells by directly and reversibly inhibiting exocytosis in response to an increase in intracellular Ca^{2+} (Manning Fox et al. 2012). The process involves SUMO1 attachment to synaptotagmin VII. The sentrin/SUMO-specific protease-1 (SENP1) is required to reverse SUMO-mediated inhibition of exocytosis and thus rescues glucose-dependent insulin secretion (Dai et al. 2011). NADPH reducing equivalents and reduced glutathione activate SENP1 function, thus increasing insulin secretion (Ferdaoussi et al. 2015). Conversely, overexpression of SENP1 reduces insulin secretion and impairs intracellular Ca^{2+} handling by inducing cell death (Hajmrle et al. 2014). SUMO-1 has an opposite effect on exocytosis in pancreatic α -cells: it enhances exocytosis and glucagon secretion in cAMP-dependent manner (Dai et al. 2014). Recently, a metabolomics profiling of the insuli-noma cell line 832/13 demonstrated a significant glucose-induced changes in purine pathway intermediates: a decrease in inosine monophosphate (IMP) and an increase in adenylosuccinate (S-AMP). SENP1 expression modified the effect of S-AMP on exocytosis in patch-clamp experiments in isolated human islet beta cells, suggesting a functional metabolic link between sumoylation, purine biosynthesis, and glucose-stimulated insulin secretion (GSIS) from human islet beta cells (Gooding et al. 2015). Taken together, these findings implicate SUMO pathway and the redox state of the cell in the regulation of glucose homeostasis. Whether SUMO plays a broader role in NADPH-dependent regulation of exocytosis in other cell types and whether NADPH levels generally play a role in the dynamic regulation of sumoylation and desumoylation in other cellular compartments remains to be determined.

9.5.3 SUMO in Glucose Transport and Metabolism

Glucose transporters (GLUTs) are a family of transmembrane glycoproteins that transport glucose across the plasma membrane (Chen et al. 2015; Giorgino et al. 2000; Thorens and Mueckler 2010). In insulin-responsive tissues including skeletal muscle and adipose, GLUT1 and GLUT4 are expressed. GLUT1 is responsible for basal glucose uptake whereas GLUT4 is responsible for insulin-responsive glucose uptake. The glucose transporters GLUT1 and GLUT4 were the first identified integral membrane proteins that are targets of sumoylation. Although the effects of sumoylation on these transporters are still not well understood, the interaction of Ubc9 with GLUT1 and GLUT4 may play a role in regulating glucose transport. Over expression of Ubc9 in L6 skeletal muscle cells decreased GLUT1 abundance by 65% while increasing GLUT4 abundance 8-fold. This effect is not explained by changes in mRNA levels, but was associated with increased protein stability (Giorgino et al. 2000; Liu et al. 2007). Similarly, Ubc9 over expression in adipocytes led to a decrease in GLUT4 degradation whereas inhibited Ubc9 expression by siRNA increased GLUT4 degradation. Over expression of the catalytically inactive Ubc9-C93A elicited the same effect on protein stability, suggesting that GLUT4 stabilization did not result from SUMO

modification, but rather was the result of Ubc9 binding (Liu et al. 2007). GLUT4 localizes to storage vesicles in insulin responsive cell types, and over expression of Ubc9 also mediated the increased targeting of GLUT4 to these storage compartments, leading to an increase in insulin-responsive glucose transport capacity (Liu et al. 2007). Although no direct role of SUMO in glucose transport has been demonstrated, the SUMO conjugation pathway clearly affects glucose-stimulated insulin secretion, and perturbations of this pathway may contribute to metabolic disease.

Cancer cells shift their metabolism toward aerobic glycolysis at the expense of oxidative mitochondrial respiration, a phenomenon known as Warburg effect (Warburg 1925; Warburg et al. 1927). Desumoylation has been recently linked to these metabolic changes. Over-expression of SUMO-specific protease 2 (SEN2) reduced glucose uptake and lactate production while increasing the cellular levels of ATP in MCF7 cells. On the other hand, SEN2 knockout in MEF cells showed increased glucose uptake and lactate production along with the decreased ATP levels. Thus, desumoylation by SEN2 enzyme is implicated as a negative regulator of aerobic glycolysis in MCF7 and MEF cells, although mediator proteins that undergo SEN2-dependent desumoylation remain largely unknown (Tang et al. 2013). One of the glycolytic enzymes emerging as being regulated by sumoylation is pyruvate kinase PKM2. PKM2 is a master regulator of metabolism and has been shown to promote tumorigenesis by regulating the Warburg effect (Filipp 2013; Luo and Semenza 2012; Wong et al. 2015). PKM2 is sumoylated, probably by PIAS3, in human osteosarcoma U-2 OS cells and the mouse NIH3T3 cell line (Spoden, 2009 #14710). PKM2 is differentially sumoylated in breast cancer metastasis (Subramonian et al. 2014). Taken together, these findings implicate sumoylation of glycolytic enzymes as an important contribution to SUMO-mediated metabolic regulation. Future studies will clarify the mechanistic details of the SUMO-mediated regulatory mechanisms of glucose metabolism and will unravel the impact of enzyme sumoylation on reprogramming metabolite fluxes through the glycolytic pathway in normal and transformed cells.

9.5.4 SUMO in Mitochondrial Biogenesis and Metabolic Disease

Mitochondria function, including oxidative capacity and rates of oxidative phosphorylation, are reduced in skeletal muscle during metabolic disease (Aon et al. 2014; Civitarese and Ravussin 2008). Type II diabetes, obesity and insulin resistance are associated with abnormal mitochondrial morphology, reduced function and an overall reduced number of mitochondria (Goodpaster 2013; Kelley et al. 2002; Koves et al. 2008). Declining cellular oxidative capacity leads to hepatic steatosis, which in turn increases hepatic glucose production and hyperglycemia (Anderson et al. 2009; Sonoda et al. 2007). Mitochondria are dynamic organelles that continuously undergo fission and fusion events in response to changes in cellular metabolism. Fusion of mitochondria has been suggested to be a mechanism by which intact mitochondria can recover the activities of damaged, depolarized mitochondria in order to maintain metabolic efficiency (Mishra and Chan 2014; Twig et al. 2008). On the other hand, mitochondrial biogenesis is stimulated in response to mitochondria damage, but also when ATP requirements are increased (Frazier et al. 2006; Toyama et al. 2016). Excessive mitochondrial fission may cause apoptosis (Bueler 2010). Therefore, regulation of fission and fusion events is essential to ensure an appropriate

balance is achieved between the number and quality of mitochondria in response to cellular metabolic needs and/or to maintain metabolic and oxidative capacity.

SUMO is required for mitochondria fission events, and may regulate rates of mitochondrial biogenesis, as elevations in SUMO-1 expression were shown to increase mitochondrial fission events (Harder et al. 2004). Fission is controlled by the GTPase dynamin-related protein 1 (DRP1) and fission protein 1 (Fig. 9.1). These proteins are key components of the fission machinery in mitochondria and peroxisomes that function both during cellular homeostasis and apoptosis (Reddy et al. 2011; Wasiak et al. 2007). Fission is initiated by the recruitment of DRP1 from the cytoplasm to the mitochondrial outer membrane by FIS 1, an outer mitochondrial membrane associated protein, and a number of other recruitment factors (MFF, MiD49, and MiD51). The recruitment of DRP1 to the mitochondria is regulated by phosphorylation events in response to energy stress. One of the targets for phosphorylation is the mitochondrial fission factor (MFF), which is phosphorylated by the energy-sensing adenosine monophosphate (AMP)-activated protein kinase (AMPK) in response to electron transport chain inhibitors such as rotenone- and antimycin A. Phosphorylated MFF is better able to recruit DRP1 to mitochondria for fission initiation (Toyama et al. 2016). DRP1 mediates membrane scission, and its activity is also regulated by two posttranslational modifications: Sumoylation and phosphorylation. DRP1 is activated by CDK1/cyclinB-mediated phosphorylation at Ser 618 resulting in mitochondrial fragmentation (Taguchi et al. 2007), whereas its GTPase activity is inhibited by phosphorylation at Ser637 by cAMP-dependent kinase A, which induces mitochondrial fusion (Chang and Blackstone 2007; Suen et al. 2008). DRP1 is also covalently modified by sumoylation, and also has been shown to directly interact with SUMO-1. Fluorescence microscopy studies revealed that SUMO-1 was present at sites of fission between fragmented mitochondria, and co-localized with DRP1 (Harder et al. 2004).

DRP1 is recruited to the mitochondrial outer membrane from the cytosol by several receptors/recruitment factors (FIS1, MFF, MiD49, and MiD51). DRP1 carries out fission of the outer membrane, and thus contributes to mitochondrial and peroxisomal division (Wai and Langer 2016). It self-assembles into a ring-like oligomeric structures wrapping around the future constriction points during fission, similarly to dynamin collars at the necks of budding vesicles during endocytosis (Smirnova et al. 2001). The mitochondrial division allows the cell to isolate defective mitochondrial segments, to degrade the damaged pieces, and to prevent damage accumulation through a process referred to as mitophagy (Yamano et al. 2016). Mutations in DRP1 cause encephalopathy, a lethal infantile neurodegenerative disease due to defective mitochondrial and peroxisomal fission (Chang et al. 2010; Waterham et al. 2007). DRP1 is a key regulator of mitochondrial fission and a direct target of sumoylation by all three SUMO isoforms. DRP1 is sumoylated by the mitochondrial-anchored SUMO E3 ligase MAPL (Braschi et al. 2009). DRP1 does not contain consensus sumoylation sequences, but instead harbors noncanonical conjugation sites present as clusters of lysine residues within the B domain (Figueroa-Romero et al. 2009). Increased SUMO-1 expression leads to increased sumoylated DRP1 protein and mitochondria' fragmentation; SUMO-1 may have a direct and protective effect on stabilizing DRP1 for mitochondrial fission (Harder et al. 2004). The activation of apoptosis triggers sumoylation of DRP1 by MAPL/ by MAPL/MUL1, which leads to stabilized ER/mitochondrial contact

sites that serve as a platform for cytochrome c release (Prudent et al. 2015). The sumoylation of DRP1 can be reversed by at least three different desumoylating enzymes: SENP2, SENP3, and SENP5. Silencing of SENP5 results in accumulation of sumoylated DRP1 leading to increased mitochondrial fission. COS-7 cells with SENP5 RNAi knockdown exhibit increased generation of ROS, presumably due to the inhibition of fusion events that eliminate dysfunctional mitochondria. On the other hand, overexpression of SENP5 in COS-7 cell line rescues SUMO-1-induced mitochondrial fragmentation (Zunino et al. 2007). DRP1 is also desumoylated by SUMO isopeptidase SENP2. Regulated sumoylation/desumoylation of DRP1 protein is critical for mitochondrial morphogenesis and is particularly important for the survival of neural cell types. SENP2 regulates DRP1 desumoylation and stability, and mice with neural-specific disruption of SENP2 develop movement difficulties, which progress to paralysis with associated dysregulation of mitochondrial dynamics (Fu et al. 2014). Therefore, appropriate levels of SUMO-1 expression and DRP1 sumoylation are essential to achieve a balance between mitochondrial fission and fusion for maintenance of mitochondria quantity and quality. SENP3 is a SUMO-2/3-specific protease that is degraded during oxygen/glucose deprivation (OGD), an in vitro model of ischemia. DRP1 is one of the key targets for SENP3-mediated desumoylation. Depletion of SENP3 by RNAi knockdown lengthens the duration of DRP1 sumoylation, leading to the suppression of DRP1-mediated cytochrome c release and caspase-mediated cell death. Thus, knockdown of SENP3 protects cells from reoxygenation-induced cell death, in support of the notion that global increases in SUMO-2/3 conjugation are a neuro-protective response to severe stress (Guo et al. 2013). These studies highlight the importance of sumoylation and desumoylation in the regulation of mitochondrial metabolism.

9.6 SUMO and Folate-Mediated One-Carbon Metabolism

Folate is a B-vitamin that functions in the cell as a metabolic cofactor that carries and chemically activates single carbons as three different oxidation states for folate-mediated one-carbon metabolism (Fox and Stover 2009). One-carbon metabolism is a metabolic network comprised of three interconnected biosynthetic pathways: the *de novo* synthesis of purines, *de novo* thymidylate biosynthesis, and the remethylation of homocysteine to form methionine (Fox and Stover 2009). Methionine can be subsequently adenosylated to form S-adenosylmethionine which serves as a cofactor for numerous cellular methylation reactions in the cell, including chromatin methylation (Fig. 9.3) (Fox and Stover 2009). Disruptions in folate metabolism are associated with numerous pathologies and developmental anomalies including cancer, cardiovascular disease, neural tube defects and cleft palate, although mechanisms have yet to be established (Stover 2004).

Folate mediated one-carbon metabolism is known to be compartmentalized in the cell; cellular folates are found in the cytoplasm, mitochondria and in the nucleus (Shin et al. 1976). Mitochondria generate one-carbons in the form of formate from the catabolism of the amino acids serine and glycine. Formate derived in mitochondria traverses to the cytoplasm to support one-carbon transfer reactions in that compartment (Fox and Stover 2009).

In the cell, the concentration of folate-activated one-carbons is limiting relative to the concentration of folate-dependent enzymes, indicating that folate-dependent biosynthetic pathways compete for a limiting pool of folate cofactors (Stover and Field 2011). This competition is most pronounced for the thymidylate and methionine biosynthesis pathways which compete for a limiting pool of methylenetetrahydrofolate (Herbig et al. 2002), which is generated by the reduction of 10-formyltetrahydrofolate catalyzed by methylene-tetrahydrofolate dehydrogenase 1 (MTHFD1) (Fig 9.3) (Field et al. 2014, 2015, 2016).

Tissues including kidney, liver, brain, and colon express serine hydroxymethyltransferase 1 (SHMT1), which functions in the cytoplasm as an alternative source of one-carbon units for the synthesis of methylene-tetrahydrofolate. Isotope tracer studies demonstrate that SHMT1-derived methylenetetrahydrofolate is preferentially partitioned towards the thymidylate synthesis pathway at the expense of methionine biosynthesis (Herbig et al. 2002). The mechanism by which SHMT1 preferentially partitions one-carbons to thymidylate synthesis was shown to involve the SUMO-dependent translocation of the entire thymidylate biosynthesis pathway into the nucleus (Anderson et al. 2007; Woeller et al. 2007) and the assembly of the metabolic complex at the sites of DNA replication (Anderson et al. 2012a, b). The three enzymes in the de novo thymidylate pathway, cytoplasmic serine hydroxymethyltransferase (SHMT1), thymidylate synthase (TYMS), and dihydrofolate reductase (DHFR) are substrates for Ubc9 catalyzed sumoylation and subsequent translocation to the nucleus during the S and G2/M phases of the cell cycle (Anderson et al. 2007; Woeller et al. 2007). In the nucleus, SHMT1 is responsible for the generation of methylene-tetrahydrofolate by catalyzing the transfer of one-carbon units from serine to tetrahydrofolate. TYMS uses methylenetetrahydrofolate as the methyl donor for the conversion of deoxythymidylate to deoxythymidylate and dihydrofolate. DHFR catalyzes the reduction of dihydrofolate to tetrahydrofolate, thereby allowing the de novo thymidylate synthesis cycle to continue. The thymidylate biosynthesis is compartmentalized in the nucleus during DNA biosynthesis and repair, S and G2/M phases respectively. During G1, the thymidylate biosynthesis pathway enzymes localize exclusively to the cytoplasm. During the S phase, SHMT1 anchors the complex to nuclear lamina and DNA replication sites (Anderson et al. 2012b). TYMS was identified as SUMO-2-conjugated protein in four large-scale proteomics studies (Golebiowski et al. 2009; Hendriks et al. 2014, 2015; Tammsalu et al. 2014).

SHMT1 interacts with several nuclear and nuclear pore associated proteins including Ubc9, RanBP9 and PCNA. SHMT1 sumoylation is essential for its compartmentalization to the nucleus; K38R/K39R SHMT1 mutants are not substrates for Ubc9-mediated sumoylation, and these SHMT1 mutant proteins do not localize to the nucleus during S-phase (Woeller et al. 2007). Furthermore, a common SHMT1 variant, L474F, alters the SHMT1-Ubc9 binding interface. SHMT1 L474F protein is not an effective substrate for Ubc9 sumoylation and is impaired in its nuclear localization. SHMT1 localization to the nucleus is dependent on the G-protein Ran; expression of a dominant negative RanT24N also impairs SHMT1 accumulation in the nucleus.

The SUMO-dependent compartmentation of thymidylate biosynthesis pathway in the nucleus accounts for the preferential partitioning of methylene-tetrahydrofolate towards *de*

de novo thymidylate biosynthesis. When DNA is damaged, several DNA repair mechanisms require dNTP synthesis (Mathews 2015). Exposure of cultured cells to ultraviolet radiation induces SHMT1 sumoylation and nuclear localization of the thymidylate biosynthesis pathway, and impairment in nuclear thymidylate synthesis sensitizes cells to UV-induced cell death (Fox et al. 2009; Fox and Stover 2009). *De novo* thymidylate synthesis is unique from other nucleotide biosynthetic pathways which are believed to occur in the cytoplasm, with the exception of synthesis during DNA damage (Mathews 2015). Nuclear thymidylate biosynthesis serves to limit the misincorporation of uracil into DNA and thereby promotes genome stability (Field et al. 2014, 2015, 2016; MacFarlane et al. 2008, 2011a, b).

While SHMT1 is involved in partitioning of folate cofactors towards nuclear thymidylate biosynthesis (Herbig et al. 2002; MacFarlane et al. 2008), SHMT2 is a mitochondrial isozyme of SHMTs that converts serine to glycine and serves as a major source of glycine in proliferating cells (Jain et al. 2012; Kim et al. 2015a). *Shmt2* gene encodes several alternatively spliced transcripts, one of which lacks exon 1 and expresses SHMT2 α protein lacking mitochondrial targeting sequence (Stover et al. 1997). Both SHMT1 and SHMT2 α enzymes are cytosolic and translocate into the nucleus in S phase, and are functionally redundant in the nuclear thymidylate biosynthesis (Anderson and Stover 2009). A mouse model for folate-responsive neural tube defects has been recently developed through disruption of the *Shmt1* gene in the mouse genome (Beaudin et al. 2012; MacFarlane et al. 2008). Homozygous deletion of the *Shmt1* gene in mice results in viable and fertile animals that exhibit depressed rates of *de novo* thymidylate synthesis and elevated levels of uracil in nuclear DNA (MacFarlane et al. 2008). The viability of these mice is attributed to the functional redundancy with SHMT2 α (Anderson and Stover 2009). When the dams are placed on a folate-deficient diet, *Shmt1*^{+/-} and *Shmt1*^{-/-} embryos exhibit sporadic exencephaly, a type of neural tube defects, independently of maternal genotype (Beaudin et al. 2011, 2012;). Interestingly, the rate of neural tube defects associated with embryonic *Shmt1* disruption can be increased by maternal uridine supplementation but rescued with maternal deoxyuridine supplementation, through stimulation of thymidylate synthesis (Martiniova et al. 2015). Moreover, the *Shmt1*^{+/-} mice crossed to the *Apc*^{Min/+} mouse model show increased susceptibility to intestinal tumors compared to wild-type mice (Macfarlane et al. 2011b). These studies connect impairments in folate- and SUMO-dependent nuclear thymidylate biosynthesis not only to the pathogenesis of folate-responsive neural tube defects but also to cancer pathophysiology. Additional roles of SUMO in folate-dependent nuclear thymidylate biosynthesis, outside its role in nuclear translocation, have yet to be established.

9.7 Conclusions

A growing body of publications over the past 10 years indicate that modification of proteins with SUMO plays an important role in maintaining metabolic homeostasis as well as in metabolic adaptation to stress. Several metabolic pathways, including but not limited to energy balance, lipid metabolism in inflammation, hepatic gluconeogenesis, glycolysis, mitochondrial biogenesis and respiration in muscle, chronic inflammation in metabolic diseases, and ions and water reabsorption in epithelial tissues have been reported to be regulated through controlled sumoylation of transcription factors. Changes in cellular

sumoylation patterns have been observed under various stress conditions, such as torpor, hypoxia, glucose starvation, and oxidative stress. Sumoylation has emerged as important regulator of mitochondrial fission and fusion events, thus controlling energy homeostasis. SUMO pathway has been implicated in insulin production and secretion. Furthermore, SUMO plays an important role in mediating compartmentation of folate-metabolizing enzymes to the nucleus during DNA biosynthesis for thymidylate production at the sites of DNA replication. The scope of metabolic processes under the control of SUMO modification, from energy to glycolysis to nucleotide synthesis and beyond, suggests that SUMO plays an important role as a regulator and integrator of metabolic responses. Therefore, understanding the commonality in these diverse processes through future studies will allow for a unified model for SUMO control of metabolism.

Abbreviations

SUMO	Small Ubiquitin-related Modifier
SIM	SUMO interacting motif
SREBPs	sterol regulatory element binding proteins
bHLH-Zip	basic helix-loop-helix leucine zipper
SRE	sterol response element
SCAP	SREBP cleavage activating protein
INSIG	insulin inducing gene
MAPKs	mitogen-activated protein kinases
HDAC3	histone deacetylase 3
ROS	reactive oxygen species
SENPs	septrin specific proteases
PPARs	peroxisome proliferators-activated receptors
KLF5	Krüppel like transcription factor 5
Cpt1b	carnitine palmitoyl transferase
Ucp2	uncoupling proteins
ICA512	islet cell autoantigen 512
STAT5	signal transducer and activator of transcription
GLUTs	glucose transporters
DRP1	dynamamin related protein 1
FIS1	fission protein 1

AICARTfase	aminoimidazole-4-carboxamide ribonucleotide transferase
DHFR	dihydrofolate reductase
GARTfase	10-formyltetrahydrofolate: 5'-phosphoribosylglycinamide N-formyltransferase
MTHFD1	methylenetetrahydrofolate dehydrogenase 1
NADPH	nicotinamide adenine dinucleotide phosphate
SHMT1	cytoplasmic serine hydroxymethyltransferase 1
SHMT2	mitochondrial serine hydroxymethyltransferase 2
TYMS	thymidylate synthase
THF	tetrahydrofolate
FPLD	familial partial lipodystrophy
LMNA	lamin A/C
PIAS3	protein inhibitor of activated STAT 3
UBC9	SUMO-conjugating enzyme UBC9, ubiquitin carrier protein 9
PKM2	pyruvate kinase, muscle, isozyme 2

References

- Agbor TA, Cheong A, Comerford KM, Scholz CC, Bruning U, Clarke A, Cummins EP, Cagney G, Taylor CT. Small ubiquitin-related modifier (SUMO)-1 promotes glycolysis in hypoxia. *J Biol Chem.* 2011; 286:4718–4726. [PubMed: 21123177]
- Alkuraya FS, Saadi I, Lund JJ, Turbe-Doan A, Morton CC, Maas RL. SUMO1 haploinsufficiency leads to cleft lip and palate. *Science.* 2006; 313:1751. [PubMed: 16990542]
- Anderson DD, Stover PJ. SHMT1 and SHMT2 are functionally redundant in nuclear de novo thymidylate biosynthesis. *PLoS One.* 2009; 4:e5839. [PubMed: 19513116]
- Anderson DD, Woeller CF, Stover PJ. Small ubiquitin-like modifier-1 (SUMO-1) modification of thymidylate synthase and dihydrofolate reductase. *Clin Chem Lab Med.* 2007; 45:1760–1763. [PubMed: 18067453]
- Anderson EJ, Lustig ME, Boyle KE, Woodlief TL, Kane DA, Lin CT, Price JW 3rd, Kang L, Rabinovitch PS, Szeto HH, Houmard JA, Cortright RN, Wasserman DH, Neuffer PD. Mitochondrial H₂O₂ emission and cellular redox state link excess fat intake to insulin resistance in both rodents and humans. *J Clin Invest.* 2009; 119:573–581. [PubMed: 19188683]
- Anderson DD, Eom JY, Stover PJ. Competition between sumoylation and ubiquitination of serine hydroxymethyltransferase 1 determines its nuclear localization and its accumulation in the nucleus. *J Biol Chem.* 2012a; 287:4790–4799. [PubMed: 22194612]
- Anderson DD, Woeller CF, Chiang EP, Shane B, Stover PJ. Serine hydroxymethyltransferase anchors de novo thymidylate synthesis pathway to nuclear lamina for DNA synthesis. *J Biol Chem.* 2012b; 287:7051–7062. [PubMed: 22235121]
- Ao Q, Su W, Guo S, Cai L, Huang L. SENP1 desensitizes hypoxic ovarian cancer cells to cisplatin by up-regulating HIF-1 α . *Sci Report.* 2015; 5:16396.

- Aon MA, Bhatt N, Cortassa SC. Mitochondrial and cellular mechanisms for managing lipid excess. *Front Physiol.* 2014; 5:282. [PubMed: 25132820]
- Arito M, Horiba T, Hachimura S, Inoue J, Sato R. Growth factor-induced phosphorylation of sterol regulatory element-binding proteins inhibits sumoylation, thereby stimulating the expression of their target genes, low density lipoprotein uptake, and lipid synthesis. *J Biol Chem.* 2008; 283:15224–15231. [PubMed: 18403372]
- Bae SH, Jeong JW, Park JA, Kim SH, Bae MK, Choi SJ, Kim KW. Sumoylation increases HIF-1 stability and its transcriptional activity. *Biochem Biophys Res Commun.* 2004; 324:394–400. [PubMed: 15465032]
- Balasubramaniyan N, Luo Y, Sun AQ, Suchy FJ. SUMOylation of the farnesoid X receptor (FXR) regulates the expression of FXR target genes. *J Biol Chem.* 2013; 288:13850–13862. [PubMed: 23546875]
- Beaudin AE, Abarinov EV, Noden DM, Perry CA, Chu S, Stabler SP, Allen RH, Stover PJ. Shmt1 and de novo thymidylate biosynthesis underlie folate-responsive neural tube defects in mice. *Am J Clin Nutr.* 2011; 93:789–798. [PubMed: 21346092]
- Beaudin AE, Abarinov EV, Malysheva O, Perry CA, Caudill M, Stover PJ. Dietary folate, but not choline, modifies neural tube defect risk in Shmt1 knockout mice. *Am J Clin Nutr.* 2012; 95:109–114. [PubMed: 22134951]
- Becker J, Barysch SV, Karaca S, Dittner C, Hsiao HH, Berriel Diaz M, Herzig S, Urlaub H, Melchior F. Detecting endogenous SUMO targets in mammalian cells and tissues. *Nat Struct Mol Biol.* 2013; 20:525–531. [PubMed: 23503365]
- Bernardi R, Pandolfi PP. Structure, dynamics and functions of promyelocytic leukaemia nuclear bodies. *Nat Rev Mol Cell Biol.* 2007; 8:1006–1016. [PubMed: 17928811]
- Bhattacharjee J, Alahari S, Sallais J, Tagliaferro A, Post M, Caniggia I. Dynamic regulation of HIF1 α stability by SUMO2/3 and SENP3 in the human placenta. *Placenta.* 2016; 40:8–17. [PubMed: 27016777]
- Borden KLB. Pondering the promyelocytic leukemia protein (PML) puzzle: possible functions for PML nuclear bodies. *Mol Cell Biol.* 2002; 22:5259–5269. [PubMed: 12101223]
- Bossis G, Melchior F. Regulation of SUMOylation by reversible oxidation of SUMO conjugating enzymes. *Mol Cell.* 2006; 21:349–357. [PubMed: 16455490]
- Bossis G, Malnou CE, Farras R, Andermarcher E, Hipskind R, Rodriguez M, Schmidt D, Muller S, Jariel-Encontre I, Piechaczyk M. Down-regulation of c-Fos/c-Jun AP-1 dimer activity by sumoylation. *Mol Cell Biol.* 2005; 25:6964–6979. [PubMed: 16055710]
- Boudreau E, Labib S, Bertrand AT, Decostre V, Bolongo PM, Sylvius N, Bonne G, Tesson F. Lamin A/C mutants disturb Sumo1 localization and sumoylation in vitro and in vivo. *PLoS One.* 2012; 7
- Braschi E, Zunino R, McBride HM. MAPL is a new mitochondrial SUMO E3 ligase that regulates mitochondrial fission. *EMBO Rep.* 2009; 10:748–754. [PubMed: 19407830]
- Brown MS, Goldstein JL. Cholesterol feedback: from Schoenheimer's bottle to Scap's MELADL. *J Lipid Res.* 2009; 50(Suppl):S15–S27. [PubMed: 18974038]
- Bruderer R, Tatham MH, Plechanovova A, Matic I, Garg AK, Hay RT. Purification and identification of endogenous polySUMO conjugates. *EMBO Rep.* 2011; 12:142–148. [PubMed: 21252943]
- Bueler H. Mitochondrial dynamics, cell death and the pathogenesis of Parkinson's disease. *Apoptosis.* 2010; 15:1336–1353. [PubMed: 20131004]
- Bursomanno S, Beli P, Khan AM, Minocherhomji S, Wagner SA, Bekker-Jensen S, Mailand N, Choudhary C, Hickson ID, Liu Y. Proteome-wide analysis of SUMO2 targets in response to pathological DNA replication stress in human cells. *DNA Repair.* 2015; 25:84–96. [PubMed: 25497329]
- Cao H, Hegele RA. Nuclear lamin A/C R482Q mutation in canadian kindreds with Dunnigan-type familial partial lipodystrophy. *Hum Mol Genet.* 2000; 9:109–112. [PubMed: 10587585]
- Chan JYH, Tsai CY, Wu CHY, Li FCH, Dai KY, Sun EYH, Chan SHH, Chang AYW. Sumoylation of hypoxia-inducible factor-1 α ameliorates failure of brain stem cardiovascular regulation in experimental brain death. *PLoS One.* 2011; 6
- Chang E, Abe J. Kinase-SUMO networks in diabetes-mediated cardiovascular disease. *Metabolism.* 2016; 65:623–633. [PubMed: 27085771]

- Chang CR, Blackstone C. Cyclic AMP-dependent protein kinase phosphorylation of Drp1 regulates its GTPase activity and mitochondrial morphology. *J Biol Chem*. 2007; 282:21583–21587. [PubMed: 17553808]
- Chang CR, Manlandro CM, Arnoult D, Stadler J, Posey AE, Hill RB, Blackstone C. A lethal de novo mutation in the middle domain of the dynamin-related GTPase Drp1 impairs higher order assembly and mitochondrial division. *J Biol Chem*. 2010; 285:32494–32503. [PubMed: 20696759]
- Chen S, Yang T, Liu F, Li H, Guo Y, Yang H, Xu J, Song J, Zhu Z, Liu D. Inflammatory factor-specific sumoylation regulates NF-kappaB signalling in glomerular cells from diabetic rats. *Inflamm Res*. 2014; 63:23–31. [PubMed: 24173240]
- Chen LQ, Cheung LS, Feng L, Tanner W, Frommer WB. Transport of sugars. *Annu Rev Biochem*. 2015; 84:865–894. [PubMed: 25747398]
- Cheng L, Ding G, Qin Q, Huang Y, Lewis W, He N, Evans RM, Schneider MD, Brako FA, Xiao Y, Chen YE, Yang Q. Cardiomyocyte-restricted peroxisome proliferator-activated receptor-delta deletion perturbs myocardial fatty acid oxidation and leads to cardiomyopathy. *Nat Med*. 2004; 10:1245–1250. [PubMed: 15475963]
- Choi SJ, Chung SS, Rho EJ, Lee HW, Lee MH, Choi HS, Seol JH, Baek SH, Bang OS, Chung CH. Negative modulation of RXR alpha transcriptional activity by small ubiquitin-related modifier (SUMO) modification and its reversal by SUMO-specific protease SUSP1. *J Biol Chem*. 2006; 281:30669–30677. [PubMed: 16912044]
- Chung SS, Ahn BY, Kim M, Kho JH, Jung HS, Park KS. SUMO modification selectively regulates transcriptional activity of peroxisome-proliferator-activated receptor gamma in C2C12 myotubes. *Biochem J*. 2011; 433:155–161. [PubMed: 20950277]
- Cimarosti H, Lindberg C, Bomholt SF, Ronn LCB, Henley JM. Increased protein SUMOylation following focal cerebral ischemia. *Neuropharmacology*. 2008; 54:280–289. [PubMed: 17991493]
- Civitares AE, Ravussin E. Mitochondrial energetics and insulin resistance. *Endocrinology*. 2008; 149:950–954. [PubMed: 18202132]
- Cui W, Sun M, Zhang S, Shen X, Galeva N, Williams TD, Staudinger JL. A SUMO-acetyl switch in PXR biology. *Biochim Biophys Acta*. 2016; [Epub ahead of print]. doi: 10.1016/j.bbagr. 2016.02.008
- Dai XQ, Plummer G, Casimir M, Kang YH, Hajmrle C, Gaisano HY, Fox JEM, MacDonald PE. SUMOylation regulates insulin exocytosis down-stream of secretory granule docking in rodents and humans. *Diabetes*. 2011; 60:838–847. [PubMed: 21266332]
- Dai XQ, Spigelman AF, Khan S, Braun M, Manning Fox JE, MacDonald PE. SUMO1 enhances cAMP-dependent exocytosis and glucagon secretion from pancreatic alpha-cells. *J Physiol*. 2014; 592:3715–3726. [PubMed: 24907310]
- Dangoumau A, Marouillat S, Burlaud Gaillard J, Uzbekov R, Veyrat-Durebex C, Blasco H, Arnoult C, Corcia P, Andres CR, Vourc'h P. Inhibition of pathogenic mutant SOD1 aggregation in cultured motor neuronal cells by prevention of its SUMOylation on lysine 75. *Neurodegener Dis*. 2016; 16:161–171. [PubMed: 26605782]
- de The H, Le Bras M, Lallemand-Breitenbach V. The cell biology of disease: acute promyelocytic leukemia, arsenic, and PML bodies. *J Cell Biol*. 2012; 198:11–21. [PubMed: 22778276]
- Desvergne B, Wahli W. Peroxisome proliferator-activated receptors: nuclear control of metabolism. *Endocr Rev*. 1999; 20:649–688. [PubMed: 10529898]
- Diezko R, Suske G. Ligand binding reduces SUMOylation of the peroxisome proliferator-activated receptor gamma (PPARgamma) activation function 1 (AF1) domain. *PLoS One*. 2013; 8:e66947. [PubMed: 23826177]
- DiRenzo J, Soderstrom M, Kurokawa R, Ogliastro MH, Ricote M, Ingrey S, Horlein A, Rosenfeld MG, Glass CK. Peroxisome proliferator-activated receptors and retinoic acid receptors differentially control the interactions of retinoid X receptor heterodimers with ligands, coactivators, and corepressors. *Mol Cell Biol*. 1997; 17:2166–2176. [PubMed: 9121466]
- Dong Q, Giorgianni F, Deng X, Beranova-Giorgianni S, Bridges D, Park EA, Raghov R, Elam MB. Phosphorylation of sterol regulatory element binding protein-1a by protein kinase A (PKA) regulates transcriptional activity. *Biochem Biophys Res Commun*. 2014; 449:449–454. [PubMed: 24853806]

- Dorval V, Fraser PE. SUMO on the road to neurodegeneration. *Biochim Biophys Acta*. 2007; 1773:694–706. [PubMed: 17475350]
- Druker J, Liberman AC, Antunica-Noguerol M, Gerez J, Paez-Pereda M, Rein T, Iniguez-Lluhi JA, Holsboer F, Arzt E. RSUME enhances glucocorticoid receptor SUMOylation and transcriptional activity. *Mol Cell Biol*. 2013; 33:2116–2127. [PubMed: 23508108]
- Du JX, Bialkowska AB, McConnell BB, Yang VW. SUMOylation regulates nuclear localization of Kruppel-like factor 5. *J Biol Chem*. 2008; 283:31991–32002. [PubMed: 18782761]
- Eckermann K. SUMO and Parkinson's disease. *Neuromol Med*. 2013; 15:737–759.
- Eifler K, Vertegaal AC. Mapping the SUMOylated landscape. *FEBS J*. 2015; 282:3669–3680. [PubMed: 26185901]
- Enserink JM. Sumo and the cellular stress response. *Cell Div*. 2015; 10:4. [PubMed: 26101541]
- Faresse N. Post-translational modifications of the mineralocorticoid receptor: how to dress the receptor according to the circumstances? *J Steroid Biochem Mol Biol*. 2014; 143:334–342. [PubMed: 24820770]
- Ferdaoussi M, Dai X, Jensen MV, Wang R, Peterson BS, Huang C, Ilkayeva O, Smith N, Miller N, Hajmrle C, Spiegelman AF, Wright RC, Plummer G, Suzuki K, Mackay JP, van de Bunt M, Gloy AL, Ryan TE, Norquay LD, Brosnan MJ, Trimmer JK, Rolph TP, Kibbey RG, Manning Fox JE, Colmers WF, Shirihai OS, Neuffer PD, Yeh ET, Newgard CB, MacDonald PE. Isocitrate-to-SENPI signaling amplifies insulin secretion and rescues dysfunctional beta cells. *J Clin Invest*. 2015; 125:3847–3860. [PubMed: 26389676]
- Fernandez-Marcos PJ, Auwerx J. Regulation of PGC-1 α , a nodal regulator of mitochondrial biogenesis. *Am J Clin Nutr*. 2011; 93:884S–8890. [PubMed: 21289221]
- Field MS, Kamynina E, Agunloye OC, Liebenthal RP, Lamarre SG, Brosnan ME, Brosnan JT, Stover PJ. Nuclear enrichment of folate cofactors and methylene-tetrahydrofolate dehydrogenase 1 (MTHFD1) protect de novo thymidylate biosynthesis during folate deficiency. *J Biol Chem*. 2014; 289:29642–29650. [PubMed: 25213861]
- Field MS, Kamynina E, Watkins D, Rosenblatt DS, Stover PJ. Human mutations in methylenetetrahydrofolate dehydrogenase 1 impair nuclear de novo thymidylate biosynthesis. *Proc Natl Acad Sci U S A*. 2015; 112:400–405. [PubMed: 25548164]
- Field MS, Kamynina E, Stover PJ. MTHFD1 regulates nuclear de novo thymidylate biosynthesis and genome stability. *Biochimie*. 2016; 126:27–30. [PubMed: 26853819]
- Figueroa-Romero C, Iniguez-Lluhi JA, Stadler J, Chang CR, Arnoult D, Keller PJ, Hong Y, Blackstone C, Feldman EL. SUMOylation of the mitochondrial fission protein Drp1 occurs at multiple nonconsensus sites within the B domain and is linked to its activity cycle. *FASEB J*. 2009; 23:3917–3927. [PubMed: 19638400]
- Filipp FV. Cancer metabolism meets systems biology: pyruvate kinase isoform PKM2 is a metabolic master regulator. *J Carcinog*. 2013; 12:14. [PubMed: 23961261]
- Flotho A, Melchior F. Sumoylation: a regulatory protein modification in health and disease. *Annu Rev Biochem*. 2013; 82:357–385. [PubMed: 23746258]
- Foran E, Rosenblum L, Bogush AI, Trotti D. Sumoylation of critical proteins in amyotrophic lateral sclerosis: emerging pathways of pathogenesis. *Neuromol Med*. 2013; 15:760–770.
- Fox JT, Stover PJ. Mechanism of the internal ribosome entry site-mediated translation of serine hydroxymethyltransferase 1. *J Biol Chem*. 2009; 284:31085–31096. [PubMed: 19734143]
- Fox JT, Shin WK, Caudill MA, Stover PJ. A UV-responsive internal ribosome entry site enhances serine hydroxymethyltransferase 1 expression for DNA damage repair. *J Biol Chem*. 2009; 284:31097–31108. [PubMed: 19734144]
- Frazier AE, Kiu C, Stojanovski D, Hoogenraad NJ, Ryan MT. Mitochondrial morphology and distribution in mammalian cells. *Biol Chem*. 2006; 387:1551–1558. [PubMed: 17132100]
- Fu CH, Ahmed K, Ding HS, Ding X, Lan JP, Yang ZH, Miao Y, Zhu YY, Shi YY, Zhu JD, Huang H, Yao XB. Stabilization of PML nuclear localization by conjugation and oligomerization of SUMO-3. *Oncogene*. 2005; 24:5401–5413. [PubMed: 15940266]
- Fu J, Yu HM, Chiu SY, Mirando AJ, Maruyama EO, Cheng JG, Hsu W. Disruption of SUMO-specific protease 2 induces mitochondria mediated neurodegeneration. *PLoS Genet*. 2014; 10:e1004579. [PubMed: 25299344]

- Gareau JR, Lima CD. The SUMO pathway: emerging mechanisms that shape specificity, conjugation and recognition. *Nat Rev Mol Cell Biol.* 2010; 11:861–871. [PubMed: 21102611]
- Germain P, Staels B, Dacquet C, Spedding M, Laudet V. Overview of nomenclature of nuclear receptors. *Pharmacol Rev.* 2006; 58:685–704. [PubMed: 17132848]
- Ghisletti S, Huang W, Ogawa S, Pascual G, Lin ME, Willson TM, Rosenfeld MG, Glass CK. Parallel SUMOylation-dependent pathways mediate gene- and signal-specific transrepression by LXRs and PPARgamma. *Mol Cell.* 2007; 25:57–70. [PubMed: 17218271]
- Giorgino F, de Robertis O, Laviola L, Montrone C, Perrini S, McCowen KC, Smith RJ. The sentrin-conjugating enzyme mUbc9 interacts with GLUT4 and GLUT1 glucose transporters and regulates transporter levels in skeletal muscle cells. *Proc Natl Acad Sci USA.* 2000; 97:1125–1130. [PubMed: 10655495]
- Goldstein JL, Brown MS. A century of cholesterol and coronaries: from plaques to genes to statins. *Cell.* 2015; 161:161–172. [PubMed: 25815993]
- Goldstein JL, DeBose-Boyd RA, Brown MS. Protein sensors for membrane sterols. *Cell.* 2006; 124:35–46. [PubMed: 16413480]
- Golebiowski F, Matic I, Tatham MH, Cole C, Yin YL, Nakamura A, Cox J, Barton GJ, Mann M, Hay RT. System-wide changes to SUMO modifications in response to heat shock. *Sci Signal.* 2009; 2
- Gooding JR, Jensen MV, Dai X, Wenner BR, Lu D, Arumugam R, Ferdaoussi M, MacDonald PE, Newgard CB. Adenylosuccinate is an insulin secretagogue derived from glucose-induced purine metabolism. *Cell Rep.* 2015; 13:157–167. [PubMed: 26411681]
- Goodpaster BH. Mitochondrial deficiency is associated with insulin resistance. *Diabetes.* 2013; 62:1032–1035. [PubMed: 23520282]
- Grygiel-Gorniak B. Peroxisome proliferator-activated receptors and their ligands: nutritional and clinical implications—a review. *Nutr J.* 2014; 13:17. [PubMed: 24524207]
- Gu J, Fan Y, Liu X, Zhou L, Cheng J, Cai R, Xue S. SENP1 protects against myocardial ischaemia/reperfusion injury via a HIF1alpha-dependent pathway. *Cardiovasc Res.* 2014; 104:83–92. [PubMed: 25082844]
- Guerra de Souza AC, Prediger RD, Cimarosti H. SUMO-regulated mitochondrial function in Parkinson's disease. *J Neurochem.* 2016; 137:673–686. [PubMed: 26932327]
- Guo C, Henley JM. Wrestling with stress: roles of protein SUMOylation and deSUMOylation in cell stress response. *IUBMB Life.* 2014; 66:71–77. [PubMed: 24470405]
- Guo C, Hildick KL, Luo J, Dearden L, Wilkinson KA, Henley JM. SENP3-mediated deSUMOylation of dynamin-related protein 1 promotes cell death following ischaemia. *EMBO J.* 2013; 32:1514–1528. [PubMed: 23524851]
- Hajmrlc C, Ferdaoussi M, Plummer G, Spigelman AF, Lai K, Manning Fox JE, MacDonald PE. SUMOylation protects against IL-1beta-induced apoptosis in INS-1 832/13 cells and human islets. *Am J Phys.* 2014; 307:E664–E673.
- Harder Z, Zunino R, McBride H. Sumol conjugates mitochondrial substrates and participates in mitochondrial fission. *Curr Biol.* 2004; 14:340–345. [PubMed: 14972687]
- Hay RT. SUMO-specific proteases: a twist in the tail. *Trends Cell Biol.* 2007; 17:370–376. [PubMed: 17768054]
- Hecker CM, Rabiller M, Haglund K, Bayer P, Dikic I. Specification of SUMO1- and SUMO2-interacting motifs. *J Biol Chem.* 2006; 281:16117–16127. [PubMed: 16524884]
- Hendriks IA, D'Souza RC, Yang B, Verlaan-de Vries M, Mann M, Vertegaal AC. Uncovering global SUMOylation signaling networks in a site-specific manner. *Nat Struct Mol Biol.* 2014; 21:927–936. [PubMed: 25218447]
- Hendriks IA, D'Souza RC, Chang JG, Mann M, Vertegaal AC. System-wide identification of wild-type SUMO-2 conjugation sites. *Nat Commun.* 2015; 6:7289. [PubMed: 26073453]
- Herbig K, Chiang EP, Lee LR, Hills J, Shane B, Stover PJ. Cytoplasmic serine hydroxymethyltransferase mediates competition between folate-dependent deoxyribonucleotide and S-adenosylmethionine biosyntheses. *J Biol Chem.* 2002; 277:38381–38389. [PubMed: 12161434]
- Hickey CM, Wilson NR, Hochstrasser M. Function and regulation of SUMO proteases. *Nat Rev Mol Cell Biol.* 2012; 13:755–766. [PubMed: 23175280]

- Hirano Y, Murata S, Tanaka K, Shimizu M, Sato R. Sterol regulatory element-binding proteins are negatively regulated through SUMO-1 modification independent of the ubiquitin/26 S proteasome pathway. *J Biol Chem*. 2003; 278:16809–16819. [PubMed: 12615929]
- Holmstrom SR, Chupreta S, So AYL, Iniguez-Lluhi JA. SUMO-mediated inhibition of glucocorticoid receptor synergistic activity depends on stable assembly at the promoter but not on DAXX. *Mol Endocrinol*. 2008; 22:2061–2075. [PubMed: 18562626]
- Hoppe JB, Salbego CG, Cimarosti H. SUMOylation: novel neuroprotective approach for Alzheimer's disease? *Aging Dis*. 2015; 6:322–330. [PubMed: 26425387]
- Hu G, Xu CS, Staudinger JL. Pregnane X receptor Is SUMOylated to repress the inflammatory response. *J Pharmacol Exp Ther*. 2010; 335:342–350. [PubMed: 20719936]
- Hua X, Yokoyama C, Wu J, Briggs MR, Brown MS, Goldstein JL, Wang X. SREBP-2, a second basic-helix-loop-helix-leucine zipper protein that stimulates transcription by binding to a sterol regulatory element. *Proc Natl Acad Sci U S A*. 1993; 90:11603–11607. [PubMed: 7903453]
- Hua G, Ganti KP, Chambon P. Glucocorticoid-induced tethered transrepression requires SUMOylation of GR and formation of a SUMO-SMRT/NCoR1-HDAC3 repressing complex. *Proc Natl Acad Sci U S A*. 2016a; 113:E635–E643. [PubMed: 26712006]
- Hua G, Paulen L, Chambon P. GR SUMOylation and formation of an SUMO-SMRT/NCoR1-HDAC3 repressing complex is mandatory for GC-induced IR nGRE-mediated transrepression. *Proc Natl Acad Sci U S A*. 2016b; 113:E626–E634. [PubMed: 26712002]
- Huang W, Ghisletti S, Saijo K, Gandhi M, Aouadi M, Tesz GJ, Zhang DX, Yao J, Czech MP, Goode BL, Rosenfeld MG, Glass CK. Coronin 2A mediates actin-dependent de-repression of inflammatory response genes. *Nature*. 2011; 470:414–418. [PubMed: 21331046]
- Huang W, Xu L, Zhou X, Gao C, Yang M, Chen G, Zhu J, Jiang L, Gan H, Gou F, Feng H, Peng J, Xu Y. High glucose induces activation of NF-kappaB inflammatory signaling through IkappaBalpha sumoylation in rat mesangial cells. *Biochem Biophys Res Commun*. 2013; 438:568–574. [PubMed: 23911785]
- Impens F, Radoshevich L, Cossart P, Ribet D. Mapping of SUMO sites and analysis of SUMOylation changes induced by external stimuli. *Proc Natl Acad Sci U S A*. 2014; 111:12432–12437. [PubMed: 25114211]
- Ishov AM, Sotnikov AG, Negorev D, Vladimirova OV, Neff N, Kamitani T, Yeh ETH, Strauss JF, Maul GG. PML is critical for ND10 formation and recruits the PML-interacting protein Daxx to this nuclear structure when modified by SUMO-1. *J Cell Biol*. 1999; 147:221–233. [PubMed: 10525530]
- Ivanschitz L, Takahashi Y, Jollivet F, Ayrault O, Le Bras M, de The H. PML IV/ARF interaction enhances p53 SUMO-1 conjugation, activation, and senescence. *Proc Natl Acad Sci U S A*. 2015; 112:14278–14283. [PubMed: 26578773]
- Jain M, Nilsson R, Sharma S, Madhusudhan N, Kitami T, Souza AL, Kafri R, Kirschner MW, Clish CB, Mootha VK. Metabolite profiling identifies a key role for glycine in rapid cancer cell proliferation. *Science*. 2012; 336:1040–1044. [PubMed: 22628656]
- Jardin C, Horn AH, Sticht H. Binding properties of SUMO-interacting motifs (SIMs) in yeast. *J Mol Model*. 2015; 21:50. [PubMed: 25690366]
- Jennewein C, Kuhn AM, Schmidt MV, Meilladec-Jullig V, von Knethen A, Gonzalez FJ, Brune B. Sumoylation of peroxisome proliferator-activated receptor gamma by apoptotic cells prevents lipopolysaccharide-induced NCoR removal from kappa B binding sites proinflammatory cytokines. *J Immunol*. 2008; 181:5646–5652. [PubMed: 18832723]
- Jentsch S, Psakhye I. Control of nuclear activities by substrate-selective and protein-group SUMOylation. *Annu Rev Genet*. 2013; 47:167–186. [PubMed: 24016193]
- Jeon TI, Osborne TF. SREBPs: metabolic integrators in physiology and metabolism. *Trends Endocrinol Metab*. 2012; 23:65–72. [PubMed: 22154484]
- Kaminsky R, Denison C, Bening-Abu-Shach U, Chisholm AD, Gygi SP, Broday L. SUMO regulates the assembly and function of a cytoplasmic intermediate filament protein in *C. elegans*. *Develop Cell*. 2009; 17:724–735.

- Kamitani T, Nguyen HP, Kito K, Fukuda-Kamitani T, Yeh ET. Covalent modification of PML by the sentrin family of ubiquitin-like proteins. *J Biol Chem*. 1998; 273:3117–3120. [PubMed: 9452416]
- Kang X, Li J, Zou Y, Yi J, Zhang H, Cao M, Yeh ETH, Cheng J. PIASy stimulates HIF1 α SUMOylation and negatively regulates HIF1 α activity in response to hypoxia. *Oncogene*. 2010; 29:5568–5578. [PubMed: 20661221]
- Kauppinen A, Suuronen T, Ojala J, Kaarniranta K, Salminen A. Antagonistic crosstalk between NF- κ B and SIRT1 in the regulation of inflammation and metabolic disorders. *Cell Signal*. 2013; 25:1939–1948. [PubMed: 23770291]
- Kelley DE, He J, Menshikova EV, Ritov VB. Dysfunction of mitochondria in human skeletal muscle in type 2 diabetes. *Diabetes*. 2002; 51:2944–2950. [PubMed: 12351431]
- Kemper JK. Regulation of FXR transcriptional activity in health and disease: emerging roles of FXR cofactors and post-translational modifications. *Biochim Biophys Acta*. 2011; 1812:842–850. [PubMed: 21130162]
- Kersten S. Integrated physiology and systems biology of PPAR α . *Mol Metab*. 2014; 3:354–371. [PubMed: 24944896]
- Kim EM, Lee HH, Kim SH, Son YO, Lee SJ, Han J, Bae J, Kim SJ, Park CG, Park Y, Hwang KW, Chun T. The mouse small ubiquitin-like modifier-2 (SUMO-2) inhibits interleukin-12 (IL-12) production in mature dendritic cells by blocking the translocation of the p65 subunit of NF κ B into the nucleus. *Mol Immunol*. 2011; 48:2189–2197. [PubMed: 21632113]
- Kim D, Fiske BP, Birsoy K, Freinkman E, Kami K, Possemato RL, Chudnovsky Y, Pacold ME, Chen WW, Cantor JR, Shelton LM, Gui DY, Kwon M, Ramkissoon SH, Ligon KL, Kang SW, Snuderl M, Vander Heiden MG, Sabatini DM. SHMT2 drives glioma cell survival in ischaemia but imposes a dependence on glycine clearance. *Nature*. 2015a; 520:363–367. [PubMed: 25855294]
- Kim DH, Xiao Z, Kwon S, Sun X, Ryerson D, Tkac D, Ma P, Wu SY, Chiang CM, Zhou E, Xu HE, Palvimo JJ, Chen LF, Kemper B, Kemper JK. A dysregulated acetyl/SUMO switch of FXR promotes hepatic inflammation in obesity. *EMBO J*. 2015b; 34:184–199. [PubMed: 25425577]
- Kim EY, Zhang Y, Beketaev I, Segura AM, Yu W, Xi Y, Chang J, Wang J. SENP5, a SUMO isopeptidase, induces apoptosis and cardiomyopathy. *J Mol Cell Cardiol*. 2015c; 78:154–164. [PubMed: 25128087]
- Komatsu T, Mizusaki H, Mukai T, Ogawa H, Baba D, Shirakawa M, Hatakeyama S, Nakayama KI, Yamamoto H, Kikuchi A, Morohashi KI. Small ubiquitin-like modifier 1 (SUMO-1) modification of the synergy control motif of Ad4 binding protein/steroidogenic factor 1 (Ad4BP/SF-1) regulates synergistic transcription between Ad4BP/SF-1 and Sox9. *Mol Endocrinol*. 2004; 18:2451–2462. [PubMed: 15192080]
- Koo YD, Choi JW, Kim M, Chae S, Ahn BY, Kim M, Oh BC, Hwang D, Seol JH, Kim YB, Park YJ, Chung SS, Park KS. SUMO-specific protease 2 (SENP2) is an important regulator of fatty acid metabolism in skeletal muscle. *Diabetes*. 2015; 64:2420–2431. [PubMed: 25784542]
- Koves TR, Ussher JR, Noland RC, Slentz D, Mosedale M, Ilkayeva O, Bain J, Stevens R, Dyck JR, Newgard CB, Lopaschuk GD, Muoio DM. Mitochondrial overload and incomplete fatty acid oxidation contribute to skeletal muscle insulin resistance. *Cell Metab*. 2008; 7:45–56. [PubMed: 18177724]
- Kroetz MB, Hochstrasser M. Identification of SUMO-interacting proteins by yeast two-hybrid analysis. *Methods Mol Biol*. 2009; 497:107–120. [PubMed: 19107413]
- Krumova P, Meulmeester E, Garrido M, Tirard M, Hsiao HH, Bossis G, Urlaub H, Zweckstetter M, Kugler S, Melchior F, Bahr M, Weishaupt JH. Sumoylation inhibits alpha-synuclein aggregation and toxicity. *J Cell Biol*. 2011; 194:49–60. [PubMed: 21746851]
- Lamoliatte F, Caron D, Durette C, Mahrouche L, Maroui MA, Caron-Lizotte O, Bonneau E, Chelbi-Alix MK, Thibault P. Large-scale analysis of lysine SUMOylation by SUMO remnant immunoaffinity profiling. *Nat Commun*. 2014; 5:5409. [PubMed: 25391492]
- Lee YJ, Hallenbeck JM. SUMO and ischemic tolerance. *NeuroMolecular Med*. 2013; 15:771–781. [PubMed: 23775726]
- Lee MH, Miyamoto S. Expanding NF κ B and SUMO ties. *Cell Cycle*. 2011; 10:3983–3984. [PubMed: 22134137]

- Lee MB, Lebedeva LA, Suzawa M, Wadekar SA, Desclozeaux M, Ingraham HA. The DEAD-Box protein DP103 (Ddx20 or gemin-3) represses orphan nuclear receptor activity via SUMO modification. *Mol Cell Biol*. 2005; 25:1879–1890. [PubMed: 15713642]
- Lee Y, Miyake S, Wakita H, McMullen DC, Azuma Y, Auh S, Hallenbeck JM. Protein SUMOylation is massively increased in hibernation torpor and is critical for the cytoprotection provided by ischemic preconditioning and hypothermia in SHSY5Y cells. *J Cereb Blood Flow Metab*. 2007; 27:950–962. [PubMed: 16955077]
- Lee JH, Park SM, Kim OS, Lee CS, Woo JH, Park SJ, Joe EH, Jou I. Differential SUMOylation of LXR alpha and LXR beta mediates transrepression of STAT1 inflammatory signaling in IFN-gamma-stimulated brain astrocytes. *Mol Cell*. 2009a; 35:806–817. [PubMed: 19782030]
- Lee Y, Castri P, Bembry J, Maric D, Auh S, Hallenbeck JM. SUMOylation participates in induction of ischemic tolerance. *J Neurochem*. 2009b; 109:257–267. [PubMed: 19200349]
- Lee YJ, Mou Y, Maric D, Klimanis D, Auh S, Hallenbeck JM. Elevated global SUMOylation in Ubc9 transgenic mice protects their brains against focal cerebral ischemic damage. *PLoS One*. 2011; 6
- Lee L, Sakurai M, Matsuzaki S, Arancio O, Fraser P. SUMO and Alzheimer's disease. *NeuroMolecular Med*. 2013; 15:720–736. [PubMed: 23979993]
- Lee L, Dale E, Staniszewski A, Zhang H, Saeed F, Sakurai M, Fa M, Orozco I, Michelassi F, Akpan N, Lehrer H, Arancio O. Regulation of synaptic plasticity and cognition by SUMO in normal physiology and Alzheimer's disease. *Sci Report*. 2014a; 4:7190.
- Lee GY, Jang H, Lee JH, Huh JY, Choi S, Chung J, Kim JB. PIASy-mediated sumoylation of SREBP1c regulates hepatic lipid metabolism upon fasting signaling. *Mol Cell Biol*. 2014b; 34:926–938. [PubMed: 24379443]
- Lee YJ, Mou Y, Klimanis D, Bernstock JD, Hallenbeck JM. Global SUMOylation is a molecular mechanism underlying hypothermia-induced ischemic tolerance. *Front Cell Neurosci*. 2014c; 8:416. [PubMed: 25538566]
- Lee J, Yang DJ, Lee S, Hammer GD, Kim KW, Elmquist JK. Nutritional conditions regulate transcriptional activity of SF-1 by controlling sumoylation and ubiquitination. *Sci Report*. 2016a; 6:19143.
- Lee YJ, Bernstock JD, Nagaraja N, Ko B, Hallenbeck JM. Global SUMOylation facilitates the multimodal neuroprotection afforded by quercetin against the deleterious effects of oxygen/glucose deprivation and the restoration of oxygen/glucose. *J Neurochem*. 2016b; 138:101–116. [PubMed: 27087120]
- Leidner J, Voogdt C, Niedenthal R, Moller P, Marienfeld U, Marienfeld RB. SUMOylation attenuates the transcriptional activity of the NF-kappaB subunit RelB. *J Cell Biochem*. 2014; 115:1430–1440. [PubMed: 24616021]
- Leuenberger N, Pradervand S, Wahli W. Sumoylated PPARalpha mediates sex-specific gene repression and protects the liver from estrogen-induced toxicity in mice. *J Clin Invest*. 2009; 119:3138–3148. [PubMed: 19729835]
- Li MY, Guo DH, Isales CM, Eizirik DL, Atkinson M, She JX, Wang CY. SUMO wrestling with type 1 diabetes. *J Mol Med*. 2005; 83:504–513. [PubMed: 15806321]
- Liu LB, Omata W, Kojima I, Shibata H. The SUMO conjugating enzyme Ubc9 is a regulator of GLUT4 turnover and targeting to the insulin-responsive storage compartment in 3T3-L1 adipocytes. *Diabetes*. 2007; 56:1977–1985. [PubMed: 17536066]
- Lloyd DJ, Trembath RC, Shackleton S. A novel interaction between lamin A and SREBP1: implications for partial lipodystrophy and other laminopathies. *Hum Mol Genet*. 2002; 11:769–777. [PubMed: 11929849]
- Luo W, Semenza GL. Emerging roles of PKM2 in cell metabolism and cancer progression. *Trends Endocrinol Metab*. 2012; 23:560–566. [PubMed: 22824010]
- MacFarlane AJ, Liu X, Perry CA, Flodby P, Allen RH, Stabler SP, Stover PJ. Cytoplasmic serine hydroxymethyltransferase regulates the metabolic partitioning of methylenetetrahydrofolate but is not essential in mice. *J Biol Chem*. 2008; 283:25846–25853. [PubMed: 18644786]
- MacFarlane AJ, Anderson DD, Flodby P, Perry CA, Allen RH, Stabler SP, Stover PJ. Nuclear localization of de novo thymidylate biosynthesis pathway is required to prevent uracil accumulation in DNA. *J Biol Chem*. 2011a; 286:44015–44022. [PubMed: 22057276]

- Macfarlane AJ, Perry CA, McEntee MF, Lin DM, Stover PJ. Shmt1 heterozygosity impairs folate-dependent thymidylate synthesis capacity and modifies risk of Apc(min)-mediated intestinal cancer risk. *Cancer Res.* 2011b; 71:2098–2107. [PubMed: 21406397]
- Makhnevych T, Sydorskyy Y, Xin X, Srikumar T, Vizeacoumar FJ, Jeram SM, Li Z, Bahr S, Andrews BJ, Boone C, Raught B. Global map of SUMO function revealed by protein-protein interaction and genetic networks. *Mol Cell.* 2009; 33:124–135. [PubMed: 19150434]
- Manning Fox JE, Hajmrle C, Macdonald PE. Novel roles of SUMO in pancreatic beta-cells: thinking outside the nucleus. *Can J Physiol Pharmacol.* 2012; 90:765–770. [PubMed: 22486776]
- Manza LL, Codreanu SG, Stamer SL, Smith DL, Wells KS, Roberts RL, Liebler DC. Global shifts in protein sumoylation in response to electrophile and oxidative stress. *Chem Res Toxicol.* 2004; 17:1706–1715. [PubMed: 15606148]
- Martiniova L, Field MS, Finkelstein JL, Perry CA, Stover PJ. Maternal dietary uridine causes, and deoxyuridine prevents, neural tube closure defects in a mouse model of folate-responsive neural tube defects. *Am J Clin Nutr.* 2015; 101:860–869. [PubMed: 25833982]
- Martins WC, Tasca CI, Cimarosti H. Battling Alzheimer's disease: targeting SUMOylation-mediated pathways. *Neurochem Res.* 2016; 41:568–578. [PubMed: 26227998]
- Mathews CK. Deoxyribonucleotide metabolism, mutagenesis and cancer. *Nat Rev Cancer.* 2015; 15:528–539. [PubMed: 26299592]
- McMillan LE, Brown JT, Henley JM, Cimarosti H. Profiles of SUMO and ubiquitin conjugation in an Alzheimer's disease model. *Neurosci Lett.* 2011; 502:201–208. [PubMed: 21843595]
- Mishra P, Chan DC. Mitochondrial dynamics and inheritance during cell division, development and disease. *Nat Rev Mol Cell Biol.* 2014; 15:634–646. [PubMed: 25237825]
- Moriuchi T, Kuroda M, Kusumoto F, Osumi T, Hirose F. Lamin A reassembly at the end of mitosis is regulated by its SUMO-interacting motif. *Exp Cell Res.* 2016; 342:83–94. [PubMed: 26921507]
- Mukhopadhyay D, Dasso M. Modification in reverse: the SUMO proteases. *Trends Biochem Sci.* 2007; 32:286–295. [PubMed: 17499995]
- Mziaut H, Trajkovski M, Kersting S, Ehninger A, Altkruger A, Lemaitre RP, Schmidt D, Saeger HD, Lee MS, Drechsel DN, Muller S, Solimena M. Synergy of glucose and growth hormone signalling in islet cells through ICA512 and STAT5. *Nat Cell Biol.* 2006; 8:435–445. [PubMed: 16622421]
- Nakagawa K, Kohara T, Uehata Y, Miyakawa Y, Sato-Ueshima M, Okubo N, Asaka M, Takeda H, Kobayashi M. PIAS3 enhances the transcriptional activity of HIF-1 α by increasing its protein stability. *Biochem Biophys Res Commun.* 2016; 469:470–476. [PubMed: 26697750]
- Niikura T, Kita Y, Abe Y. SUMO3 modification accelerates the aggregation of ALS-linked SOD1 mutants. *PLoS One.* 2014; 9:e101080. [PubMed: 24971881]
- Nunez-O'Mara A, Berra E. Deciphering the emerging role of SUMO conjugation in the hypoxia-signaling cascade. *Biol Chem.* 2013; 394:459–469. [PubMed: 23362194]
- Ohshima T, Koga H, Shimotohno K. Transcriptional activity of peroxisome proliferator-activated receptor gamma is modulated by SUMO-1 modification. *J Biol Chem.* 2004; 279:29551–29557. [PubMed: 15123625]
- Oishi Y, Manabe I, Tobe K, Ohsugi M, Kubota T, Fujiu K, Maemura K, Kubota N, Kadowaki T, Nagai R. SUMOylation of Kruppel-like transcription factor 5 acts as a molecular switch in transcriptional programs of lipid metabolism involving PPAR- δ . *Nat Med.* 2008; 14:656–666. [PubMed: 18500350]
- Paakinaho V, Kaikkonen S, Levonen AL, Palvimo JJ. Electrophilic lipid mediator 15-deoxy-Delta12,14-prostaglandin j2 modifies glucocorticoid signaling via receptor SUMOylation. *Mol Cell Biol.* 2014; 34:3202–3213. [PubMed: 24980431]
- Park S, Chang CY, Safi R, Liu X, Baldi R, Jasper JS, Anderson GR, Liu T, Rathmell JC, Dewhirst MW, Wood KC, Locasale JW, McDonnell DP. ERR α -regulated lactate metabolism contributes to resistance to targeted therapies in breast cancer. *Cell Rep.* 2016; 15:323–335. [PubMed: 27050525]
- Pascual G, Fong AL, Ogawa S, Gamliel A, Li AC, Perissi V, Rose DW, Willson TM, Rosenfeld MG, Glass CK. A SUMOylation-dependent pathway mediates transrepression of inflammatory response genes by PPAR- γ . *Nature.* 2005; 437:759–763. [PubMed: 16127449]

- Pourcet B, Pineda-Torra I, Derudas B, Staels B, Glineur C. SUMOylation of human peroxisome proliferator-activated receptor alpha inhibits its transactivity through the recruitment of the nuclear corepressor NCoR. *J Biol Chem*. 2010; 285:5983–5992. [PubMed: 19955185]
- Priyanka KD, Rana M, Subbarao N, Puri N, Tyagi RK. Transcription regulation of nuclear receptor PXR: role of SUMO-1 modification and NDSM in receptor function. *Mol Cell Endocrinol*. 2016; 420:194–207. [PubMed: 26549688]
- Prudent J, Zunino R, Sugiura A, Mattie S, Shore GC, McBride HM. MAPL SUMOylation of Drp1 stabilizes an ER/mitochondrial platform required for cell death. *Mol Cell*. 2015; 59:941–955. [PubMed: 26384664]
- Reddy PH, Reddy TP, Manczak M, Calkins MJ, Shirendeb U, Mao P. Dynamin-related protein 1 and mitochondrial fragmentation in neurodegenerative diseases. *Brain Res Rev*. 2011; 67:103–118. [PubMed: 21145355]
- Rytinki MM, Palvimo JJ. SUMOylation attenuates the function of PGC-1 alpha. *J Biol Chem*. 2009; 284:26184–26193. [PubMed: 19625249]
- Sahin U, de The H, Lallemand-Breitenbach V. PML nuclear bodies: assembly and oxidative stress-sensitive sumoylation. *Nucleus*. 2014; 5:499–507. [PubMed: 25482067]
- Saitoh H, Hinchey J. Functional heterogeneity of small ubiquitin-related protein modifiers SUMO-1 versus SUMO-2/3. *J Biol Chem*. 2000; 275:6252–6258. [PubMed: 10692421]
- Sarge KD, Park-Sarge OK. Sumoylation and human disease pathogenesis. *Trends Biochem Sci*. 2009; 34:200–205. [PubMed: 19282183]
- Schuler M, Ali F, Chambon C, Duteil D, Bornert JM, Tardivel A, Desvergne B, Wahli W, Chambon P, Metzger D. PGC1alpha expression is controlled in skeletal muscles by PPARbeta, whose ablation results in fiber-type switching, obesity, and type 2 diabetes. *Cell Metab*. 2006; 4:407–414. [PubMed: 17084713]
- Seifert A, Schofield P, Barton GJ, Hay RT. Proteotoxic stress reprograms the chromatin landscape of SUMO modification. *Sci Signal*. 2015; 8:rs7. [PubMed: 26152697]
- Shao RJ, Zhang FP, Tian F, Friberg PA, Wang XY, Sjoland H, Billig H. Increase of SUMO-1 expression in response to hypoxia: direct interaction with HIF-1 alpha in adult mouse brain and heart in vivo. *FEBS Lett*. 2004; 569:293–300. [PubMed: 15225651]
- Shimizu M, Yamashita D, Yamaguchi T, Hirose F, Osumi T. Aspects of the regulatory mechanisms of PPAR functions: analysis of a bidirectional response element and regulation by sumoylation. *Mol Cell Biochem*. 2006; 286:33–42. [PubMed: 16534556]
- Shin YS, Chan C, Vidal AJ, Brody T, Stokstad EL. Subcellular localization of gamma-glutamyl carboxypeptidase and of folates. *Biochim Biophys Acta*. 1976; 444:794–801. [PubMed: 186108]
- Simon DN, Domaradzki T, Hofmann WA, Wilson KL. Lamin A tail modification by SUMO1 is disrupted by familial partial lipodystrophy-causing mutations. *Mol Biol Cell*. 2013; 24:342–350. [PubMed: 23243001]
- Smirnova E, Griparic L, Shurland DL, van der Bliek AM. Dynamin-related protein Drp1 is required for mitochondrial division in mammalian cells. *Mol Biol Cell*. 2001; 12:2245–2256. [PubMed: 11514614]
- Song T, Li GL, Jing GP, Jiao XH, Shi JN, Zhang B, Wang L, Ye XM, Cao FL. SUMO1 polymorphisms are associated with non-syndromic cleft Dip with or without cleft palate. *Biochem Biophys Res Commun*. 2008; 377:1265–1268. [PubMed: 18983974]
- Sonoda J, Mehl IR, Chong LW, Nofsinger RR, Evans RM. PGC-1beta controls mitochondrial metabolism to modulate circadian activity, adaptive thermogenesis, and hepatic steatosis. *Proc Natl Acad Sci U S A*. 2007; 104:5223–5228. [PubMed: 17360356]
- Soyal SM, Nofziger C, Dossena S, Paulmichl M, Patsch W. Targeting SREBPs for treatment of the metabolic syndrome. *Trends Pharmacol Sci*. 2015; 36:406–416. [PubMed: 26005080]
- Speckman RA, Garg A, Du F, Bennett L, Veile R, Arioglu E, Taylor SI, Lovett M, Bowcock AM. Mutational and haplotype analyses of families with familial partial lipodystrophy (Dunnigan variety) reveal recurrent missense mutations in the globular C-terminal domain of lamin A/C. *Am J Hum Genet*. 2000; 66:1192–1198. [PubMed: 10739751]

- Spoden GA, Morandell D, Ehehalt D, Fiedler M, Jansen-Durr P, Hermann M, Zwerschke W. The SUMO-E3 ligase PIAS3 targets pyruvate kinase M2. *J Cell Biochem.* 2009; 107(2):293–302. [PubMed: 19308990]
- Stehmeier P, Muller S. Phospho-Regulated SUMO Interaction Modules Connect the SUMO System to CK2 Signaling. *Mol Cell.* 2009; 33:400–409. [PubMed: 19217413]
- Stein S, Schoonjans K. Molecular basis for the regulation of the nuclear receptor LRH-1. *Curr Opin Cell Biol.* 2015; 33:26–34. [PubMed: 25463843]
- Stover PJ. Physiology of folate and vitamin B12 in health and disease. *Nutr Rev.* 2004; 62:S3–12. [PubMed: 15298442]
- Stover PJ, Field MS. Trafficking of intracellular folates. *Adv Nutr.* 2011; 2:325–331. [PubMed: 22332074]
- Stover PJ, Chen LH, Suh JR, Stover DM, Keyomarsi K, Shane B. Molecular cloning, characterization, and regulation of the human mitochondrial serine hydroxy-methyltransferase gene. *J Biol Chem.* 1997; 272:1842–1848. [PubMed: 8999870]
- Subramonian D, Raghunayakula S, Olsen JV, Beningo KA, Paschen W, Zhang XD. Analysis of changes in SUMO-2/3 modification during breast cancer progression and metastasis. *J Proteome Res.* 2014; 13:3905–3918. [PubMed: 25072996]
- Suen DF, Norris KL, Youle RJ. Mitochondrial dynamics and apoptosis. *Genes Dev.* 2008; 22:1577–1590. [PubMed: 18559474]
- Taguchi N, Ishihara N, Jofuku A, Oka T, Mihara K. Mitotic phosphorylation of dynamin-related GTPase Drp1 participates in mitochondrial fission. *J Biol Chem.* 2007; 282:11521–11529. [PubMed: 17301055]
- Tahmasebi S, Ghorbani M, Savage P, Yan K, Gocevski G, Xiao L, You L, Yang XJ. Sumoylation of Kruppel-like factor 4 inhibits pluripotency induction but promotes adipocyte differentiation. *J Biol Chem.* 2013; 288:12791–12804. [PubMed: 23515309]
- Tallec LP, Kirsh O, Lecomte MC, Viengchareun S, Zennaro MC, Dejean A, Lombes M. Protein inhibitor of activated signal transducer and activator of transcription 1 interacts with the N-terminal domain of mineralocorticoid receptor and represses its transcriptional activity: Implication of small ubiquitin-related modifier 1 modification. *Mol Endocrinol.* 2003; 17:2529–2542. [PubMed: 14500761]
- Tammsalu T, Matic I, Jaffray EG, Ibrahim AF, Tatham MH, Hay RT. Proteome-wide identification of SUMO2 modification sites. *Sci Signal.* 2014; 7:rs2. [PubMed: 24782567]
- Tammsalu T, Matic I, Jaffray EG, Ibrahim AF, Tatham MH, Hay RT. Proteome-wide identification of SUMO modification sites by mass spectrometry. *Nat Protoc.* 2015; 10:1374–1388. [PubMed: 26292070]
- Tang S, Huang G, Tong X, Xu L, Cai R, Li J, Zhou X, Song S, Huang C, Cheng J. Role of SUMO-specific protease 2 in reprogramming cellular glucose metabolism. *PLoS One.* 2013; 8:e63965. [PubMed: 23691130]
- Tang MR, Wang YX, Han SY, Guo S, Wang D. SUMO1 genetic polymorphisms may contribute to the risk of nonsyndromic cleft lip with or without palate: a meta-analysis. *Genet Test Mol Biomarkers.* 2014; 18:616–624. [PubMed: 25111678]
- Tempe D, Vives E, Brockly F, Brooks H, De Rossi S, Piechaczyk M, Bossis G. SUMOylation of the inducible (c-Fos:c-Jun)/AP-1 transcription complex occurs on target promoters to limit transcriptional activation. *Oncogene.* 2014; 33:921–927. [PubMed: 23396363]
- Thorens B, Mueckler M. Glucose transporters in the 21st Century. *Am J Phys.* 2010; 298:E141–E145.
- Tirard M, Almeida OFX, Hutzler P, Melchior F, Michaelidis TM. Sumoylation and proteasomal activity determine the transactivation properties of the mineralocorticoid receptor. *Mol Cell Endocrinol.* 2007; 268:20–29. [PubMed: 17314004]
- Tojo M, Matsuzaki K, Minami T, Honda Y, Yasuda H, Chiba T, Saya H, Fujii-Kuriyama Y, Nakao M. The aryl hydrocarbon receptor nuclear transporter is modulated by the SUMO-1 conjugation system. *J Biol Chem.* 2002; 277:46576–46585. [PubMed: 12354770]
- Tong L, Wu Z, Ran M, Chen Y, Yang L, Zhang H, Zhang L, Dong H, Xiong L. The role of SUMO-conjugating enzyme Ubc9 in the neuroprotection of isoflurane preconditioning against ischemic neuronal injury. *Mol Neurobiol.* 2015; 51:1221–1231. [PubMed: 24961570]

- Toyama EQ, Herzig S, Courchet J, Lewis TL Jr, Loson OC, Hellberg K, Young NP, Chen H, Polleux F, Chan DC, Shaw RJ. Metabolism. AMP-activated protein kinase mediates mitochondrial fission in response to energy stress. *Science*. 2016; 351:275–281. [PubMed: 26816379]
- Trajkovski M, Mziaut H, Altkruger A, Ouwendijk J, Knoch KP, Muller S, Solimena M. Nuclear translocation of an ICA512 cytosolic fragment couples granule exocytosis and insulin expression in β -cells. *J Cell Biol*. 2004; 167:1063–1074. [PubMed: 15596545]
- Tremblay AM, Wilson BJ, Yang XJ, Giguere V. Phosphorylation-dependent sumoylation regulates estrogen-related receptor- α and - γ transcriptional activity through a synergy control motif. *Mol Endocrinol*. 2008; 22:570–584. [PubMed: 18063693]
- Treuter E, Venticlef N. Transcriptional control of metabolic and inflammatory pathways by nuclear receptor SUMOylation. *Biochim Biophys Acta*. 2011; 1812:909–918. [PubMed: 21172431]
- Twig G, Hyde B, Shirihai OS. Mitochondrial fusion, fission and autophagy as a quality control axis: the bioenergetic view. *Biochim Biophys Acta*. 2008; 1777:1092–1097. [PubMed: 18519024]
- Vadrot N, Duband-Goulet I, Cabet E, Attanda W, Barateau A, Vicart P, Gerbal F, Briand N, Vigouroux C, Oldenburg AR, Lund EG, Collas P, Buendia B. The p.R482W substitution in A-type lamins deregulates SREBP1 activity in Dunnigan-type familial partial lipodystrophy. *Hum Mol Genet*. 2015; 24:2096–2109. [PubMed: 25524705]
- Vazquez-Carrera M. Unraveling the effects of PPAR β /delta on insulin resistance and cardiovascular disease. *Trends Endocrinol Metab*. 2016; 27:319–334. [PubMed: 27005447]
- Venticlef N, Jakobsson T, Ehrlund A, Dandimopoulos A, Mikkonen L, Ellis E, Nilsson LM, Parini P, Janne OA, Gustafsson JA, Steffensen KR, Treuter E. GPS2-dependent corepressor/SUMO pathways govern anti-inflammatory actions of LRH-1 and LXR β in the hepatic acute phase response. *Genes Dev*. 2010; 24:381–395. [PubMed: 20159957]
- Vu EH, Kraus RJ, Mertz JE. Phosphorylation-dependent sumoylation of estrogen-related receptor α 1. *Biochemistry*. 2007; 46:9795–9804. [PubMed: 17676930]
- Wadosky KM, Willis MS. The story so far: post-translational regulation of peroxisome proliferator-activated receptors by ubiquitination and SUMOylation. *Am J Phys*. 2012; 302:H515–H526.
- Wai T, Langer T. Mitochondrial dynamics and metabolic regulation. *Trends Endocrinol Metab*. 2016; 27:105–117. [PubMed: 26754340]
- Wang CY, She JX. SUMO4 and its role in type 1 diabetes pathogenesis. *Diabetes Metab Res Rev*. 2008; 24:93–102. [PubMed: 17990297]
- Wang YX, Zhang CL, Yu RT, Cho HK, Nelson MC, Bayuga-Ocampo CR, Ham J, Kang H, Evans RM. Regulation of muscle fiber type and running endurance by PPAR δ . *PLoS Biol*. 2004; 2:e294. [PubMed: 15328533]
- Wang J, Chen L, Wen S, Zhu HP, Yu W, Moskowitz IP, Shaw GM, Finnell RH, Schwartz RJ. Defective sumoylation pathway directs congenital heart disease. *Birth Defects Res*. 2011; 91:468–476.
- Warburg O. The metabolism of carcinoma cells. *J Cancer Res Ther*. 1925; 9:148–163.
- Warburg O, Wind F, Negelein E. The metabolism of tumors in the body. *J Gen Physiol*. 1927; 8:519–530. [PubMed: 19872213]
- Wasiak S, Zunino R, McBride HM. Bax/Bak promote sumoylation of DRP1 and its stable association with mitochondria during apoptotic cell death. *J Cell Biol*. 2007; 177:439–450. [PubMed: 17470634]
- Waterham HR, Koster J, van Roermund CW, Mooyer PA, Wanders RJ, Leonard JV. A lethal defect of mitochondrial and peroxisomal fission. *N Engl J Med*. 2007; 56:1736–1741.
- Weber LW, Boll M, Stampfl A. Maintaining cholesterol homeostasis: sterol regulatory element-binding proteins. *World J Gastroenterol*. 2004; 10:3081–3087. [PubMed: 15457548]
- Wilkinson KA, Henley JM. Mechanisms, regulation and consequences of protein SUMOylation. *Biochem J*. 2010; 428:133–145. [PubMed: 20462400]
- Woeller CF, Anderson DD, Szebenyi DME, Stover PJ. Evidence for small ubiquitin-like modifier-dependent nuclear import of the thymidylate biosynthesis pathway. *J Biol Chem*. 2007; 282:17623–17631. [PubMed: 17446168]
- Wong N, Ojo D, Yan J, Tang D. PKM2 contributes to cancer metabolism. *Cancer Lett*. 2015; 356:184–191. [PubMed: 24508027]

- Xu J, Sun HY, Xiao FJ, Wang H, Yang Y, Wang L, Gao CJ, Guo ZK, Wu CT, Wang LS. SENP1 inhibition induces apoptosis and growth arrest of multiple myeloma cells through modulation of NF-kappaB signaling. *Biochem Biophys Res Commun*. 2015; 460:409–415. [PubMed: 25791478]
- Yamano K, Matsuda N, Tanaka K. The ubiquitin signal and autophagy: an orchestrated dance leading to mitochondrial degradation. *EMBO Rep*. 2016; 17:300–316. [PubMed: 26882551]
- Yamashita D, Yamaguchi T, Shimizu M, Nakata N, Hirose F, Osumi T. The transactivating function of peroxisome proliferator-activated receptor gamma is negatively regulated by SUMO conjugation in the amino-terminal domain. *Genes Cells*. 2004; 9:1017–1029. [PubMed: 15507114]
- Yan DY, Davis FJ, Sharrocks AD, Im HJ. Emerging roles of SUMO modification in arthritis. *Gene*. 2010; 466:1–15. [PubMed: 20627123]
- Yang W, Paschen W. SUMO proteomics to decipher the SUMO-modified proteome regulated by various diseases. *Proteomics*. 2015; 15:1181–1191. [PubMed: 25236368]
- Yang W, Sheng H, Homi HM, Warner DS, Paschen W. Cerebral ischemia stroke and small ubiquitin-like modifier (SUMO) conjugation - a new target for therapeutic intervention? *J Neurochem*. 2008a; 106:989–999. [PubMed: 18410505]
- Yang W, Sheng H, Warner DS, Paschen W. Transient focal cerebral ischemia induces a dramatic activation of small ubiquitin-like modifier conjugation. *J Cereb Blood Flow Metab*. 2008b; 28:892–896. [PubMed: 18167501]
- Yang W, Sheng HX, Warner DS, Paschen W. Transient global cerebral ischemia induces a massive increase in protein sumoylation. *J Cereb Blood Flow Metab*. 2008c; 28:269–279. [PubMed: 17565359]
- Yang W, Thompson JW, Wang ZF, Wang LL, Sheng HX, Foster MW, Moseley MA, Paschen W. Analysis of oxygen/glucose-deprivation-induced changes in SUMO3 conjugation using SILAC-based quantitative proteomics. *J Proteome Res*. 2012; 11:1108–1117. [PubMed: 22082260]
- Yang P, Hu S, Yang F, Guan XQ, Wang SQ, Zhu P, Xiong F, Zhang S, Xu J, Yu QL, Wang CY. Sumoylation modulates oxidative stress relevant to the viability and functionality of pancreatic beta cells. *Am J Transl Res*. 2014; 6:353–360. [PubMed: 25075252]
- Yeh ETH. SUMOylation and de-SUMOylation: wrestling with life's processes. *J Biol Chem*. 2009; 284:8223–8227. [PubMed: 19008217]
- Yokota K, Shibata H, Kurihara I, Kobayashi S, Suda N, Murai-Takeda A, Saito I, Kitagawa H, Kato S, Saruta T, Itoh H. Coactivation of the N-terminal transactivation of mineralocorticoid receptor by Ubc9. *J Biol Chem*. 2007; 282:1998–2010. [PubMed: 17105732]
- Yokoyama C, Wang X, Briggs MR, Admon A, Wu J, Hua X, Goldstein JL, Brown MS. SREBP-1, a basic-helix-loop-helix-leucine zipper protein that controls transcription of the low density lipoprotein receptor gene. *Cell*. 1993; 75:187–197. [PubMed: 8402897]
- Zhang YQ, Sarge KD. Sumoylation regulates lamin A function and is lost in lamin A mutants associated with familial cardiomyopathies. *J Cell Biol*. 2008; 182:35–39. [PubMed: 18606848]
- Zhang Y, Gan Z, Huang P, Zhou L, Mao T, Shao M, Jiang X, Chen Y, Ying H, Cao M, Li J, Li J, Zhang WJ, Yang L, Liu Y. A role for protein inhibitor of activated STAT1 (PIAS1) in lipogenic regulation through SUMOylation-independent suppression of liver X receptors. *J Biol Chem*. 2012; 287:37973–37985. [PubMed: 22969086]
- Zhong S, Muller S, Ronchetti S, Freemont PS, Dejean A, Pandolfi PP. Role of SUMO-1-modified PML in nuclear body formation. *Blood*. 2000; 95:2748–2753. [PubMed: 10779416]
- Zhou W, Ryan JJ, Zhou H. Global analyses of sumoylated proteins in *Saccharomyces cerevisiae*-induction of protein sumoylation by cellular stresses. *J Biol Chem*. 2004; 279:32262–32268. [PubMed: 15166219]
- Zunino R, Schauss A, Rippstein P, Andrade-Navarro M, McBride HM. The SUMO protease SENP5 is required to maintain mitochondrial morphology and function. *J Cell Sci*. 2007; 120:1178–1188. [PubMed: 17341580]

Fig. 9.1.

The sumoylation of SREBPs recruits a co-repressor complex which includes HDAC3. The recruitment of HDAC3 containing complex reduces the transcriptional activity of SREBPs. SUMO is only required for the formation of the co-repressor complex, as the complex continues to repress once SUMO is removed. Alternatively, SREBPs can be phosphorylated by MAPKs which inhibit sumoylation by competing for sites nearby the sumoylation motif. SREBP phosphorylation allows for transcriptional activation of lipid biosynthesis by expressing genes that contain sterol-response elements

Fig. 9.2.

(a) Under basal conditions, SUMO modified KLF5 is part of a co-repressor complex that contains unliganded PPAR- δ . The KLF5 co-repressor complex inhibits the transcription of the lipid oxidation gene Cpt1b and uncoupling protein genes Ucp2 and Ucp3. (b) Upon PPAR- δ ligand stimulation, KLF5 is desumoylated by SENP1 allowing for the exchange of co-repressors for co-activators. (c) Desumoylation of KLF induces the interaction of KLF5 and PPAR- δ allowing for the induction of Cpt1b, Ucp2, and Ucp3 transcription

Fig. 9.3.

Compartmentation of folate-mediated one-carbon metabolism in the cytoplasm, mitochondria, and nucleus. One-carbon metabolism in the cytoplasm is required for the de novo synthesis of purines and thymidylate, and for remethylation of homocysteine to methionine. One-carbon metabolism in the nucleus synthesizes dTMP from dUMP and serine. *AICARTase*, aminoimidazole-4-carboxamide ribonucleotide transferase; *DHFR*, dihydrofolate reductase; *GARTase*, 10-formyltetrahydrofolate:5'-phosphoribosylglycinamide N-formyltransferase; *MTHFD1*, Methylene-tetrahydrofolate Dehydrogenase; *NADPH*, nicotinamide adenine dinucleotide phosphate; *SHMT1*, Cytoplasmic Serine Hydroxymethyltransferase; *TYMS*, Thymidylate Synthase; *THF*, tetrahydrofolate

Table 9.1

Role of Sumoylation in metabolism through the regulation of the activities of transcription factors

Metabolic transcription factor	Affected metabolic pathways	SUMO connections/effect of sumoylation on activity and metabolism	References
Pregnane and Xenobiotic Receptor (PXR)	Metabolism and elimination of noxious endobiotics and xenobiotics; role in inflammatory bowel disease and cancer; glucose and lipid metabolism in liver	Sumoylation by SUMO-1/SUMO-acetylation switch/enhanced activity, increased expression of CYP3A4, CYP2C9, MDR1 and UGT1A1 genes	Cui et al. (2016), Hu et al. (2010) and Priyanka et al. (2016)
Steroidogenic Factor 1 (SF-1) nuclear receptor	Energy balance; development of the ventral medial nucleus of the hypothalamus (VMH) and the maintenance of normal body weight; sexual development and reproduction; gonadal and adrenal steroidogenesis	Sumoylation by SUMO via PIASy and PIASxalpha/SUMO-mediated repression of activity	Lee et al. (2005), Komatsu et al. (2004) and Lee et al. (2016a)
Liver Receptor Homolog 1 (LRH-1, or Nr5a2, PHR-1, hB1F)	Binds phospholipids; steroid synthesis and ovulation; production and secretion of the pancreatic digestive juice; lipid metabolism in inflammation	Sumoylation by SUMO-1/ repression of activity through association with PML nuclear bodies; anti-inflammatory hepatic transrepression (acute phase response)	Stein and Schoonjans (2015), Treuter and Venteclef (2011) and Venteclef et al. (2010)
Peroxisome Proliferator-Activated Receptor alpha (PPAR α)	Female-specific repression of hepatic genes involved in steroid metabolism and immunity	Sumoylation/protection against estrogen-induced intrahepatic cholestasis	Leuenberger et al. (2009) and Pourcet et al. (2010)
Peroxisome Proliferator-Activated Receptor beta/delta (PPAR β/δ)	Fatty acid metabolism in skeletal muscle	Desumoylation via SENP2/ desumoylation of PPAR β/δ , recruitment to the promoters of genes involved in fatty acid oxidation; fatty acid metabolism in C2C12 myotubes	Koo et al. (2015)
Peroxisome Proliferator-Activated Receptor gamma (PPAR γ)	Adipogenesis, glucose homeostasis and inflammation in adipocytes; antagonism of inflammatory responses by transrepression of nuclear factor kappa B (NF-kappaB) target genes	Sumoylation by SUMO-1, SUMO-2 via PIAS1 and PIASx β / desumoylation via SENP2/Ligand binding-mediated decrease in sumoylation; SUMO-mediated repression of transcriptional activity; transrepression of NF-kB signaling in inflammation; sumoylation-mediated prevention of clearance of the corepressor complex	Chung et al. (2011), Diezko and Suske (2013), Ghisletti et al. (2007), Jennewein et al. (2008), Ohshima et al. (2004), Pascual et al. (2005), Shimizu et al. (2006), Wadosky and Willis (2012) and Yamashita et al. (2004)
Sterol Regulatory Element Binding Protein 1 and 2 (SREBP-1, SREBP-2)	Lipid biosynthesis and accumulation	Sumoylation via PIASy/Inhibition of SREBP transcriptional activity indirectly through the recruitment of a co-repressor complex that includes histone deacetylase 3 (HDAC3); turning off of hepatic lipogenesis	Arito et al. (2008) and Lee et al. (2014a)
Krüppel-like transcription factors 4 and 5 (KLF4, KLF5)	Cell proliferation; cell cycle; apoptosis; migration, differentiation, and stemness; pluripotency; energy consumption	Sumoylation of KLF5/ sumoylation leads to nuclear localization and transcriptionally-repressive regulatory complexes with unliganded PPAR β/δ and co-repressors/desumoylation is a regulatory switch mediating the transcriptional activation of energy consumption	Du et al. (2008), Oishi et al. (2008) and Tahmasebi et al. (2013)
Promyelocytic Leukemia (PML)	Transcription; mRNA transport; DNA damage response; telomere maintenance; cellular stress response; apoptosis; stem cell maintenance and senescence	Sumoylation by SUMO-1, SUMO-2, SUMO-3/assembly of PML nuclear bodies (PML _{NB}); stabilization of p53	Bernardi and Pandolfi (2007), Borden (2002), de The et al. (2012), Fu et al. (2005), Ishov et al. (1999), Ivanschitz et al. (2015), Kamitani et al.

Metabolic transcription factor	Affected metabolic pathways	SUMO connections/effect of sumoylation on activity and metabolism	References
			(1998), Zhong et al. (2000)
Hypoxia-inducible factor 1 alpha (HIF-1 α)	Adaptive response to hypoxia; enhanced glycolysis; overexpressed in solid tumors	Protein inhibitor of activated STAT3 (PIAS3)-mediated sumoylation/SEN1-mediated desumoylation/	Agbor et al. (2011), Ao et al. (2015), Bae et al. (2004), Bhattacharjee et al. (2016) and Chan et al. (2011), Gu et al. (2014), Kang et al. (2010), Nakagawa et al. (2016), Shao et al. (2004) and Tojo et al. (2002)
Retinoid X receptor alpha (RXR α)	Heterodimeric partner necessary for PPAR action	Sumoylation by SUMO-1/ desumoylation by SUSP1 (SEN6)/SUMO-mediated repression of activity	Choi et al. (2006)
Nuclear Bile Acid Receptor, Farnesoid X receptor (FXR)	Bile acid homeostasis; control of lipid and glucose levels; expression of target genes in response to bile acid signaling in enterohepatic tissues	Sumoylated by SUMO-1/ repression of activity; dysregulated acetyl/SUMO switch of FXR in obesity-related metabolic disorders	Balasubramanian et al. (2013), Kemper (2011) and Kim et al. (2015b)
PPAR γ coactivator 1 alpha (PGC1 α)	Co-activator of PPARs, ERR α , FoxO1, HNF4 α , NRF1; regulation of mitochondrial biogenesis and energy expenditure; adaptive thermogenesis; hepatic gluconeogenesis; mitochondrial biogenesis and respiration in muscle	Sumoylation by SUMO-1/SUMO-mediated repression of activity; decreased mitochondrial biogenesis	Fernandez-Marcos and Auwerx (2011), Guerra de Souza et al. (2016) and Rytinki and Palvimo (2009)
Nuclear Factor kappa B (NF κ B)	Inhibitor protein I κ B α ; multiple myeloma; innate immunity and energy metabolism; chronic inflammation in metabolic diseases	Desumoylation via SENP-1/	Chen et al. (2014) Huang et al. (2013), Kauppinen et al. (2013), Kim et al. (2011), Lee and Miyamoto (2011), Leidner et al. (2014) and Xu et al. (2015)
Oxysterol or Liver X Receptors alpha and beta (LXR α and LXR β)	Cholesterol homeostasis; inhibition of inflammation;	Sumoylation by PIAS1 or HDAC4/anti-inflammatory transrepression in macrophages; suppression of pro-inflammatory TLR4-induced transcription by preventing the NCoR clearance step	Ghisletti et al. (2007), Huang et al. (2011), Lee et al. (2009a), Venteclef et al. (2010) and Zhang et al. (2012)
Glucocorticoid (GR)	Anti-inflammatory effects through tethered transrepression	Sumoylation/formation of (SUMOs)-NCoR1/SMRT-HDAC3 repressing complex	Druker et al. (2013), Holmstrom et al. (2008), Hua et al. (2016a, b) and Paakinaho et al. (2014)
Mineralocorticoid Receptor (MR)	Regulation the ions and water reabsorption in epithelial tissues (nephron, trachea colon, salivary glands); tissue-specific response in non-epithelial tissues	Sumoylation/negative regulation of synergy	Faresse (2014), Tallec et al. (2003), Tirard et al. (2007) and Yokota et al. (2007)
Estrogen-Related Receptors alpha and gamma (ERR α , ERR γ)	Metabolic reprogramming during TLR-induced inflammation; key metabolic regulator; mitochondrial biogenesis; glycolysis; lactate oxidation in cancer metabolism	Sumoylation/association with coregulators; repression of activity	Park et al. (2016), Tremblay et al. (2008) and Vu et al. (2007)