SUMO, hypoxia and the regulation of metabolism

Terence A. Agbor and Cormac T. Taylor
School of Medicine and Medical Science and UCD Conway Institute, University College Dublin, Belfield, Dublin 4, Ireland

Abstract

Post-translational modification is a critical event in the dynamic regulation of protein stability, location, structure, function, activity and interaction with other proteins and as such plays an important role in organism complexity. Over the last 10 years, the extensive and critical role of one such protein modification by SUMO (small ubiquitin-related modifier) has become apparent. The focus of this mini-review will be on recent reports of a possible functional role for the SUMO pathway in the adaptive cellular response to metabolic challenge, such as oxygen deprivation (hypoxia). Here, we will briefly review the evolving evidence for this pathway in the regulation of a number of metabolic regulators and discuss a possible role for SUMOylation in the regulation of basic metabolic function.

Post-translational modification of proteins

Recent developments, which have facilitated genomic cloning, have allowed the first estimations of the number of genes encoded within the nuclear DNA of various species. Rather surprisingly, the number of genes encoded does not show great correlation with organism complexity [1]. For example, although the human genome contains an estimated 23 000–25 000 genes, the Arabidopsis genome contains a similar number of genes despite its encoding a significantly less complex organism. With this in mind, it has become clear that post-transcriptional modifications of mRNA and post-translational modifications of encoded proteins play a critical role in conferring organism complexity [1].

Post-translational modification of proteins is a complex and critical event that allows the regulation of a range of protein parameters including stability, structure, function, activity, intracellular location and interaction with other proteins [4]. A range of post-translational modifications can occur, which may be chemical (e.g. phosphorylation, acetylation, methylation, hydroxylation, glycosylation and nitrosylation), structural (e.g. disulfide bridge formation and proteolytic cleavage) or involve the addition of small protein tags (e.g. ubiquitination and NEDDylation). One of the last kinds of modification, involving the addition of a small protein tag, which has recently received significant attention, is SUMOylation [5,6]. In the present review, we will concentrate on recent evidence implicating the SUMO (small ubiquitin-related modifier) pathway in the regulation of cellular metabolism, particularly under conditions of metabolic stress such as hypoxia.

Protein modification by SUMO

Since its discovery just over a decade ago, SUMOylation of proteins has become recognized as a dynamic and fundamentally important post-translational modification in a range of processes [5]. The importance of this
pathway is underscored by observations that genetic loss of SUMO in *Saccharomyces cerevisiae*, *Caenorhabditis elegans*, *Arabidopsis* and mice is lethal [6]. The human genome encodes three functional SUMO isoforms (SUMO-1, SUMO-2 and SUMO-3) and one isoform that may not be processed to its mature form (SUMO-4). SUMO-1 differs significantly in structure from SUMO-2 and SUMO-3, which are very similar, and modifies a distinct yet overlapping group of proteins. The mechanisms of SUMOylation and its consequences for a range of proteins have recently been expertly reviewed in [5,6] and only the salient points will be outlined below.

First, similar to ubiquitination, the mechanism underlying the reversible and covalent SUMOylation of proteins involves the co-ordinated activities of E1 (activating), E2 (conjugating) and E3 (ligating) enzymes that are involved in SUMO conjugation, and a family of SENPs (SUMO-isopeptidases) that are involved both in SUMO maturation and in deconjugation. Critically, targets of protein SUMOylation can undergo repetitive and rapid cycles of SUMOylation and deSUMOylation, leading to the observation that only a small percentage of target protein is modified at a given moment. However, such a modification may still have a substantial physiological effect [7]. Secondly, SUMOylation of proteins generally, but not exclusively, occurs on lysine residues at exposed ψKXE consensus motifs, where ψ is a large hydrophobic amino acid and X is any amino acid [5,6]. Both nuclear and cytoplasmic proteins can be modified by SUMO and the consequences of SUMOylation include changes in protein localization, stability, activity and interactions with other proteins. Finally, SUMO modification may involve the addition of a single SUMO molecule (monoSUMOylation), multiple SUMO molecules (polySUMOylation) or the addition of heterogeneous tails consisting of SUMO and ubiquitin. Differential roles for these subtypes of modification are currently becoming clear [8].

The regulation of SUMOylation has recently become an area of intense investigation and it has become clear that other modifications including phosphorylation, oxidation and ubiquitination may act to control the degree of SUMOylation of a target protein [5,6]. Cellular conditions that have been associated with altered patterns of protein SUMOylation include heat shock, osmotic stress and oxidative stress [6]. Increased global SUMOylation of proteins has also been observed in cells exposed to metabolic stress including hypoxia, an event which may have important implications for the control of the cellular metabolic response to decreased oxygen supply [9,10].

**Regulating metabolism**

Since its introduction into the earth’s atmosphere as a by-product of bacterial photosynthesis, molecular oxygen has played a critical role in human evolution [11]. The fundamental mechanisms by which cells generate energy in the form of ATP have been known for over 30 years and involve the utilization of molecular oxygen in the aerobic metabolism of glucose by the combined activity of the glycolytic pathway, which occurs in the cytoplasm, and the tricarboxylic acid cycle and electron transport chain, which are housed within mitochondria. These fundamental metabolic processes have been recently reviewed elsewhere [12]. While these processes have been well characterized for some time, it is only with recent genetic and biological tools that we have been able to begin to investigate the mechanisms by which these metabolic processes are regulated as a cell responds to changing environmental conditions, such as nutrient deprivation, fluctuating pH and hypoxia.

The HIF (hypoxia-inducible factor) is a central transcriptional regulator of a cell’s adaptive response to hypoxia [17]. When oxygen supply to a cell is sufficient to satisfy bioenergetics demands, HIF protein expression is repressed by oxygen-dependent hydroxylation of key proline and asparagine residues by a family of hydroxylase enzymes including PHDs (prolyl hydroxylases) (PHD1–3) and an asparagine hydroxylase known as FIH (factor inhibiting HIF). HIF hydroxylation leads to ubiquitination, degradation and transcriptional silencing in a manner dependent on the availability of sufficient oxygen to satisfy metabolic demand. In hypoxia, where oxygen is limited, this oxygen-dependent silencing is repressed, leading to rapid stabilization and transactivation of HIF. Over 200 known target genes for HIF include pro-angiogenic (e.g. vascular endothelial growth factor), vasodilatory [e.g. iNOS (inducible nitric oxide synthase)] and erythropoietic (e.g. erythropoetin) genes, which contribute to adaptation to hypoxia. Another recently appreciated role for HIF is in the regulation of genes involved in the control of cellular metabolism [12,18]. HIF-dependent regulation of a number of metabolic genes in hypoxia serves to enhance glycolysis while decreasing the metabolic function, thus optimizing the cellular metabolic strategy for efficient energy production in hypoxia [12,18]. Importantly, while the cellular adaptive response to hypoxia is critical to survival during metabolic stress, it can also be maladaptive in hypoxic tumours, facilitating tumour survival and disease progression.

**SUMO and the regulation of metabolism by HIF**

The first evidence that SUMOylation of proteins may be associated with altered cellular metabolic states came in 2003 with the demonstration of increased global protein SUMOylation *in vitro* under conditions of decreased oxygen tension (hypoxia; [9]). The study was supported by further studies demonstrating increased patterns of protein SUMOylation in mouse brain and heart following exposure to whole animal hypoxia [10]. In these studies, it was proposed that the basis of hypoxia-dependent increases in protein SUMOylation appears to involve, at least in part, transcriptional up-regulation of SUMO mRNA [9,10]. Subsequent *in vivo* studies, which examined protein SUMOylation in situations of severe metabolic stress including hibernation torpor and...
focal cerebral ischaemia, further supported an in vivo role for increased protein SUMOylation during metabolic stress [13–16]. While these studies demonstrated increased global protein SUMOylation in hypoxia/isaemia/torpor, they did not specifically identify which proteins were targets for SUMOylation under these conditions.

Initial studies investigating the role of hypoxia in the regulation of protein SUMOylation revealed HIF itself to be a target for SUMOylation [10,19]. Recently, further studies have implicated SUMOylation in the control of this transcription factor; however, whether SUMOylation serves to increase or decrease HIF-dependent transcription remains controversial [20–23]. Thus the modulation of HIF and its transcriptional activity in hypoxia is the first mechanism by which SUMOylation may have an impact on cellular metabolism and tissue survival during hypoxia.

The mitochondrion, as the cell’s main site of ATP production, represents a critical organelle in the maintenance of metabolic homeostasis. Recent work has indicated the importance of mitochondrial morphology in the regulation of metabolic function and uncovered complex pathways regulating mitochondrial fission and fusion. A second way by which the SUMO pathway may have an impact on metabolic processes is through the regulation of the balance between mitochondrial fission and fusion, which is critical for a number of processes including the maintenance of numbers of neuronal synapses [5,6]. DRP-1 (dynamin-related protein-1) is a GTPase that plays a critical role in mitochondrial fission and is itself a target for SUMOylation, an event which appears to result in its stabilization. Furthermore, it appears that a further set of as yet unidentified mitochondrial proteins are SUMO substrates, indicating that our understanding of the role of SUMOylation in mitochondrial function is far from complete. The potential roles for SUMO in the regulation of mitochondrial morphology are reviewed elsewhere [5,6].

Because the aerobic metabolism of glucose is the primary source of energy for all eukaryotic cells, it is not surprising that the cellular transport of glucose is a critical event in basal metabolism. A third mechanism by which the SUMO pathway can have an impact on cellular metabolic strategy is through the regulation of membrane glucose transporters. Two membrane transporters of glucose, GLUT1 and GLUT4, have been demonstrated to be substrates for SUMOylation. However, the functional relevance of this modification remains unclear.

**Conclusion**

The SUMOylation of proteins represents a dynamic post-translational modification that may have a significant impact on a variety of protein parameters. While much has been learned about this system in the last decade, significant questions remain as to the specific physiological roles of this process. However, substantial evidence is building that SUMOylation of key regulators of metabolism may represent a newly discovered way by which cells protect themselves during times of metabolic stress (Figure 1).

**Figure 1 | Regulation of metabolism by SUMOylation**

There are at least three points at which SUMO may regulate metabolism under conditions of metabolic stress. First, glucose enters a cell through glucose transporters which may be regulated by SUMOylation. Secondly, mitochondrial morphology may also be under the control of SUMOylation. Thirdly, the transcriptional regulator HIF, which regulates the expression of a range of metabolic genes, may also be a functional target for SUMOylation.

Work in our laboratory is supported by grants from the Science Foundation Ireland and the Marie Curie Foundation.

**References**


©The Authors Journal compilation ©2008 Biochemical Society

Received 11 January 2008
doi:10.1042/BST0360445