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Why always lysine? The ongoing tale of one of the most modified amino acids

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ABSTRACT

The complex physiology of living organisms must be finely-tuned to permit the flexibility required to respond to the changing environment. Evolution has provided an interconnected and intricate array of regulatory mechanisms to facilitate this fine-tuning. The number of genes cannot alone explain the complexity of these mechanisms. Rather, signalling is regulated at multiple levels, from genomic to transcriptional, translational and post-translational. Post-translational modification (PTM) of proteins offers an additional level of regulation after protein synthesis that allows a rapid, controlled and reversible response to environmental cues. Many amino acid side chains are post-translationally modified. These modifications can either be enzymatic, such as the phosphorylation of serine, threonine and tyrosine residues, or non-enzymatic, such as the nitrosylation of cysteine residues. Strikingly, lysine residues are targeted by a particularly high number of PTMs including acetylation, methylation, ubiquitination and sumoylation. Additionally, lysines have recently been identified as the target of the non-enzymatic PTM *poly*-phosphorylation. This novel PTM sees linear chains of inorganic polyphosphates (polyP) covalently attached to lysine residues. Interestingly, polyphosphorylation is indirectly dependent on inositol pyrophosphates, a class of cellular messengers. The attachment of polyP to lysine occurs through the phosphoramidate bond, which, unlike the phosphester bond, is unstable under the conditions used in common mass spectroscopy. This characteristic, together with the diversity of lysine PTMs, suggests that many other lysine modifications may still remain unidentified, raising the intriguing possibility that lysine PTMs may be the major means by which signalling pathways modify protein behaviour.

1. Introduction

The complexity of higher organisms is linked not only to the greater gene number but also to the evolution of an extensive range of regulatory features. One of the most efficient and dynamic ways that evolved to expand the genetic code, is protein post-translational modification (PTM). These modifications change the physicochemical properties of the amino acids side chains, significantly affecting the structural and functional diversity of proteins. Of the 20 standard amino acids coded by the

Abbreviations: PTM, post-translational modifications; KAT, lysine acetyl transferases; PHB, poly[(R)-3-hydroxybutyrate]; PASK, poly acidic, serine and lysine rich domain; PARP, poly ADP ribose polymerase; SAM, S-adenosyl methionine.

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ribosomes, lysine is a hotspot for enzymatic and chemical PTMs. Lysine is not only the most modified amino acid, but also the one subjected to the widerest range of PTMs (Table 1; (Bischoff and Schlüter, 2012)).

Lysine (K) and the structurally similar amino acid arginine (R) are essential α-amino acids (Fig. 1). Lysine contains a long flexible side-chain containing three methyl groups and a terminal ε-amino group (a primary amine). Under physiological conditions, the primary amine is positively charged. Arginine, on the other hand, contains a positively charged guanidinium group. Both lysine and arginine are prone to being located in the outer hydrophilic surface of proteins, with the ε-amino and guanidinium groups, respectively, exposed to solvent due to the significant hydrophobicity of these side chains. These highly reactive groups make these amino acids essential for general protein stability by forming ionic interactions and hydrogen bonds in proteins, DNA and by interacting with water molecules. This effect is particular true for arginine residues as they bring more stability to proteins than lysine due to their geometric structure (Sokalingam et al., 2012); the three asymmetrical nitrogen atoms in the guanidinium group of arginine allow interactions in three possible directions, but only one direction of interaction can be generated from the ε-amino group of lysine (Sokalingam et al., 2012). This allows arginine to form a large number of electrostatic interactions than lysine, which likely results in stronger interactions. For these reasons lysine and arginine have essential roles for the overall protein architecture and function. Modifications affecting their charge often have substantial if not deleterious consequences.

The main aim of this essay is to highlight the great variability of modifications occurring at lysine residues and to speculate on the significance of such diversity. That the reversible reactions of acetylation and methylation are the most well studied lysine PTMs may not directly correlate with either the abundance or importance of these modifications, but may merely reflect the stability of these modifications under the methods available for their detection. Lysine PTMs were originally described more than 50 years ago but only recently, with the improvements in mass spectroscopy and other analytical tools, lysine acetylation and methylation are being better understood and studied in depth. While the scope of the current essay is not to extensively review each lysine PTM (for that we refer the interested reader to the excellent recent reviews listed in Table 1), to appreciate their history, the high diversity and to speculate about the meaning of such variability we must briefly introduce some lysine PTMs.

2. Lysine acetylation

Acetylation was reported more than fifty years ago on histones. Initially, it was described as the reaction of the acetyl group from acetyl-CoA with the α-amino group of an N-terminal amino acid (Allfrey et al., 1964). Later it was described as the reaction with the ε-amino group of a lysine residue (Gershey et al., 1968) resulting in the neutralization of lysine's positive charge. Most lysine acetylation is carried out by lysine acetyl transferases (KATs) however, mostly in the mitochondria where

Table 1
List of lysine modifications.

Lysine modifications	Effect	First reported	Reviewed
Acetylation	Introduces an acetyl functional group into different amino acids the most common of which is lysine.	(Allfrey et al., 1964); (Gershey et al., 1968)	(Choudhary et al., 2014)
Methylation	Adds a methyl group to a substrate or substitutes an atom or group by a methyl group; typically takes place on arginine or lysine residues.	(Ambler and Rees, 1959)	(Paik et al., 2007)
Ubiquitination	Adds an ubiquitin to a lysine residue of a protein substrate.	(Goldstein et al., 1975)	(Kerscher et al., 2006)
Sumoylation	Adds a sumo to a lysine residue of a protein substrate.	(Matunis et al., 1996)	(Flotho and Melchior, 2013)
Phosphorylation	Adds a phosphoryl group to a protein substrate.	(Smith et al., 1974); (Chen et al., 1977)	(Cieśla et al., 2011)
Polyphosphorylation	Adds an inorganic polyphosphate chain onto a lysine residue within an acidic protein domain.	(Azevedo et al., 2015)	This study
Citrullination or Deimination	Converts an arginine into citrulline in a protein.	(Rogers, 1962)	(Wang and Wang, 2013)
Succinylation	Attachment of a succinyl group to lysine residues from succinyl-CoA.	(Zhang et al., 2011)	(Weinert et al., 2013)
Hydroxylation	Addition of a hydroxyl group to the δ-C atom of lysine with the formation of hydroxylysine.	(Van Slyke and Sinex, 1958)	(Yamauchi and Sricholpech, 2012)
Malonylation	Attachment of a malonyl group to lysine residues from malonyl-CoA.	(Peng et al., 2011)	(Hirschey and Zhao, 2015)
Glutarylation	Attachment of a glutaryl group to lysine residues from glutaryl-CoA.	(Tan et al., 2014)	(Hirschey and Zhao, 2015)
Propionylation	Attachment of a propionyl group to lysine residues from propionyl-CoA.	(Chen et al., 2007)	(Choudhary et al., 2014)
Butyrylation	Attachment of a butyryl group to lysine residues from butyryl-CoA.	(Chen et al., 2007)	(Choudhary et al., 2014)
Crotonylation	Attachment of a crotonyl group to lysine residues from crotonyl-CoA.	(Tan et al., 2011)	(Choudhary et al., 2014)
ADP-ribosylation (mono or poly)	Adds ADP ribose moieties to lysine residues	(Hilz et al., 1978)	(Leung, 2014)

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