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Protein lipoylation: an evolutionarily conserved metabolic regulator of health and disease

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Lipoylation is a rare, but highly conserved lysine posttranslational modification. To date, it is known to occur on only four multimeric metabolic enzymes in mammals, yet these proteins are staples in the core metabolic landscape. The dysregulation of these mitochondrial proteins is linked to a range of human metabolic disorders. Perhaps most striking is that lipoylation itself, the proteins that add or remove the modification, as well as the proteins it decorates are all evolutionarily conserved from bacteria to humans, highlighting the importance of this essential cofactor. Here, we discuss the biological significance of protein lipoylation, the importance of understanding its regulation in health and disease states, and the advances in mass spectrometry-based proteomic technologies that can aid these studies.

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Introduction

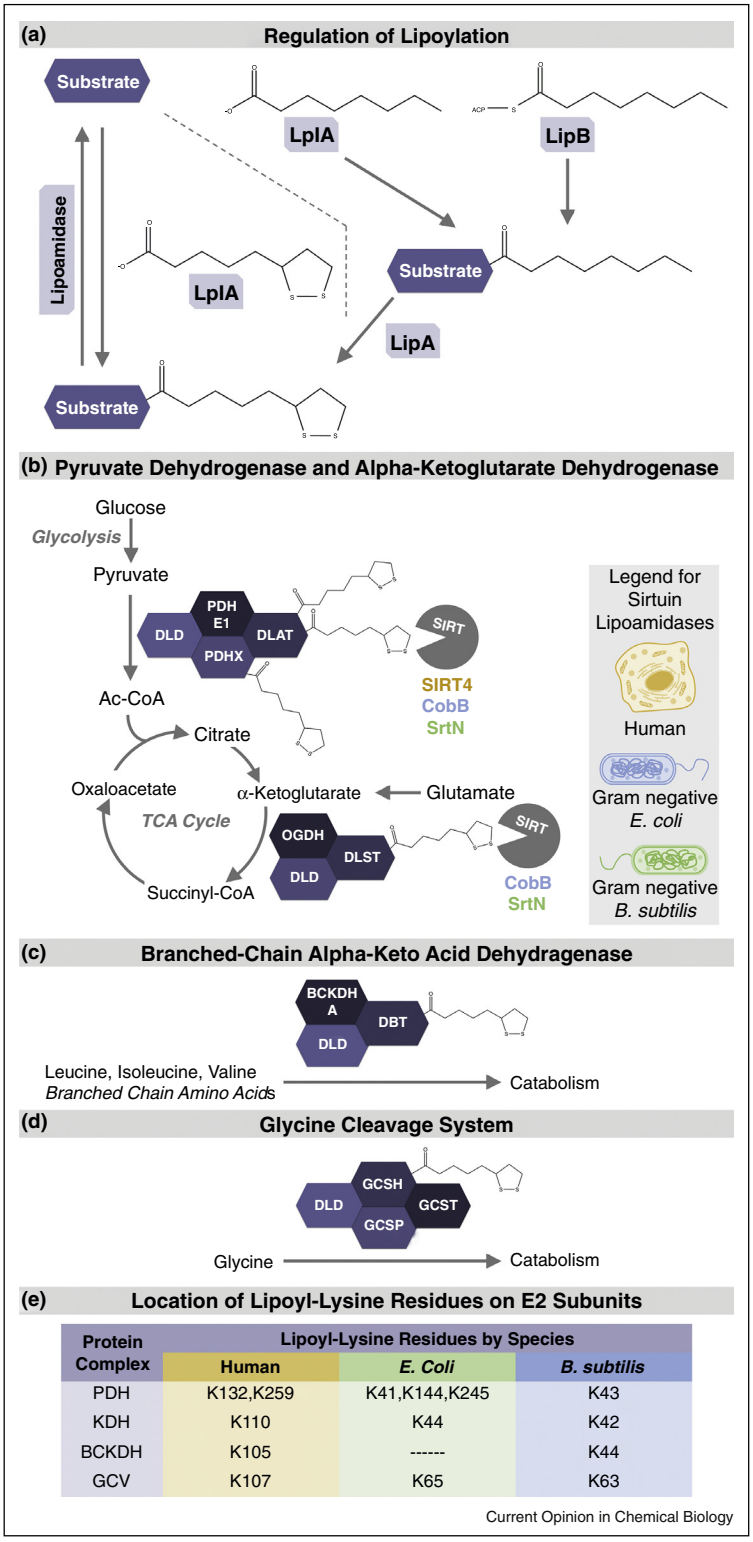
Lipoamide is a cofactor central to cellular metabolism [1•,2]. Present as a lysine posttranslational modification (PTM) on essential multimeric metabolic complexes, this functional group is required for the enzymatic activities of these protein complexes [3,4•]. For example, the pyruvate dehydrogenase (PDH) and alpha-ketoglutarate (KDH) complexes regulate distinct carbon entry points into the central metabolic pathway of the TCA cycle. On both complexes, lipoylation is critical for proper enzyme function, and removal of this modification is part of a cellular mechanism to inhibit their activities. The evolutionary conservation of these lipoylated metabolic enzymes in organisms ranging from bacteria to mammals [2,5,6] underlines the critical role of lipoylation in core metabolic pathways. This theme of conservation is seen across the lipoylated complexes, the proteins that add or remove this modification, as well as the function of lipoylation [4•,5,6,7••,8•]. Given this striking evolutionary conservation for this rare modification, it is perhaps not surprising that these lipoylated enzymes are critically linked to maintenance of health and development of disease. PDH dysregulation is known to contribute to numerous human metabolic disorders, cancer, viral infection, and Alzheimer's disease [9,10•,11–13]. Therefore, advancing the current understanding of the regulation of lipoylation is necessary for defining the underlying molecular causes of these diseases. The low frequency and unique physical characteristics of lipoylation may also offer a therapeutic target for regulating metabolic activities that are disrupted in disease states. Here, we review the function and regulation of protein lipoylation, the importance of understanding its dysregulation, the gap in the knowledge regarding these regulatory mechanisms, and the advanced technologies that can aid these studies. Recent developments in proteomics, such as improvements in quantitative mass spectrometry (MS) and ion mobility, promise to provide new ways to investigate lipoylation in different cell types, tissues, and biological contexts.

Biochemical structure and function

Lipoylation is a posttranslational modification that involves the covalent attachment of lipoamide to a lysine residue via an amide bond [1•,2,5,14,15,16••]. The lipoamide cofactor is an eight-carbon organosulfurous molecule, with C6 and C8 attached to sulfur atoms in a pentatomic ring (Figure 1a). Lipoic acid can have two enantiomeric forms, although only the R(+) form is reactive and produced endogenously [17,18]. Given the large size of lipoyl, for example greater in mass than acetylation or phosphorylation, this modification has the ability to both impact protein structure and provide a 'swinging arm' function for enzymatic reactions [19]. The rotational flexibility of this functional group allows it to move between different subunits within the enzyme complex [3,4•]. This function facilitates substrate channeling and electron transfer during oxidation–reduction reactions. It has been shown to catalyze reactions including hydrogen transfers, decarboxylation and other acyl group transfers [14,15].

Unlike other posttranslational modifications that are dependent upon local amino acid motifs, substrate lipoylation does not seem to be significantly impacted by

Figure 1



Protein Complex	Lipoyl-Lysine Residues by Species		
	Human	*E. Coli*	*B. subtilis*
PDH	K132,K259	K41,K144,K245	K43
KDH	K110	K44	K42
BCKDH	K105	------	K44
GCV	K107	K65	K63

The evolutionarily conserved metabolic role of lipoylation. **(a)** Regulation of lipoylation on substrates. Lipoic acid can be added directly by LplA, or in a stepwise manner using LipB or LplA, followed by LipA. Delipoylation is mediated by lipoamidases (ACP: acyl-carrier protein). **(b)** Pyruvate dehydrogenase (PDH) and alpha-ketoglutarate dehydrogenase (KDH) complexes regulate two points of carbon entry into the TCA cycle. Inhibition of these two complexes has been demonstrated in humans and bacteria by the sirtuin (SIRT)-mediated lipoamidase activity. Font color of each SIRT represents the name of the lipoamidase sirtuin for that species (yellow: human, blue: *E. coli*, green: *B. subtilis*). **(c)** Lipoylated branched-chain