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EDITORIAL

Protein post-translational modifications in cell signalling and disease

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This Forum Issue of *Free Radical Research* addresses the role of protein post-translational modifications in cell signalling and disease with a comprehensive selection of chapters that focus on evaluation strategies, mechanisms and biological significance of protein post-translational modifications.

The role of S-glutathio(ny)lation in cell and apoptotic signalling—reviewed by Dalle Donne et al. [1]—provides an extensive overview of the literature on the biochemical characteristics of S-glutathionylation, cytosolic and mitochondrial targets and their subsequent role in apoptosis. Mitochondrial α-ketoglutarate dehydrogenase—one of the five α-ketoacid dehydrogenase pathways in mitochondria—appears as a sensitive target for S-glutathionylation and is also addressed in the chapter by McLain et al. [2], thus conferring to this enzyme an important redox sensing function by virtue of its catalytic co-factor in the E1 sub-unit, lipoic acid. Lipoic acid glutathionylation and α-ketoglutarate dehydrogenase inhibition are reversible processes that may regulate the flux of reducing equivalents to the electron transport chain and oxidant production in the mitochondrial environment.

Mitochondrial protein post-translational modifications are covered in several chapters in this Forum Issue: Kerner et al. [3] address the significance of protein modifications in the outer mitochondrial membrane for transport processes and mitochondrial signalling. The chapters by Castro et al. [4] and Chinta and Andersen [5] focus on nitric oxide-driven post-translational modifications: the former concentrates on the selective nitration of mitochondrial tyrosine and its impact on bioenergetics with implications for neurodegenerative diseases, metabolic syndrome and ageing and the latter describes the biochemical mechanisms and functional consequences of nitric oxide-derived post-translational modifications on tyrosine and cysteine residues of complex I of the respiratory chain with implications for Parkinson's disease. Butterfield et al. [6] present in their manuscript an extensive analysis of the available literature on 3-nitrotyrosine and 4-hydroxynonenal as two protein post-translational modifications important for the progression of Alzheimer's disease. Grimm et al. [7] further describe how neurodegenerative disorders are characterized by an abnormal accumulation of oxidatively damaged proteins in brain to induce oxidative stress and proteasomal as well as mitochondrial dysfunction, which ultimately promote neuronal cell death as the key neurodegenerative event in Alzheimer's disease and other conditions such as amyotrophic lateral sclerosis.

Protein post-translational modifications are further encountered in metabolic disorders such as diabetes and uremia. These modifications include glycation, nitration and oxidation-derived epitopes that are investigated as free or protein-bound biomarkers by means of different methods. These aspects are discussed by Thornalley and Rabbani [8], who describe current approaches to investigate hotspots of protein damage in biological fluids and tissues using models of interpretation that help determine their pathogenic effects. Succination of protein cysteines represents another modification recently identified in diabetes, which is described in the review paper by Frizzell et al. [9]. S-(2-succinyl) cysteine occurs as an irreversible modification of intracellular proteins by the reaction with the Krebs

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cycle intermediate fumarate. The glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase, cytoskeletal components and chaperone proteins in the endoplasmic reticulum are identified as targets. Succination is suggested to play a role in the causal mechanisms of mitochondrial and endoplasmic reticulum stress in diabetes. Metabolic consequences of protein succination may come from the evidence that the adipose hormone adiponectin is also targeted by this post-translational modification.

Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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