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Sirtuins, metabolism, and DNA repair

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Cells evolve to actively coordinate nutrient availability with cellular activity in order to maintain metabolic homeostasis. In addition, active pathways to repair DNA damage are crucial to avoid deleterious genomic instability. In recent years, it has become increasingly clear that availability of intermediate metabolites may play an important role in DNA repair, suggesting that these two seemingly distant cellular activities may be highly coordinated. The sirtuin family of proteins now described as deacylases (they can also remove acyl groups other than acetyl moieties), it appears to have evolved to control both metabolism and DNA repair. In this review, we discuss recent advances that lay the foundation to understanding the role of sirtuins in these two biological processes, and the potential crosstalk to coordinate them.

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Introduction

Sirtuins are members of a family of evolutionarily conserved enzymes with NAD+-dependent deacylase activity. Since the discovery of *Sir2* (*s*ilencing *i*nformation *r*egulator 2) in the budding yeast *Saccharomyces cerevisiae* as a transcriptional silencer of the mating-type loci more than 20 years ago [1], many studies have demonstrated diverse biological roles for sirtuins, such as in genome stability, cellular metabolism, and lifespan regulation [2,3]. Mammalian sirtuins have seven isoforms (SIRT1-7), each one with unique subcellular localization and distinct functions [4]. SIRT1 and SIRT2 can be found in both nucleus and cytoplasm, SIRT6 and SIRT7 are almost exclusively nuclear and SIRT3, SIRT4, and SIRT5 are located in the mitochondria [5]. Studies on sirtuin biology have shown great progress in the past two decades, emphasizing the critical importance of these enzymes in human biology and disease.

Because of their NAD+ dependency, it had been speculated that sirtuins play a crucial role in modulating energy metabolism. Indeed, sirtuins are broadly recognized as critical regulators of multiple metabolic pathways, including glucose, glutamine, and lipid metabolism [6]. For cells to thrive, energy and metabolic demands have to be carefully coordinated with nutrients availability. As sensors of energy and redox status in cells, these protein deacylases can directly modulate activity of key metabolic enzymes — by posttranslational modifications — as well as regulate transcription of metabolic genes. In addition, several sirtuins play additional roles in metabolic homeostasis. For instance, both SIRT1 and SIRT2 control autophagy responses under various nutrient stress conditions, as modulators of FOXO signaling pathway [7]. Autophagy will be covered in detail in an accompanying article in this issue.

Nuclear sirtuins have also evolved as regulators of genome integrity. Our cells experience $\sim 1 \times 10^4$ to 1×10^5 DNA lesions per day [8], hence they have developed repair machineries to avoid detrimental outcomes from oxidative and genotoxic stress. In the past decade, the roles of sirtuins in maintaining genomic stability have been described, as regulators of DNA repair pathways [9], chromatin structure [10], and telomere maintenance [11,12].

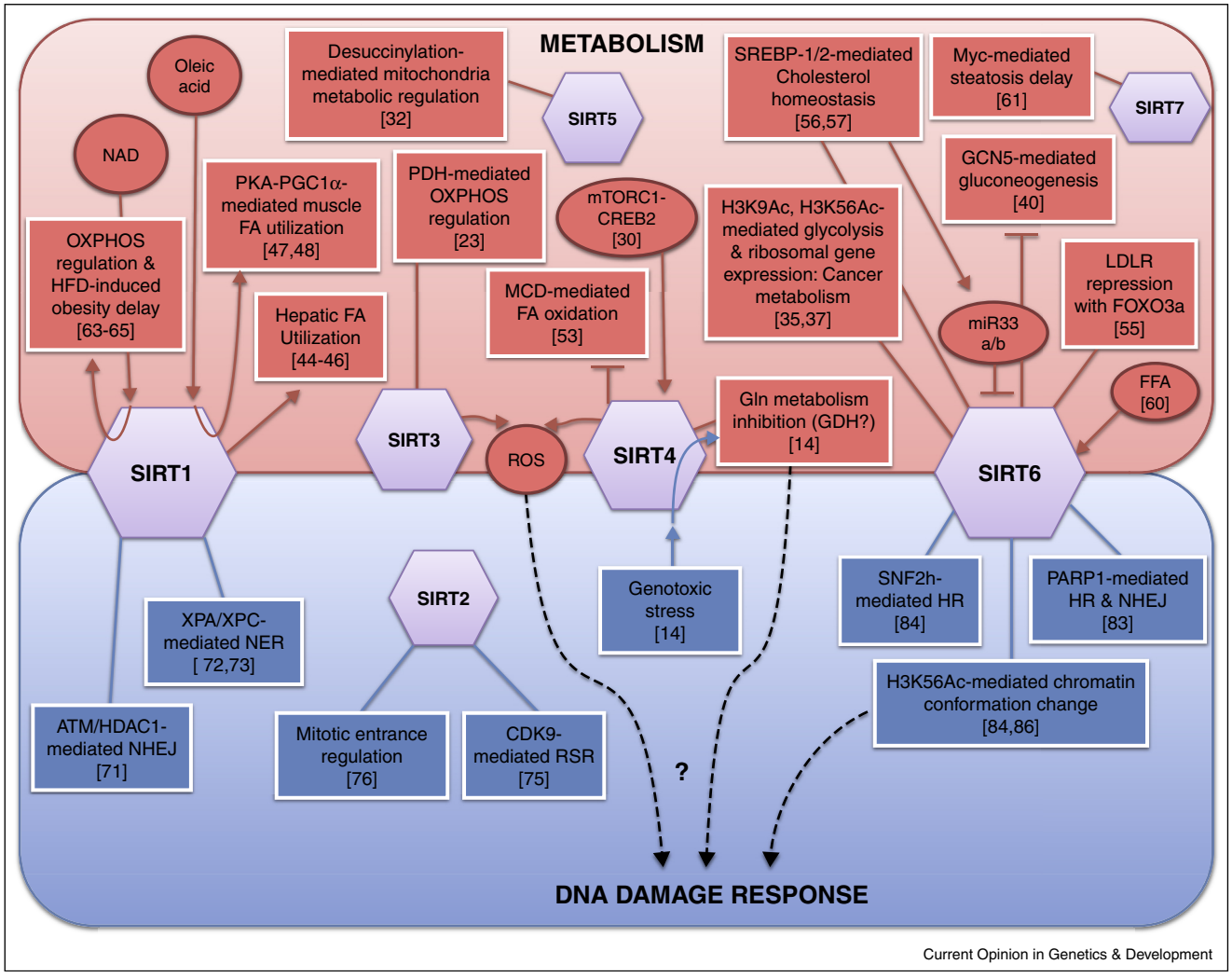
On the basis of the fact that sirtuins possess dual roles in metabolism and DNA repair, sirtuins can serve as nodal points in regulating both processes. Intriguingly, new studies have started to appreciate that DNA damage can directly trigger adaptive metabolic responses [13,14••], indicating that these two seemingly separate biological entities may function in a highly coordinated fashion (Figure 1). In this review, we will focus on recent progress in understanding the roles of sirtuins in both metabolism and DNA repair, and the possible crosstalk between these two phenomena.

Sirtuins in metabolism

Glucose and glutamine metabolism

Since glucose is a primary nutrient for cell survival and proliferation, systemic glucose levels should be tightly regulated throughout tissues. Crucial organs such as liver, muscle, and pancreas are main modulators of glucose homeostasis. At the cellular level, once glucose enters a cell, it is converted into pyruvate in the cytoplasm through glycolysis in a multi-enzyme, strictly regulated

Figure 1



Sirtuins functions in metabolism and DNA repair. A diagram depicting the different functions for the mammalian sirtuins in cellular metabolism (red) and DNA repair (blue). Specific targets and biological roles are summarized.

process. In most cells, pyruvate will then enter the TCA cycle to generate energy through oxidative phosphorylation (OXPHOS) in a highly efficient process (34–36 mols of ATP per mol of glucose). However, in specific cases, pyruvate will be diverted in the cytoplasm to produce lactate, a less efficient way to produce ATP, but a critical adaptive mechanism in cells where OXPHOS is impeded (hypoxia, for instance) or to produce intermediate metabolites for biomass in highly proliferating cells (Figure 1).

Extensive studies have previously shown that SIRT1 can modulate both gluconeogenesis and glycolysis by regulating important metabolic factors, including PGC1α and FOXO [15]. More recently, intracellular levels of NAD+ have been shown to regulate SIRT1 deacetylase activity, affecting high fat diet (HFD)-induced obesity and aging, as discussed below (reviewed in [16]).

SIRT3 is a major mitochondrial protein deacetylase [17•], regulating multiple metabolic proteins such as the TCA cycle protein isocitrate dehydrogenase 2 (IDH2) [18] and key proteins in the electron transfer chain (ETC) [19–21]. In skeletal muscle, SIRT3 plays an important role in regulating metabolic adaptive responses. Decreased levels of SIRT3 cause increasing oxidative stress and insulin resistance [22] and recent studies showed that active deacetylation of pyruvate dehydrogenase (PDH) E1α by SIRT3 provides metabolic flexibility under nutrient stress conditions [23]. Wang and his colleagues discovered that SIRT3 can deacetylate FOXO3a, in turn enhancing FOXO3a activity and expression of its targets,