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Minireview Series on Sirtuins: From Biochemistry to Health and Disease

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The sirtuins are an ancient family of proteins found in all forms of life, displaying a structure and catalytic function that have been maintained from bacteria to humans. In an NAD^+-dependent process, sirtuins perform protein deacylation from lysine-modified ϵ-amino groups, although NAD^+-dependent protein ADP-ribosylation has been reported. The founding member of the family, Sir2 (silent mating-type information regulator 2) from yeast, was identified as a gene required for maintaining silent chromatin (1). After establishing that yeast Sir2 functions as a histone deacetylase, this enzymatic activity provided the mechanistic basis for the role of yeast Sir2 within the silencing machinery (2). Confirmation of enzymatic activity from homologs in other species fueled deeper interest in both the biological functions and protein targets of sirtuins (3). Engendering more general interest were reports linking sirtuins to organismal longevity and their counteractive functions in age-associated cellular decline and metabolic dysfunction (4). Because of potential roles in aging, human health issues, and their unique enzymatic functions, sirtuins have garnered the attention of the general public, and researchers are eager to uncover how these molecular activities explain the physiological outcomes of sirtuin-influenced pathways. Here, we briefly introduce a thematic minireview series that focuses on sirtuin functions, providing an up-to-date summary of where the field is now and where it is likely to move in the upcoming years.

In the minireview entitled "Sirtuin Catalysis and Regulation," Feldman *et al.* introduce the deacetylation reaction catalyzed by sirtuin proteins. The authors discuss the chemical mechanism of catalysis, substrate selection, and acyl group specificity among the known activities of the seven mammalian sirtuins. Molecular regulation by transcription, post-translation, and synthesis of co-substrate NAD^+ is covered. Also, the authors provide a brief summary of efforts to control sirtuin function through the development of small-molecule modulators, specifically activators of SIRT1 function and the controversy surrounding resveratrol as a direct target of SIRT1. As in all of the minireviews in this series, the authors cite the recent evidence that several sirtuins display specificity toward distinct acylated lysines, including propionylation, succinylation, and malonylation.

In the minireview "Structural Basis for Sirtuin Activity and Inhibition," Yuan and Marmorstein discuss the overall structural conservation of the catalytic core domain and how invariant catalytic residues support NAD^+ binding and facilitate catalysis. The authors include a comprehensive table of sirtuin structures and their importance in understanding our current structure-based knowledge. Yuan and Marmorstein highlight how the variability in the peptide/protein-binding pocket dictates substrate selection, particularly how succinylated substrates bind preferentially to SIRT5. Structural evidence supporting proposed catalytic mechanisms is discussed. In addition, the authors discuss the structural basis for inhibition and suggest how nicotinamide, ADP-ribose, and suramin inhibitors could be exploited for future development of more selective inhibitors.

Newman *et al.* summarize the role of sirtuins in regulation of intermediary metabolism in the minireview entitled "Mitochondrial Protein Acylation and Intermediary Metabolism: Regulation by Sirtuins and Implications for Metabolic Disease." The authors focus primarily on the latest developments with the mitochondrial SIRT3, which plays a key role in nitrogen metabolism, fatty acid oxidation, and mitigating reactive oxygen species damage. Specific enzyme targets are cited in support of SIRT3-dependent regulation in these mitochondrial processes. The authors describe recent data that support a role for SIRT3 in opposing several aspects of metabolic syndrome. Included is a detailed discussion of metabolic processes that give rise to acetyl-CoA, succinyl-CoA, and malonyl-CoA and the possible connections between the metabolic fluctuations of these metabolites and how protein acylation levels might be controlled by the resident mitochondrial sirtuins, SIRT3–SIRT5.

In the minireview "From Sirtuin Biology to Human Diseases: An Update," Sebastián *et al.* explore the role of sirtuins in the maintenance of organismal metabolic homeostasis and age-related afflictions that include cancer, neurodegeneration, and cardiovascular disease. They highlight studies that support a counteracting role for sirtuins in age-related phenomenon: SIRT3 prevents age-related hearing loss in mice fed a calorie-restricted diet, and SIRT6 overexpression extends the life span of male mice. The role of SIRT1, SIRT3, and SIRT6 in promoting fatty acid breakdown is discussed in detailed, although the observations of SIRT1 function in fat metabolism appear complex and contradictory in several cases and might reflect tissue- and time-specific effects. Similarly, in relation to cancer, the ability of SIRT1 to suppress or promote tumorigenesis depends on tissue type and the signaling networked involved. Sebastián *et al.* elaborate on the roles of SIRT3 and SIRT6 in cancer metabolism, where sirtuins seem to oppose the Warburg effect. The authors discuss the anti-inflammatory functions reported for sirtuins and several studies that implicate SIRT1, SIRT3, SIRT6, and SIRT7 as regulators of cardiac hypertrophy. Although generally a protective role is ascribed to several sir-

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tuins, there are conflicting reports on the benefits *versus* harmful actions of SIRT1 in cardiac function. Last, the authors briefly describe how SIRT1 in the brain is linked to improved memory and decreased neuropathology related to models of Alzheimer, Parkinson, and Huntington diseases.

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