PREFACE

Forty years ago, Vince Allfrey discovered the reversible acetylation of histone proteins and proposed that this posttranslational modification could regulate gene expression *(1)*. The role of histone acetylation in transcriptional regulation remained controversial until 1996, when two papers reported the identification of the first acetyltransferase, GCN5 *(2)* and the first histone deacetylase, HDAC1 *(3)*. The realization that these enzymes were homologous to previously identified yeast transcriptional regulators established histone acetylation as a key regulatory mechanism for gene expression.

These discoveries have triggered a wave of interest in histone posttranslational modifications and have led to the discovery of 18 potential human histone deacetylases in the past eight years. Human histone deacetylases are divided into three families, Class I (HDAC1, -2, -3, and -8) and Class II HDACs (HDAC4, -5, -6, -7, 9, -10, and -11), are homologous to the yeast histone deacetylases Rpd3 and Hda1, respectively, and share some degree of sequence homology. In contrast, the Class III histone deacetylases are homologous to the yeast protein Sir2 and use NAD as a cofactor. The human class III HDACs are called sirtuins (SIRT1–7). In many cases, these deacetylases target nonhistone proteins for deacetylation, suggesting that their biological activities go beyond gene regulation. Despite the youth of this research field, the first inhibitors of histone deacetylases are in clinical trials as novel anticancer agents.

The purpose of *Histone Deacetylases: Transcriptional Regulation and Other Cellular Functions* is to summarize this rapidly evolving field. Much has been learned about these proteins, including the identification of the enzymes, the elucidation of their enzymatic mechanisms of action, and the identification of their substrates and partners. Structures have been solved for a number of enzymes, alone or in complex with small-molecule inhibitors. Several HDAC genes have been knocked out in mice and their biological roles have been defined. Despite these impressive advances, our knowledge is still fragmentary and much remains to be done.

We hope that this book will serve as a landmark survey of what has been accomplished in these first eight years. We also hope that we have successfully outlined for our readers a clear agenda of what needs to be done in the next few years to define fully the role of HDACs in biology and in disease.

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2. Brownell JE, Zhou J, Ranalli T, et al. *Tetrahymena* histone acetyltransferase A: a homolog to yeast Gcn5p linking histone acetylation to gene activation. Cell 1996;84:843–851.
3. Taunton J, Hassig CA, Schreiber SL. A mammalian histone deacetylase related to the yeast transcriptional regulator Rpd3p. Science 1996;272:408–411.