# Post-transcriptional Mechanisms in Endocrine Regulation

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Editors

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# Preface

The endocrine system is both diverse and complex, controlling a wide array of physiological processes and cellular responses. Hormones induce a variety of effects on cells, including regulation of metabolic processes, by increasing the levels or activity of enzymes and proteins in the target cells. Hormone responses can be amplified through cascades of signal transduction pathways leading to changes in gene expression including synthesis, processing, stability, and translation of mRNAs. Moreover, hormone responses can change enzyme activity through covalent modifications. While activation of gene expression and covalent modification of proteins have been the intense focus of studies for over the past several decades, recent advances in the RNA biology have provided new insights into the role of post-transcriptional mechanisms involved in cellular responses to hormones and other biomolecules.

Throughout biology, post-transcriptional regulatory mechanisms play an essential role in controlling dynamic gene expression. The outcome of this regulation includes control of the amount, timing, and location of protein expression. Regulation is mediated by cis-acting RNA sequences and structures and transacting RNA-binding proteins and noncoding RNAs, including microRNAs. Recent advances in the characterization of these regulatory factors have revealed enormous regulatory potential; thousands of new RNA-binding proteins and microRNAs, which control protein expression in fascinating ways, have been identified in mammals. The goal of this book is to highlight the advances made in the understanding of the regulatory mechanisms by which hormones control these processes.

The first chapter of this volume provides an overview of our current understanding of the various components of post-transcriptional mechanisms including regulatory factors, elements, and general mechanisms that control protein expression. The intent is to provide early stage investigators with an introduction, emphasizing key concepts underlying post-transcriptional regulatory mechanisms.

In subsequent chapters, specific system-based studies on post-transcriptional regulation are described. These chapters were composed by leading experts who summarize current state of knowledge, remaining key questions, and provide perspective for future research goals.

Chapter 2 describes the intricate regulation of expression of insulin and insulin-like growth factors (IGF). The mRNAs encoding these peptide hormones are subject to multiple regulatory mechanisms including alternative RNA processing, regulated mRNA stability, and modulation of translation efficiency. RNA-binding proteins, RNA degrading and modifying enzymes, and noncoding regulatory RNAs (i.e., microRNAs) control expression of insulin and IGF. This work has important relevance to the physiology of energy homeostasis, diabetes, and cancer.

In Chap. 3, mechanisms of regulation of cytokine mRNA during inflammatory response are presented. Emphasis is placed on the cis-acting elements of cytokine mRNAs including the now classic adenosine-uridine rich elements (AREs), which act as bifunctional switches to modulate cytokine mRNA stability. The authors introduce the concepts of combinatorial regulatory control and competitive binding, which form regulatory networks to control cytokine production and modulate innate immune responses. Defects in these control mechanisms contribute to inflammatory autoimmune diseases and cancer.

Chapters 4–7 deal with post-transcriptional regulation of target cell function by reproductive hormones. These processes have important roles in reproductive processes and dysfunction contributes to diseases such as infertility and cancer. In Chap. 4, a novel mechanism of regulation of luteinizing hormone receptor (LHR) mRNA expression by an mRNA-binding protein is presented. In response to physiological changes in the secretion of LH, the expression of LHR mRNA in the ovary undergoes rapid changes, the most striking change occurring after LH surge to induce ovulation. During this period the LH receptor mRNA expression is transiently downregulated by increasing LHR mRNA degradation that is mediated by an unanticipated LHR mRNA-binding protein—a steroid metabolism protein that "moonlights" as an RNA-binding regulator. This chapter highlights important concepts including regulation though mRNA localization, mRNA stability, and translational control. In Chap. 5, the regulation of estrogen receptor, a member of the nuclear receptor family, by its own ligand is described. Evidence is presented showing that estrogen stabilizes its receptor by increasing the binding of a specific protein to the receptor's mRNA. Moreover, microRNAs contribute to translational control of estrogen receptor.

Chapter 6 focuses on the regulation of ovarian function by microRNAs. This chapter provides information on the synthesis and processing of microRNAs. The mechanisms of translational control and mRNA degradation caused by microRNAs are presented. The regulation of microRNAs by differential processing and competitive inhibition by endogenous competitor RNAs is also considered. The authors then describe the important roles of microRNAs and their processing enzymes in controlling ovarian gene expression during reproductive cycles.

Chapter 7 provides a detailed discussion of post-transcriptional control in the germline. Regulation of translation, RNA localization, and decay pervades the germline, gametes, and early embryos in part due to the quiescence of transcription during early developmental stages. Maternal mRNAs are deposited in developing oocytes, stored in a repressed state within RNA-protein granules, and subsequently activated to drive development in response to hormonal cues and fertilization.

Moreover, post-transcriptional control specifies body pattern formation and designates the primordial germline. This chapter highlights multiple key regulators that control these crucial events.

Chapter 8 focuses on VEGF-A, a hormone that controls angiogenesis during development and wound healing, among other processes. Proper control of VEGF-A is crucial and dysregulation contributes to cancer and other disorders. Control of VEGF-A is intricate, as the authors guide the reader through the diverse mechanisms that control VEGF-A expression and function including alternative mRNA processing, mechanisms of destabilization and stabilization of the mRNA, and translational control, mediated by cis-acting RNA elements, RNA-binding proteins, and microRNAs.

Prostaglandins are lipid hormones that control reproductive physiology and inflammation. Chapter 9 explores the pathway of prostanoid biosynthesis and the post-transcriptional mechanisms that control these enzymes. Multiple RNA-binding proteins and microRNAs control translation, stability, and localization of mRNAs encoding prostanoid biosynthesis enzymes. This regulation involves regulated and coordinated mRNA degradation pathways and enzymes. Additionally, mRNA localization to specialized intracellular granules contributes to the control of prostaglandin synthesis. These layers of regulation ensure proper control of prostaglandins, which is crucial since unregulated expression contributes to cancer and inflammatory diseases.

Chapter 10 explores post-transcriptional regulation of production of the secreted peptide hormone leptin. Leptin is produced by fat cells and contributes to the control of appetite and energy storage and homeostasis. This hormone has a major impact on obesity and dieting. Leptin production is controlled at the post-transcriptional level by insulin signaling through the important mammalian target of rapamycin pathway (mTOR), which controls translation efficiency of mRNAs.

Post-transcriptional mechanisms that control parathyroid hormone gene expression are explored in Chap. 11. Parathyroid hormone has crucial role in the control of mineral metabolism and bone strength. Regulation of this secreted peptide hormone is achieved by RNA-binding proteins that interact with the hormone's mRNA to stabilize or degrade the mRNA in response to serum calcium, phosphate, and vitamin D.

Chapter 12 illuminates the pathways of steroid hormone biosynthesis, which broadly influence metabolism, physiology, reproduction, and immune function. The authors explain the roles of post-transcriptional and post-translational mechanisms that operate to control steroid production, emphasizing the roles of microRNAs in translational control and mRNA degradation of the biosynthetic enzymes.

Glucocorticoids are steroid hormones that control immune function and stress response. Chapter 13 examines the post-transcriptional regulation by glucocorticoid including modulation of cytokine translation and mRNA stability. Multiple mechanisms appear to contribute to regulation. Glucocorticoid receptor, a ligand-activated transcription factor, regulates RNA synthesis to modulate signal transduction and the expression and activity of RNA-binding proteins and microRNAs. These effects drive changes in mRNA stability and translation. Surprisingly, recent evidence

indicates that glucocorticoid receptor can bind to mRNA directly to control degradation of specific mRNAs in the cytoplasm.

Chapter 14 surveys post-transcriptional regulation by brain-derived neurotrophic factor (BDNF) in the nervous system. Protein expression in neurons is controlled by intricate mechanisms including RNA localization to synapses and repression and activation of specific mRNAs in response to signals. These mechanisms contribute to the control of neuronal activity, synaptic plasticity, and longer-term memory formation. BDNF plays an important role in controlling activity-dependent gene expression in neurons by globally enhancing translation through mTOR pathway. Certain mRNAs are specifically affected by BDNF signaling, and this selectivity is determined by the activities of specific RNA-binding factors that control translation and mRNA stability.

We thank the authors for their time and effort to contribute to this book and for their cooperation for timely submission. We hope the information presented in this book will be a valuable source of current state of knowledge for experts as well as beginners who wish to pursue future research in this exciting area.

Finally we thank Springer for the opportunity to edit this volume dealing with post-transcriptional mechanism in endocrine regulation. Special thanks to former Editor, Meredith Clinton, of Endocrinology at Springer for her support in the initial stages and Kelly Wilson, Associate Editor, Endocrinology, Springer Science and Business Media, for her support in making our effort a reality. We appreciate the assistance of Kelly Studer, Administrative Assistant at the University of Michigan, who cheerfully provided us administrative support during the course of this project.

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