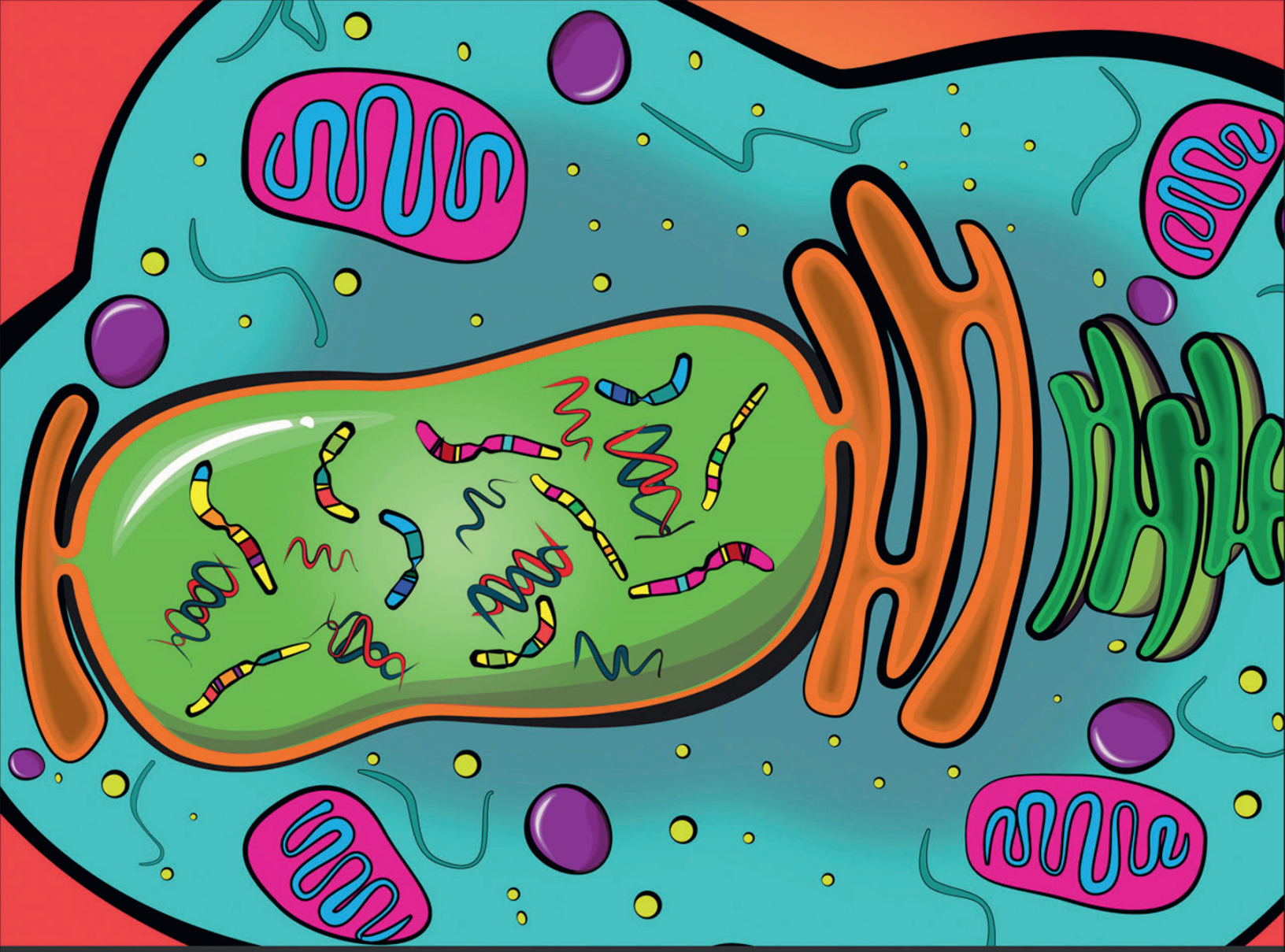

REGULATION OF ORGANELLE AND CELL COMPARTMENT SIGNALING

EDITED BY
RALPH A. BRADSHAW AND EDWARD A. DENNIS

Regulation of Organelle and Cell Compartment Signaling

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Regulation of Organelle and Cell Compartment Signaling

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Preface

Since cell signaling is a major area of biomedical/biological research and continues to advance at a very rapid pace, scientists at all levels, including researchers, teachers, and advanced students, need to stay current with the latest findings, yet maintain a solid foundation and knowledge of the important developments that underpin the field. Carefully selected articles from the 2nd edition of the *Handbook of Cell Signaling* offer the reader numerous, up-to-date views of intracellular signal processing, including membrane receptors, signal transduction mechanisms, the modulation of gene expression/translation, and cellular/organotypic signal responses in both normal and disease states. In addition to material focusing on recent advances, hallmark papers from historical to cutting-edge publications are cited. These references, included in each article, allow the reader a quick navigation route to the major papers in virtually all areas of cell signaling to further enhance his/her expertise.

The Cell Signaling Collection consists of four independent volumes that focus on *Functioning of Transmembrane Receptors in Cell Signaling, Transduction Mechanisms in Cellular Signaling, Regulation of Organelle and Cell Compartment Signaling,* and *Intercellular Signaling in Development and Disease*. They can be used alone, in various combinations or as a set. In each case, an overview article, adapted from our introductory chapter for the Handbook, has been included. These articles, as they appear in each volume, are deliberately overlapping and provide both historical perspectives and brief summaries of the material in the volume in which they are found. These summary sections are not exhaustively referenced since the material to which they refer is.

The individual volumes should appeal to a wide array of researchers interested in the structural biology, biochemistry, molecular biology, pharmacology, and pathophysiology of cellular effectors. This is the ideal go-to books for individuals at every level looking for a quick reference on key aspects of cell signaling or a means for initiating a more in-depth search. Written by authoritative experts in the field, these papers were chosen by the editors as the most important articles for making the Cell Signaling Collection an easy-to-use reference and teaching tool. It should be noted that these volumes focus mainly on higher organisms, a compromise engendered by space limitations.

We wish to thank our Editorial Advisory Committee consisting of the editors of the Handbook of Cell Signaling, 2nd edition, including Marilyn Farquhar, Tony Hunter, Michael Karin, Murray Korc, Suresh Subramani, Brad Thompson, and Jim Wells, for their advice and consultation on the composition of these volumes. Most importantly, we gratefully acknowledge all of the individual authors of the articles taken from the Handbook of Cell Signaling, who are the 'experts' upon which the credibility of this more focused book rests.

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January, 2011

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Section A

Overview

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Chapter 1

Organelle Signaling*

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Cell signaling, which is also often referred to as signal transduction or, in more specialized cases, transmembrane signaling, is the process by which cells communicate with their environment and respond temporally to external cues that they sense there. All cells have the capacity to achieve this to some degree, albeit with a wide variation in purpose, mechanism, and response. At the same time, there is a remarkable degree of similarity over quite a range of species, particularly in the eukaryotic kingdom, and comparative physiology has been a useful tool in the development of this field. The central importance of this general phenomenon (sensing of external stimuli by cells) has been appreciated for a long time, but it has truly become a dominant part of cell and molecular biology research in the past three decades, in part because a description of the dynamic responses of cells to external stimuli is, in essence, a description of the life process itself. This approach lies at the core of the developing fields of proteomics and metabolomics, and its importance to human and animal health is already plainly evident.

ORIGINS OF CELL SIGNALING RESEARCH

Although cells from polycellular organisms derive substantial information from interactions with other cells and extracellular structural components, it was humoral components that first were appreciated to be intercellular messengers. This idea was certainly inherent in the 'internal secretions' initially described by Claude Bernard in 1855 and thereafter, as it became understood that ductless glands, such as the spleen, thyroid, and adrenals, secreted material into the bloodstream. However, Bernard did not directly identify hormones as such. This was left to Bayliss and Starling and their description of secretin in 1902 [1].

Recognizing that it was likely representative of a larger group of chemical messengers, the term *hormone* was introduced by Starling in a Croonian Lecture presented in 1905. The word, derived from the Greek word meaning 'to excite or arouse,' was apparently proposed by a colleague, W. B. Hardy, and was adopted, even though it did not particularly connote the messenger role but rather emphasized the positive effects exerted on target organs via cell signaling (see Wright [2] for a general description of these events). The realization that these substances could also produce inhibitory effects, gave rise to a second designation, 'chalones,' introduced by Schaefer in 1913 (see Schaefer [3]), for the inhibitory elements of these glandular secretions. The word 'autocoid' was similarly coined for the group as a whole (hormones and chalones). Although the designation chalone has occasionally been applied to some growth factors with respect to certain of their activities (e.g., transforming growth factor β), autocoid has essentially disappeared. Thus, if the description of secretin and the introduction of the term hormone are taken to mark the beginnings of molecular endocrinology and the eventual development of cell signaling, then we have passed the hundredth anniversary of this field.

The origins of endocrinology, as the study of the glands that elaborate hormones and the effect of these entities on target cells, naturally gave rise to a definition of hormones as substances produced in one tissue type that traveled systemically to another tissue type to exert a characteristic response. Of course, initially these responses were couched

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in organ and whole animal responses, although they increasingly were defined in terms of metabolic and other chemical changes at the cellular level. The early days of endocrinology were marked by many important discoveries, such as the discovery of insulin [4], to name one, that solidified the definition, and a well-established list of hormones, composed primarily of three chemical classes (polypeptides, steroids, and amino acid derivatives), was eventually developed. Of course, it was appreciated even early on that the responses in the different targets were not the same, particularly with respect to time. For example, adrenalin was known to act very rapidly, while growth hormone required a much longer time frame to exert its full range of effects. However, in the absence of any molecular details of mechanism, the emphasis remained on the distinct nature of the cells of origin versus those responding and on the systemic nature of transport, and this remained the case well into the 1970s. An important shift in endocrinological thinking had its seeds well before that, however, even though it took about 25 years for these 'new' ideas that greatly expanded endocrinology to be enunciated clearly.

Although the discovery of polypeptide growth factors as a new group of biological regulators is generally associated with nerve growth factor (NGF), it can certainly be argued that other members of this broad category were known before NGF. However, NGF was the source of the designation *growth factor* and has been, in many important respects, a Rosetta stone for establishing principles that are now known to underpin much of signal transduction. Thus, its role as the progenitor of the field and the entity that keyed the expansion of endocrinology, and with it the field of cell signaling, is quite appropriate. The discovery of NGF is well documented [5] and how this led directly to identification of epidermal growth factor (EGF) [6], another regulator that has been equally important in providing novel insights into cellular endocrinology, signal transduction and, more recently, molecular oncology. However, it was not till the sequences of NGF and EGF were determined [7, 8] that the molecular phase of growth factor research began in earnest. Of particular importance was the postulate that NGF and insulin were evolutionarily related entities [9], which suggested a similar molecular action (which, indeed, turned out to be remarkably clairvoyant), and was the first indication that the identified growth factors, which at that time were quite limited in number, were like hormones. This hypothesis led quickly to the identification of receptors for NGF on target neurons, using the tracer binding technology of the time (see Raffioni *et al.* [10] for a summary of these contributions), which further confirmed their hormonal status. Over the next several years, similar observations were recorded for a number of other growth factors, which in turn led to the redefinition of endocrine mechanisms to include paracrine, autocrine, and juxtacrine interactions [11]. These studies were followed by first isolation and molecular characterization using various biophysical methods and then cloning of their cDNAs, initially for the insulin and EGFR receptors [12–14] and then many others. Ultimately, the powerful techniques of molecular biology were applied to all aspects of cell signaling and are largely responsible for the detailed depictions we have today. They have allowed the broad understanding of the myriad of mechanisms and responses employed by cells to assess changes in their environment and to coordinate their functions to be compatible with the other parts of the organism of which they are a part.

RECEPTORS AND INTRACELLULAR SIGNALING

At the same time that the growth factor field was undergoing rapid development, major advances were also occurring in studies on hormonal mechanisms. In particular, Sutherland and colleagues [15] were redefining hormones as messengers and their ability to produce second messengers. This was, of course, based primarily on the identification of cyclic AMP (cAMP) and its production by a number of classical hormones. However, it also became clear that not all hormones produce this second messenger nor was it stimulated by any of the growth factors known at that time. This enigma remained unresolved for quite a long time until tyrosine kinases were identified [16, 17] and it was shown, first with the EGF receptor [18], that these modifications were responsible for initiating the signal transduction for many of those hormones and growth factors that did not stimulate the production of cAMP.

Aided by the tools of molecular biology, it was a fairly rapid transition to the cloning of most of the receptors for hormones and growth factors and the subsequent development of the main classes of signaling mechanisms. These data allowed the six major classes of cell surface receptors for hormones and growth factors to be defined, which included, in addition to the receptor tyrosine kinases (RTKs) described previously, the G-protein coupled receptors (GPCRs) (including the receptors that produce cAMP) that constitute the largest class of cell surface receptors; the cytokine receptors, which recruit the soluble JAK tyrosine kinases and directly activate the STAT family of transcription factors; serine/threonine kinase receptors of the TGFβ superfamily; the tumor necrosis factor (TNF) receptors that activate nuclear factor kappa B (NFκB) via TRAF molecules, among other pathways; and the guanylyl cyclase receptors. Structural biology has not maintained the same pace, and there are still both ligands and receptors for which we do not have three-dimensional information as yet.

In parallel with the development of our understanding of ligand/receptor organization at the plasma membrane, a variety of experimental approaches have also revealed the general mechanisms of transmembrane signal transduction in terms of the major intracellular events that are induced by these various receptor classes. There are three principal means by which intracellular signals are propagated: protein posttranslational modifications (PTMs), lipid

messengers, and ion fluxes. There are also additional moieties that play significant roles, such as cyclic nucleotides, but their effects are generally manifested in downstream PTMs. There is considerable interplay between the three, particularly in the more complex pathways.

By far the most significant of the PTMs is phosphorylation of serine, threonine, and tyrosine residues. Indeed, there are over 500 protein kinases in the human genome with more than 100 phosphatases. Many of these modifications activate various enzymes, which are designated effectors, but it also has become increasingly clear that many PTM additions were inducing new, specific sites for protein–protein interactions. These 'docking sites' introduced the concept of both adaptors, such as Grb or Shc proteins, and the larger, multisite scaffolds, such as insulin receptor substrate (IRS) that bound to the sites introduced by the PTMs through specific motifs and as the process is repeated, successively built up multicomponent signaling structures [19]. There has now emerged a significant number of binding motifs, recognizing, in addition to PTMs, phospholipids and proline-rich peptide segments to name a few, that are quite widely scattered through the large repertoire of signaling molecules and that are activated by different types of receptors in a variety of cell types.

TRANSCRIPTIONAL RESPONSES

Although the intracellular signaling pathways are characterized by a plethora of modifications and interactions that alter existing proteomic and metabolomic landscapes, the major biological responses, such as mitosis, differentiation, and apoptosis, require alterations in the phenotypic profile of the cell and these need be directed by changes in transcription and translation (see Figure 1.1). Indeed, signaling can be thought of at two levels: responses (events) that affect (or require) preexisting structures (proteins) and those that depend on generating new proteins. Temporally, rapid responses are perforce of the first type, while longer-term responses generally are of the second. Thus, it may be viewed that the importance of the complex largely cytoplasmic machinery, involving receptors, effectors, adaptors and scaffolds, has two purposes: to generate immediate changes and then to ultimately reprogram the transcriptional activities for more permanent responses.

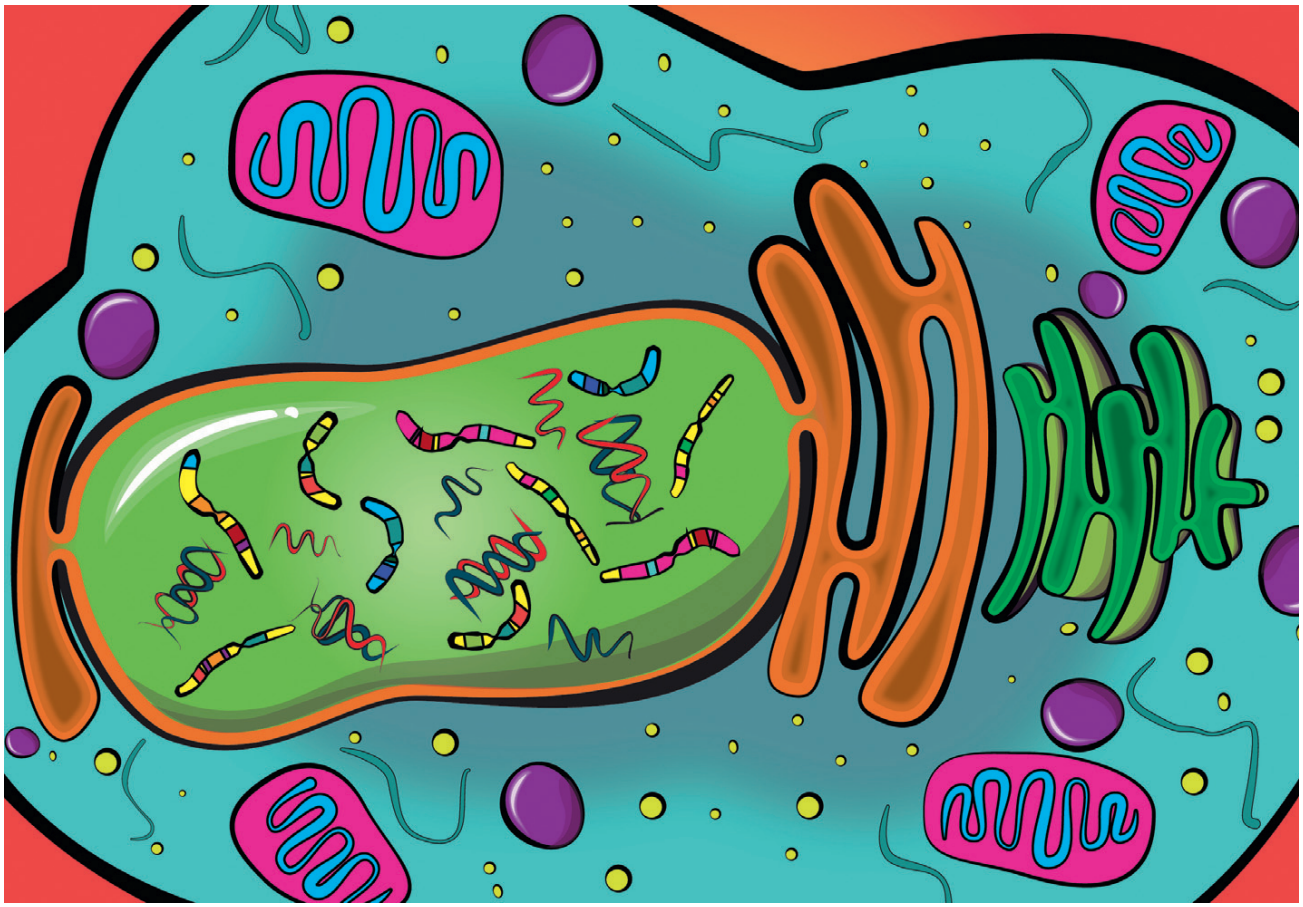

FIGURE 1.1 Subcellular organelles play critical roles in compartmentalizing signaling events. Of central importance are the numerous nuclear receptors/effectors and the subsequent regulation of transcriptional and translational processes. Signaling in various compartments and organelles, such as mitochondria, the Golgi, and the endoplasmic reticulum, as well as peroxisomes, lysosomes, and other vesicles, play critical roles in converting extracellular signals to meet specialized cellular requirements.

The process of gene expression in eukaryotes can be considered at several levels: the generation of the primary RNA transcript, its processing and transport, translation of the mRNA into protein, and finally its turnover. Since the amount of the potential activity associated with a given protein is fundamentally dependent on both its rate of synthesis and its rate of degradation, the turnover of the protein itself is also critical to signaling processes and is certainly largely, if not completely, affected by signaling events, too. In eukaryotes, transcription and mRNA processing take place in the nucleus; translation and mRNA turnover are cytoplasmic events. All of these processes are controlled or affected by signal transduction pathways.

The most common form of regulation is based on the phosphorylation of either sequence-specific transcription factors or proteins that directly interact with such transcription factors. These events can occur in the cytoplasm by kinases activated during signal transduction or by activated kinases that are transferred to the nuclear compartment. Thus, the phosphorylation event(s) can affect the subcellular distribution of the transcription factor (e.g., NFAT, NF-κB), that is, it is present in the cytoplasm and modification directs its nuclear transport, its ability to bind DNA, or its ability to activate or repress transcription (e.g., CREB, c-Jun). The regulation can be achieved through phosphorylation of the transcription factor itself or through phosphorylation of an interacting protein, such as an inhibitor (e.g., IκB), which regulates the activity or subcellular distribution of the transcription factor.

One class of transcription factors, the nuclear receptor family, requires ligand binding before they are functional. Members of this family form the core of signal transduction pathways that regulate gene expression in response to steroid and thyroid hormones, fatty acids, bile acids, cholesterol metabolites, and certain xenobiotic compounds. In fact, this can be viewed as an extension of lipid signaling, as most of the ligands for these receptors are hydrophobic in character. The ligands exert their affects through allosteric regulation, which has a dramatic effect on either the DNA binding or transcriptional activation properties of the transcription factor. Unlike the multicomponent pathways that control transcription in response to activation of cell surface receptors, nuclear receptors are multifunctional proteins that incorporate signal detection, amplification, and execution in one molecule. This branch of the family of signal transduction mechanisms does not utilize cell surface receptors but are activated by ligands that are passively transported across the plasma membrane and associate with their receptors either in the cytoplasm or the nucleus.

Although sequence-specific transcription factors represent the most common target for signal transduction pathways, some of the coactivators, corepressors, or mediators with which these factors interact, may also be subject to regulation. Coactivators, co-repressors, and mediators are often large multicomponent protein complexes that are recruited to promoters or enhancers through interactions with sequence-specific transcription factors. These protein complexes may act either through chromatin modifications or direct interactions with the RNA polymerase holoenzyme. In addition to modulation of chromatin structure via recruitment of chromatin modifiers to sequence-specific transcription factors, signal-responsive protein kinases may directly phosphorylate histones and regulate chromatin structure via a more direct route. Additional posttranslational modifications, such as the acetylation, methylation, and ubiquitinylation, that modify the N-terminal region of these nucleosome components and contribute to the 'histone code', are an essential part of the epigenetic mechanisms that also regulate gene expression, although the connection of these events, in terms of both modification and demodification, to transmembrane signaling has not yet been well defined.

The importance of transcriptional and posttranscriptional control of gene expression in adapting to adverse environmental conditions is underscored by the various stress responses that cells can undergo. Heat shock and UV and the different responses that are elicited by DNA damage, provide valuable insight relevant to transcriptional responses to many other aspects of cell regulation and signal transduction. In addition to metabolic control, these stress responses are evolutionarily ancient and are conserved in many eukaryotic orders.

ORGANELLE SIGNALING

Following the synthesis of a mRNA precursor and its conversion, by exon-intron splicing, to the mature mRNA, it is transported to the cytoplasm where it is translated into its cognate protein. Translation itself is a tightly regulated process, taking place on soluble ribosomes, or in the case of proteins targeted to the endoplasmic reticulum (ER), extruded across the ER membrane by ribosomes that have docked there. The correct folding in both compartments is aided by chaperones and, in either case, there are quality control mechanisms and pathways dedicated to the removal of misfolded or otherwise damaged proteins as these can be quite toxic if not efficiently removed. In the ER, this is known as the unfolded protein response (UPR) and is of marked importance in insuring that the ER protein secretion pathway, which is responsible for providing new cell surface receptors, is functioning properly. These degradation processes usually involved recognition, tagging with polyubiquitin moieties, and degradation via proteasomes.

The mitochondrion is a seemingly self-contained entity, whose origin in eukaryotic cells is thought to have been via adventitious incorporation of a primitive prokaryote into an early precursor to form a symbiotic relationship. Its principal role appeared for a long time to be the major organelle responsible for generating cellular energy currency,

particularly nucleotide triphosphates. As such, it was not generally thought of as being important in signaling activities. However, its critical role in apoptosis (by releasing cytochrome c and other programmed cell death participants) dramatically altered this view. Mitochondria do not, as a rule, actively export macromolecules – rather they import the majority of their constituent proteins, whose synthesis is directed by nuclear chromosomes and occurs in the cytoplasm, via a mechanism, related to but distinct from, the ER transport system – but they do release a variety of ions and metabolites that act as small molecule messengers. These are controlled by a number of inner membrane-bound channels and transporters (the best known of which is the ADP/ATP transporter, putatively the most abundant eukaryotic protein). These can variously affect metabolism, largely as allosteric effectors, and gene expression. Thus, they are important contributors to the overall signaling capacity of the cell.

Two biological phenomena of critical importance in all organisms are cell generation (cell division or mitosis/meiosis) and cell death (apoptosis and necrosis). Both are extensively regulated and not surprisingly, much of this control is under the aegis of cell signaling events. The progression through the cell cycle and its various checkpoints is a symphony of protein modifications coupled to programmed protein turnover. The key players are a complement of kinases, known as cyclin-dependent kinases (Cdks), whose activation and deactivation are involved in every stage of the cycle. Interaction with cyclins, required for their activity, allows them to cycle in an on-off manner, and the ubiquitin-dependent degradation of the cyclins controls the vectoral nature of the cycle. The cyclin–Cdk complexes can be further regulated by phosphorylation or complexation with other proteins, which also allows for pausing at checkpoints if the cell senses it should not continue with the division process. There are also feedforward mechanisms that allow early steps to regulate successive ones. Apoptosis is equally tightly regulated and its progression easily recognized by distinct phenotypic responses (membrane blebbing, cell shrinking, and chromosomal condensation) as the cell progresses to its end. It is predicated on a family of cysteine proteases, called caspases (because they cleave their substrates to the C-terminal side of aspartic acid residues) that are activated in either an extrinsic or intrinsic pathway. The ten caspases generally exist as inactive precursors (zymogens) and can be subclassified into executioner, initiator, and inflammatory types. These have different structural features and different roles in apoptosis. One apoptotic pathway is directly related to the TNF superfamily, transmembrane receptors that contain a death domain. When activated, these lead to the activation of caspase 8, which in turn, activates the executioner caspase 3. Apoptosis is also triggered by cellular stress, and this leads to the involvement of the mitochondria (as noted previously). In a complex pathway involving many proteins, an apoptosome is formed which also leads to the eventual activation of the executioner caspases. Clearly, the connections between these two fundamental processes are of great importance and are closely related to a number of human diseases, notably cancer and neural degeneration.

FOCUS AND SCOPE OF THIS VOLUME

The chapters of this volume have been selected from a larger collection [19] and have been organized to emphasize transcriptional regulation and the function of nuclei and other subcellular organelles in signaling activities. They have been contributed by recognized experts and they are authoritative to the extent that size limitations allow. It is our intention that this survey will be useful in teaching, particularly in introductory courses, and to more seasoned investigators new to this area.

It is not possible to develop any of the areas covered in this volume in great detail, and expansion of any topic is left to the reader. The references in each chapter provide an excellent starting point, and greater coverage can also be found in the parent work [19]. It is important to realize that this volume does not cover other aspects of cell signaling such as receptor organization and function, transduction mechanisms, and organ-level manifestations, including disease correlates. These can be found in other volumes in this series [20–22].

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Section B

Nuclear Signaling