Preface

Protein synthesis, a key pathway in overall gene expression, contributes to the establishment of specific protein levels in cells. Many such proteins, such as enzymes, are involved in various aspects of cell metabolism, making the process of translation important in the overall coordination of cellular events. Aberrations in protein synthesis may result in disease states, such as cancer and diabetes. However, substantial defects in the process of protein synthesis are expected to be embryonic lethal, such that only mild and barely detectable changes are seen in actual human disease. This fact generates a challenging situation for the researcher and medical practitioner: to understand diseases involving protein synthesis, a precise and detailed understanding of translation is required in order to perceive the subtle changes involved. This volume focuses on the regulation of protein synthesis, with emphasis on those features encountered in disease states. It attempts to provide the necessary understanding of the details of protein synthesis that may enable the reader to comprehend the basis of the disease state and to conceive of appropriate therapeutic interventions. As most of the regulation of protein synthesis occurs at the initiation stage, we focus primarily on this aspect of the pathway.

The basic mechanism of protein synthesis in bacteria has been elucidated in great detail. In this system, atomic resolution of the structures of the ribosome and its various protein factors has been achieved, and sophisticated kinetic analyses of the various steps have been carried out. There is a general understanding of the translation pathways for human cells since the process is very similar to that in bacteria, except that the initiation phase is much more complex. Unfortunately, our understanding of eukaryotic protein synthesis is less precise, as the structure of the ribosome is not yet known in sufficient detail, and kinetic studies are only just beginning. The current state of our understanding of the molecular mechanism of protein synthesis in human cells is reviewed in Chapter 1, with emphasis on the limitations of our knowledge. This forms the basis of our understanding of the various mechanisms of translational control that follow.

Mechanisms of translational control at the initiation phase are the main topics of this volume. Regulation by phosphorylation of initiation and elongation factors is a common mechanism, and such regulation is determined by a variety of signal transduction mechanisms that affect their activities (Chapters 2 and 3).

A second general mechanism involves microRNAs, which affect protein synthesis either directly or through the degradation of specific mRNAs (Chapter 5). A third general mechanism involves regulating the availability of mRNAs to the translational apparatus, through their sequestration in stress granules or processing bodies (Chapter 4). What is striking about these mechanisms is their coordination with other aspects of cell activity, thereby integrating translation with the overall cell metabolism.

Three examples of such coordination of protein synthesis with cell metabolism concern early development (Chapter 6), synaptic plasticity (Chapter 8) and control of cell proliferation (Chapter 7). How small aberrations in the regulation of protein synthesis can result in disease states are described and emphasized in these and the earlier chapters. For example, only a small (ca. 30%) stimulation of overall protein synthesis greatly enhances the translation of oncogenic mRNAs, leading to cell malignancy. The insights generated by these analyses should be applicable to other areas of medicine as well.

Viruses are small pathogens that rely on the cellular translation machinery for the synthesis of their proteins. Much insight into the process of protein synthesis has been obtained by studying viral translation, and the results of such efforts are reviewed in Chapter 9. The way viruses take over the cell's translation machinery and the manner in which cells protect themselves also provide new information about basic mechanisms. In the last chapter (Chapter 10), a novel therapeutic approach is proposed based in large part on the fact that the basic machinery of protein synthesis is RNA-driven. The use of RNA aptamers as therapeutic devices to affect protein synthesis rates is one of a number of new approaches to treating disease states.

I am grateful to the authors, without whom this book would not have been possible. Each has written a superb, authoritative chapter that I am confident will be useful to a wide audience of researchers and physicians. I am also indebted to the staff of Elsevier, and Delsy Retchagar in particular, for their constant help and patience. I hope that the readers of this volume find its content stimulating and enlightening.

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