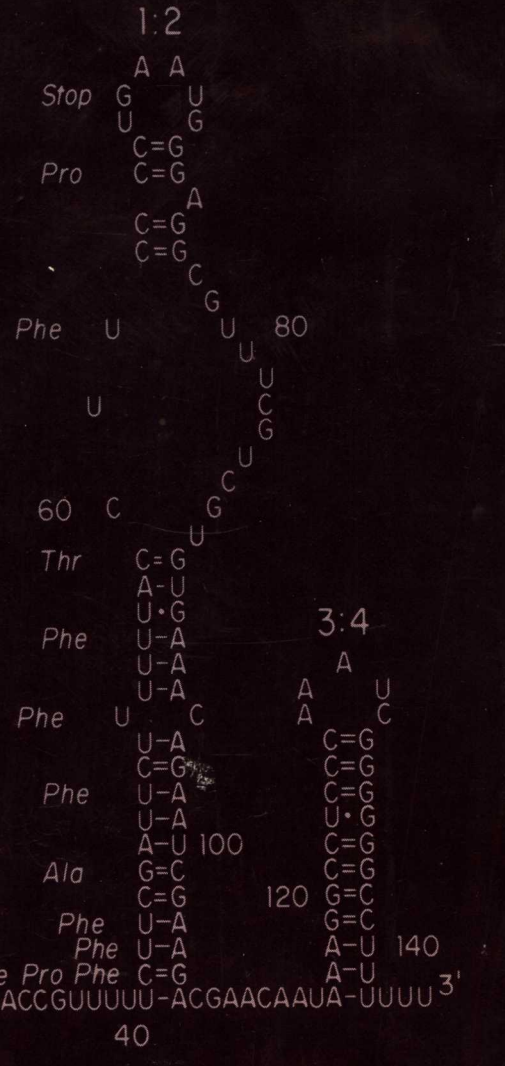
Translational Regulation of Gene Expression



Edited by

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Joseph Ilan
Case Western Reserve University
Cleveland, Ohio

Plenum Press • New York and London

Library of Congress Cataloging in Publication Data

Translational regulation of gene expression.

Includes bibliographical references and index.
1. Genetic translation. 2. Gene expression. 3. Genetic regulation. I. Ilan, Joseph.
QH450.5.T73 1987 574.87'322 87-15322
ISBN 0-306-42640-4

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Preface

Given the accelerated growth of knowledge in the field of gene expression, it seemed timely to discuss current developments in the area of translational regulation of gene expression as well as to evaluate emerging technology.

Translational regulation occurs with prokaryotic as well as with eukaryotic messenger RNA (mRNA) *in vivo* and *in vitro*. In prokaryotes, through genetic manipulations and mutagenesis, the mechanisms are much better understood, as for example the mechanism of attenuation. In bacteria, different translational efficiencies for the same mRNA may vary by 1000-fold. Translational regulation was first observed in 1966 with RNA phages of *Escherichia coli* by Lodish and Zinder. However, translational regulation of proteins from DNA genomes is also well described for bacteria, as for example gene 32 protein of bacteriophage T4 and *E. coli* ribosomal proteins.

In eukaryotes, the utilization of an individual mRNA species with different efficiencies is poorly understood. For example, mRNA for ribosomal proteins is translationally regulated during *Drosophila* oogenesis, without any clue to the mechanism involved. It was observed that ribosomal protein mRNA during *Drosophila* oogenesis and embryogenesis is selectively on or off the polysomes during different developmental stages. In contrast, bacterial ribosomal protein is also translationally regulated by autogenous regulation. The mechanism is well understood and involves binding of the gene product to its transcript in competition with rRNA.

Regulation of specific mRNA translation in eukaryotes has been described for many diverse systems. Specific mRNA translation is known to be regulated during embryogenesis of invertebrates as well as vertebrates. It is regulated in specialized differentiated cells such as hepatocytes, myocytes, and reticulocytes. It is regulated during heat shock, fibroin production, and during photomorphogenesis.

A significant site of regulation of mRNA translation is at the level of initiation of protein synthesis. Initiation of protein synthesis in eukaryotes is very different from that in prokaryotes. Eukaryotic mRNA is monocistronic, and eukaryotic ribosomes do not initiate at internal AUG codons as in bacteria. The first AUG encountered by the ribosome is the functional initiation codon. Almost all eukaryotic cellular mRNAs carry a methylated cap structure that is recognized specifically by cap-binding proteins. These proteins are postulated to unwind a secondary structure at the 5′ end of the eukaryotic mRNA. In eukaryotic mRNA, there is no sequence homology at the 5′ noncoding region to serve as a ribosome binding site such as the Shine–Dalgarno sequence in bacteria.

At the level of initiation, the proposed mechanism for different translational efficiencies of mRNA is variation of secondary structure among mRNA species. However, this hypothesis has not been thoroughly tested. For such testing, the availability of highly purified mRNA is essential for structural analysis. With eukaryotes, this analysis was possible for very limited special messages such as α- and β-globin. The introduction of plasmid vectors containing phage RNA promoter (SP6, T7, and T3), which transcribe micrograms of pure message, has revolutionized the experimental analysis of eukaryotic mRNA. With such systems, one can increase or decrease secondary structure of a defined mRNA by *in vitro* mutagenesis and analyze structure–function relationships and the protein factors involved.

However, initiation of mRNA translation in eukaryotes is not the only point of potential discrimination in translational efficiency. A prime example is the translational control of a transcriptional activator in the regulation of amino acid biosynthesis in yeast. In addition, there are many examples of regulation of specific mRNA translation at the elongation step level following hormone treatment *in vivo* as well as regulation of specific mRNA translation by transfer RNA. In this book, we try to put forward the current development, the excitement, and the emergence of new ideas and methodology as applied to the translational regulation of gene expression.

Joseph Ilan

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