Translational Control of Protein Synthesis: The Early Years

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For the past fifty-five years, much of my research has focused on the function and biogenesis of red blood cells, including the cloning and study of many membrane proteins such as glucose and anion transporters and the erythropoietin receptor. We have also elucidated the mechanisms of membrane insertion, folding, and maturation of many plasma membrane and secreted proteins. Despite all of this work and more, I remain extremely proud of our very early work on the regulation of mRNA translation: work on bacteriophage f2 RNA in the 1960s and on translation of \( \alpha \) - and \( \beta \)-globin mRNAs in the early 1970s. Using techniques hopelessly antiquated by today’s standards, we correctly elucidated many important aspects of translational control, and I thought readers would be interested in learning how we did these experiments.

Introduction: My Own Early Years and Development as an Independent Scientist

I was born in Cleveland, Ohio, on November 16, 1941. My father was a manager at a small company manufacturing electrical fittings for houses and autos, and my mother was a teacher before her marriage. After her three children were in school, she earned her B.A. and for many years taught third grade in Cleveland Heights. I suppose I was precocious: my first publication was in 1946, a letter published in a children’s column in the Cleveland Press!

I started at Chesterfield Elementary School in Cleveland but transferred to Taylor Elementary School in Cleveland Heights when my family (in fact, our entire neighborhood as a result of racially motivated blockbusting) moved to the suburbs in 1951. At Taylor, I was appointed head of the school crossing guards, giving me authority over about twenty fifth- and sixth-grade students. Unsurprisingly, I found out that I liked running things. After three years in junior high, I entered Cleveland Heights High School, where I distinguished myself as the bass drummer, keeping time for a 164-piece marching band.

Importantly, I also participated in a small research project, measuring the levels of various nitrogenous compounds in the blood, directed by Dr. Ethel Laughlin, a chemistry teacher. (And in 1982, I was elected to the Cleveland Heights High School Alumni Hall of Fame, an honor I share with my two younger brothers, Leonard and Richard).

During the summers of 1958–1960, I worked at Western Reserve (now Case Western Reserve) Medical School with Dr. Robert Eckel, studying potassium transport in red blood cells. This led to my first scientific publications (1, 2), and I have been studying red blood cells ever since! Equally importantly, this experience, and the many conversations I had with physician-clinicians and researchers in the hospital, convinced me that I should not go to medical school but rather earn a Ph.D. degree and concentrate full time on research.

I entered Kenyon College as a scholarship student in 1959 and graduated three years later with degrees in both chemistry and mathematics. The small classes and focused personal attention I received there from many faculty members (in two classes, I was the only student) convinced me of the importance of undergraduate teaching and integrating teaching with research. I have tried...
to live up to this ideal by teaching mainly undergraduates at the Massachusetts Institute of Technology (MIT). For many more years than I care to count (Fig. 1), I have taught a lecture course in cell biology and an upper-level seminar course in biotechnology. From 1989 to 2007, I had the honor of serving as a member of the Kenyon College Board of Trustees, and I returned to Kenyon in early 2012 to teach a mini-seminar course on stem cells.

During the summer of 1961, I worked at Stanford University in the chemistry laboratory of Dr. Carl Djerassi, a Kenyon alumnus and “discoverer of the birth control pill.” I learned how large research laboratories, using multiple state-of-the-art experimental techniques such as mass spectrometry and nuclear magnetic resonance, can produce important scientific results (3). I also saw how close contacts between universities and companies (Syntex, producer of steroid components of the pill, in this case) can be mutually profitable and result in excellent science. Twenty years later, I was guided by these principles when I was privileged to be part of a group of scientists that founded Genzyme (recently purchased by Sanofi-Aventis); later, I helped found three other companies, including Millennium Pharmaceuticals (now part of Takeda).

For the past fifty-five years, much of my research has indeed focused on the function and biogenesis of red blood cells. In the 1970s, in my laboratory at MIT, we studied the biogenesis of several red cell membrane proteins (4–7). In the 1980s, we cloned the genes encoding the red cell glucose transport protein, known now as GLUT1 (8), and the red cell anion exchange protein Band 3 (9). This led to a long series of studies on the cloning of two other glucose transporters, GLUT2 (10) and the insulin-responsive transporter GLUT4 (11), and on the functions of these proteins in glucose metabolism in many types of body cells (12–15).

In 1989, we reported the cloning of the erythropoietin receptor and the identification of the cytokine receptor superfamily (16, 17), and this has led to a long and ongoing set of projects on the activation of and signal transduction by the erythropoietin receptor in erythroid progenitor cells and the regulation of transcription, apoptosis, cell division, and enucleation during erythropoiesis (Refs. 18–21; see older work reviewed in Refs. 22–25).

Whether by accident or design I still do not know, upon arrival at MIT, I was given an office next door to David Baltimore, my old friend from Rockefeller University days, and we shared three large research laboratories. David and
his postdoctoral fellow (then wife) Alice Huang introduced me to vesicular stomatitis virus (VSV). One VSV gene, the G or glycoprotein, became invaluable in studies we carried out in the 1970s, defining the endoplasmic reticulum-to-Golgi-to-plasma membrane pathway for biosynthesis of cell surface glycoproteins (26–28). Later, in collaboration with Günter Blobel’s group, Flora Katz and Jim Rothman developed in vitro cell-free protein-synthesizing systems in which we could translate the VSV G mRNA and insert it into endoplasmic reticulum membranes (29). Jim then used this system to demonstrate obligatory co-translational insertion of this transmembrane glycoprotein into the endoplasmic reticulum membrane and co-translational attachment of the two asparagine-linked oligosaccharides (30, 31).

Despite all of this work and more, carried out by over 200 extremely talented M.D. and Ph.D. students and postdoctoral fellows, MIT undergraduates, and technical assistants I have mentored during the past forty-five years (Fig. 2), I still remain extremely proud of our early work on the regulation of mRNA translation: work on bacteriophage f2 in the 1960s and on translation of α- and β-globin mRNAs in the early 1970s.

**Regulation of Translation of the Three Genes of RNA Bacteriophage f2**

I began these studies in 1966 as a postdoctoral fellow with Francis Crick and Sydney Brenner at the Medical Research Council Laboratory of Molecular Biology in Cambridge, United Kingdom. All of the conclusions we drew from this work, that mRNA secondary structure and primary sequence regulate initiation of translation of many prokaryotic and eukaryotic genes, remain true today, and these experiments were done with techniques that are primitive by today’s amazing experimental technologies. Remember that DNA cloning had not yet been developed then, and we lacked the sequence of any DNA or RNA save for a few tRNAs!

My Ph.D. thesis under Norton Zinder at Rockefeller focused on a genetic analysis of the RNA bacteriophage f2, generating and analyzing amber (nonsense) and temperature-sensitive mutants. I identified mutations in three phage genes: the coat protein, a subunit of the RNA polymerase, and a new “maturation” protein, essential for proper assembly of the virus.

The year 1966 was an important one in molecular biology, as it saw the completion of the genetic code and the beginnings of an understanding of the molecular regulation of gene expression. In particular, Bob Webster in Norton Zinder’s laboratory had shown that the f2 coat protein, synthesized in an *Escherichia coli* cell-free system, had at its N terminus a formylmethionine residue preceding the normal N-terminal alanine residue. Contemporaneously, Gary Gussin and Mario Capecchi in Jim Watson’s laboratory identified N-formylmethionyl-tRNA and showed that it was the tRNA used for initiation of bacterial protein synthesis.
Translational control of protein synthesis was one of the big questions that excited me, especially the regulation of polypeptide chain initiation in bacteria by N-formylmethionyl-tRNA. As I wrote in the introduction to my *Nature* paper two years later, “One way in which an organism can regulate the synthesis of specific proteins is by translation of the different genes on a polygenic mRNA at different rates and different times” (32), but, except for RNA phages, there were few systems with which one could study this problem.

Because all phage proteins were believed to initiate with N-formylmethionyl-tRNA, I used N-formyl[^35S]methionyl-tRNA to label the N termini of phage proteins produced in an *E. coli* cell-free system. I first recovered the total protein population, digested it with a mixture of trypsin and chymotrypsin, and resolved all of the peptides by two-dimensional paper chromatography and electrophoresis. Autoradiography revealed only six ^35S-labeled peptides. I quickly showed that three contained an N-terminal N-formyl[^35S]methionine and that the others were the corresponding peptides from which the blocking N-formyl residue had been removed by an enzyme in the cell extract. Furthermore, the three with an N-terminal N-formyl[^35S]methionine corresponded to the N termini of the three phage proteins: the coat, maturation, and polymerase proteins! Thus, I had an assay for analyzing and quantifying the rate and extent of initiation of the three cistrons on this polycistronic mRNA.

My experiments indeed generated several insights into translational control. First, by analyzing the kinetics of protein synthesis, I showed that initiation of translation of the coat and maturation proteins occurred simultaneously and independently of each other but that much more coat protein was produced. This was among the first indications that different AUG initiation codons on a polygenic RNA initiate protein synthesis at different rates. Second, I showed that initiation of translation of the phage RNA polymerase gene kinetically followed that of the coat protein. Third, initiation of the polymerase gene actually depended on continued translation of the coat gene because an amber mutation early in the coat gene not only blocked synthesis of the full-length coat protein but also reduced the rate of initiation of the polymerase gene. Thus, we had replicated in a cell-free translation system the polar effect of an amber mutation on translation of the downstream gene in a polygenic mRNA.

I then hypothesized that ribosome movement along the phage RNA during translation of the coat protein gene somehow “opened up” the RNA secondary structure and exposed the AUG initiation codon of the polymerase gene. Supporting this, I showed that a fragment of the phage RNA that lacked the coat gene initiated translation of much more polymerase protein than did the normal RNA and that this initiation occurred without a lag period. Apparently, deletion of the coat gene indeed opened up the RNA secondary structure (32).

Later in my own laboratory at MIT, I focused on understanding the mechanisms underlying the differential rates of initiation of translation of bacterial and bacteriophage mRNAs. First, together with Hugh Robertson, a Ph.D. student with Zinder at Rockefeller, we showed definitively that the third f2 protein produced in an *E. coli* cell-free system was indeed the maturation protein (33) and also that nascent f2 RNAs could direct synthesis of all three phage proteins (34).

During this period, initiation factors for protein synthesis were being identified and purified, and a major question was whether initiation factors or ribosomes regulated the rates or specificities of polypeptide chain initiation. To address this question, I developed a cell-free translation system from *Bacillus stearothermophilus*. Strikingly, *B. stearothermophilus* extracts could synthesize the f2 maturation protein but not the two other phage proteins. I went on to show that the specificity was due solely to the 30 S ribosome subunit; the source of the 50 S subunit or any of the initiation factors made no difference (35). I also carried out several other experiments to show that RNA secondary structure indeed restricted initiation of both the f2 maturation protein and RNA polymerase genes; chemical or thermal melting of the RNA increased initiation of translation of these genes by manyfold (36–38).

**Mechanism and Regulation of Polypeptide Chain Initiation in Mammalian Cells**

The real question for me during the late 1960s was the mechanism of initiation of translation of mammalian mRNAs because there was no N-formylmethionyl-tRNA in any eukaryotic cell. David Housman, my second graduate student, together with Tom RajBhandary, a new MIT faculty colleague, showed that hemoglobin polypeptide synthesis initiates with an initiator methionyl-tRNA that is not formylated. It was then known that eukaryotic cells contained two species of methionyl-tRNA and that one of them could be formylated by the *E. coli* transformylase. David showed that the artificially formylated yeast N-formylmethionyl-tRNA initiated synthesis of hemoglobin in a rabbit reticulocyte cell-free system and that the normal initiator methionine, but not the initiator N-formylmethionine, was subsequently removed by a cellular enzyme (39).
This led to a long series of studies on the regulation of translation of α- and β-globin mRNAs, showing (well before globin mRNAs were cloned or could be quantified directly) that reticulocytes had more mRNA encoding the α-globin chain than the β-globin chain but that translation of α-globin mRNAs was initiated less efficiently compared with β-globin mRNA (40–43). These studies all made use of rabbit reticulocytes; these cells have no nucleus and make no DNA or RNA. By contrast, in culture, reticulocytes synthesize large amounts of hemoglobin at a linear rate for many minutes, and, more importantly, they are regulated so as to make essentially equal amounts of α- and β-globin polypeptides.

Work by Hunt et al. (44, 45) suggested that the regulation of synthesis of the two globin chains is complex; they observed that, in intact cells, β-globin chains are made on polyribosomes that contain 30–40% more ribosomes than do those synthesizing α-globin chains. We soon confirmed this result for intact human and rabbit reticulocytes and also for crude lysates from rabbit reticulocytes, which synthesize hemoglobin at a linear rate for long periods of time (40, 43, 46). These experiments, in hindsight, were ridiculously complex because we had to use a very indirect way of measuring the two mRNAs by monitoring the localization on polyribosomes of nascent α- and β-globin polypeptides.

In brief, we labeled either intact reticulocytes or a reticulocyte cell-free protein-synthesizing lysate with huge amounts of [35S]methionine. After protein synthesis had proceeded for a few minutes, we added cycloheximide to freeze polypeptide chain elongation and then lysed the intact cells. The cell lysates were layered atop a sucrose gradient, and we then measured the amount of nascent polypeptides and the 60 S and 40 S subunits were at the top. Using a long needle and a pump, we collected fractions from the gradient, and we then measured the amount of nascent α- and β-globin chains on each size of polysome. To do this, we added large amounts of [3H]methionine-labeled hemoglobin to each fraction as an internal control and then precipitated all of the protein in each fraction. We dissolved the protein pellets in buffer and digested them with trypsin and then resolved the tryptic peptides by paper electrophoresis in giant gasoline-filled tanks. We focused on one internal methionine-containing peptide from the α-globin polypeptide and one from the β-globin polypeptide; from the ratio of [35S]methionine to [3H]methionine in these two peptides, we could then calculate the relative abundance of nascent α- and β-globin polypeptides on each size of polysome. In both intact human and rabbit reticulocytes, as well in lysates of rabbit reticulocytes synthesizing hemoglobin at a constant linear rate, we found that β-globin chains are made on larger polyribosomes than those synthesizing α-globin chains.

Each experiment took about two weeks to complete. Now, of course, measurements of α- and β-globin mRNAs can be accomplished in an afternoon by reverse transcription-polymerase chain reactions.

But how could one explain the fact that reticulocytes synthesized equal amounts of α- and β-globin chains, and yet β-globin chains are made on larger polyribosomes than those synthesizing α-globin chains?

Hunt et al. (47) had measured the rate of elongation of α- and β-globin chains in rabbit reticulocytes and concluded that α-globin chains are translated 30–70% faster than β-globin chains. They noted that this difference in translation rate would be sufficient to account for the difference in polysome size and suggested that the rate and mechanism of polypeptide initiation are the same for the two chains.

In contrast, we used [14C]tyrosine to label α- and β-globin chains synthesized in rabbit reticulocyte lysates and measured the time it took for [14C]tyrosine incorporated into different positions in nascent α- and β-globin chains to be incorporated into released, full-length polypeptides. We found no difference in the rate of translation of α- and β-globin chains in these cell-free extracts of rabbit reticulocytes (~200 s per chain at 25 °C) or in the rate of release of completed globin chains from polyribosomes (~15 s per chain) (42).

Taken together, these results indicated that each β-globin mRNA initiates synthesis of ~40% more β-globin compared with α-globin synthesis initiated by each α-globin mRNA. Hence, I concluded that reticulocytes must contain 30–40% more α- than β-globin mRNA to synthesize equal numbers of the two hemoglobin chains, reprising the differential rates of polypeptide chain initiation of the coat and maturation proteins on bacteriophage f2 RNA.

This conclusion was consistent with results of indirect measurements I subsequently carried out of the relative amounts of α- and β-globin mRNAs (40). I reasoned that, under normal conditions, initiation limits the rate of polypeptide synthesis; once a ribosome binds to the initiating AUG, it will move rapidly enough down the mRNA, elongating the chain such that another ribosome can quickly initiate on the same mRNA. This would allow differences in the rate of chain initiation on two mRNAs to manifest in corresponding differences in the rates of polypeptide syn-
thesis. I predicted that addition of drugs known to slow the rate of polypeptide chain elongation (cycloheximide, anisomycin, and emetine, for instance) would slow elongation sufficiently such that differences in the rate of polypeptide chain initiation would no longer become rate-limiting. Even though overall protein synthesis would be inhibited, the ratio of different proteins produced would reflect the amounts of the corresponding mRNAs. Indeed, I found that addition of many such elongation inhibitors caused an increase in the ratio of $\alpha$- to $\beta$-globin chains (made in either lysates or intact reticulocytes) from 1 to $\sim 1.5$, supporting the notion that reticulocytes indeed contained more $\alpha$- than $\beta$-globin mRNAs (40).

Conversely, I expected that nonspecific inhibitors of polypeptide chain initiation would inhibit translation of the poorer mRNA, in this case, $\alpha$-globin mRNA. Indeed, a large number of synthetic polyribonucleotides and polydeoxyribonucleotides inhibited globin synthesis in cell-free extracts of rabbit reticulocytes; without exception, all of these polymers preferentially inhibited initiation of $\alpha$-globin chains.

My favorite paper on this subject was published in Nature in 1974 (41). Using one of the original programmable calculators (desktop computers were still 10 years and more away), I wrote a set of kinetic equations for initiation and elongation of protein synthesis; the essence of this model was that once a ribosome initiated polypeptide synthesis, another ribosome could not initiate on the same mRNA until the first had moved an arbitrary distance (which I set at 25 codons) along the mRNA so that the initiation codon was no longer buried by the ribosome. The model showed clearly that treatments that reduce the overall rate of polypeptide chain initiation would inhibit translation of mRNAs with lower rate constants for polypeptide chain initiation. Experimentally, I showed that treatment of rabbit reticulocytes with several such inhibitors reduced the ratio of $\alpha$- to $\beta$-globin chains almost exactly to the predicted amount.

**Polypeptide Chain Initiation and Human Disease**

An important contribution to my education as a scientist was made by my first sabbatical visitor during the 1970–1971 academic year. David Nathan, M.D., was then a young associate professor in the Hematology Division at Boston Children’s Hospital; later, he became head of Hematology, then physician-in-chief at Children’s, and then president of the Dana-Farber Cancer Institute. David was a student in the molecular biology course I was teaching (the first ever taught at MIT), and we started talking about the potential implications of the emerging discipline of molecular biology for understanding several human diseases.

David was studying the genetic disease $\beta$-thalassemia, a syndrome in which the rate of production of $\beta$-globin chains is depressed. $\alpha$-Globin chains accumulate and form inclusions that damage the cell membrane and cause the ineffective erythropoiesis that dominates the clinical manifestations of $\beta$-thalassemia. The cause of the depression of $\beta$-globin chain synthesis in $\beta$-thalassemia was unknown, but two hypotheses were commonly discussed: first was decreased $\beta$-globin mRNA production due to diminished content or transcription of the $\beta$-globin gene, and second was production of a mutant $\beta$-globin mRNA with one or more codon substitutions that would cause a delay in initiation, elongation, or termination of the nascent $\beta$-globin chain.

We realized that we could begin to resolve this issue by measuring the sizes of polysomes synthesizing $\beta$-globin. The first hypothesis predicted fewer but normal size polysomes synthesizing $\beta$-globin. In contrast, the second hypothesis predicted abnormal size polysomes synthesizing $\beta$-globin chains and smaller $\beta$-globin polysomes if initiation of polypeptide synthesis was reduced. Together with my Ph.D. student David Housman and David Nathan’s fellow Y. W. Kan, we did the experiment (46).

David Nathan would show up in the laboratory around 10 a.m. with a vial of blood that he collected from a local patient; because of the anemia, these individuals had a lot of reticulocytes in their blood that synthesized $\beta$- and $\alpha$-globins. Blood from patients with other genetic anemias that also contained many reticulocytes was used as the control. (One day, David arrived disheveled about two hours late. The owner of the gas station became concerned when David emerged from the restroom with another man and with a vial of blood in his hands and called the police.)

These intact cells were incubated with $[^{35}\text{S}]$methionine; as I described above, the relative amounts of nascent $\beta$- and $\alpha$-globin chains on polysomes of different sizes were measured by tryptic digestion of pooled polysomes and by determination of the specific activities of $\alpha$- and $\beta$-globin peptides that contain methionine. Strikingly, $\beta$-globin chain synthesis predominated on heavy polysomes in thalassemic as well as in non-thalassemic cells. Because $\beta$-globin chains in thalassemia are made on normal size polyribosomes, we concluded that the defect in thalassemia does not involve reduction in the rate of initiation of translation due to the production of a mutant $\beta$-globin mRNA and suggested that the decreased production of $\beta$-globin chains results from a decreased amount of functional $\beta$-globin mRNA (46).
Gratifyingly, we were proved correct when, a decade later, cloning of the globin mRNAs allowed direct measurements of their levels in normal and diseased reticulocytes. Increased levels of α- relative to β-globin mRNA also were confirmed by direct analysis; in part, this is due to the fact that the diploid human genome contains four copies of the α- but two of the β-globin genes.

This study had two important long-term consequences. David Nathan indeed realized that molecular biology would revolutionize medicine. Starting with his hematologist fellows at Boston Children’s Hospital and then extending to physician-scientists being trained in other specialties, David sent them to MIT or Harvard laboratories to master emerging molecular, biochemical, and cell biological techniques. To import these new technologies, he then hired the best of his fellows as assistant professors in their own laboratories at Children’s. For this and other changes that David introduced in the training of physician-scientists, he was awarded the National Medal of Science in 1990.

In turn, I realized the impact that studies of the molecular basis of human disease were going to have both on the development of novel therapies and on an understanding of basic molecular mechanisms. I have trained in my laboratory over thirty M.D. and M.D./Ph.D. scientists, most of whom have gone on to become eminent leaders in fields as diverse as hematology, cardiology, nephrology, and diabetes and metabolism. I have been part of a National Heart, Lung, and Blood Institute program project grant with hematologists at Boston Children’s Hospital for almost forty years, and in 2010, the grant was renewed for five more. In 2006, I joined the Board of Trustees at Boston Children’s Hospital, where I head the Board Research Committee and do my best to help the hospital raise philanthropic gifts to support basic, translational, and clinical research.

Earlier I mentioned my involvement in founding Genzyme in 1980. I became quite engaged in developing its first major drugs to treat Gaucher disease, one of several genetic lysosome storage diseases. In particular, I helped with the development of Cerezyme, a recombinant version of glucocerebrosidase that, when injected, becomes bound to the mannose receptor on macrophages, internalized by receptor-mediated endocytosis, and then transferred to lysosomes, where it takes up residence and degrades the glycolipids that would otherwise accumulate and cause pathology of the spleen, liver, and other organs.

I mention this because, at the time, I was simply fascinated by the possibility of using cell biology to develop drugs for untreatable diseases. Only later did we realize that the disease runs in my own family. A month ago, one of my seven grandchildren started infusions of the Gaucher drug. In fact, the prenatal diagnosis that informed us he had the disease also told us that his disease would be treatable by the drug Genzyme helped develop.

But this is part of long story that will require an article of its own. The conclusion should be obvious: that basic research and clinical developments go hand in hand and that, throughout my career, I have been privileged to participate in both.

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