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L. L. Kisselev

RNA–Protein Interactions at the Initial and Terminal Stages of Protein Biosynthesis as Investigated by Lev Kisselev

(On the Occasion of His 70th Anniversary)

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Abstract—This review highlights studies by Lev L. Kisselev and his colleagues on the initial and terminal stages of protein biosynthesis, which cover the period of the last 45 years (1961-2006). They investigated spatial structure of tRNAs, structure and functions of aminoacyl-tRNA-synthetases of higher organisms, and the final step of protein synthesis, termination of translation. L. Kisselev and his team have made three major contributions to these fields of molecular biology; (i) they proposed the hypothesis on the role of anticodon triplet of tRNA in recognition by cognate aminoacyl-tRNA synthetase, which has been experimentally confirmed and is now included in textbooks; (ii) identified primary structures and functions of two eukaryotic protein factors (eRF1 and eRF3) playing a pivotal role in translation termination; (iii) characterized a structural basis for stop codon recognition by eRF1 within the ribosome and discovered the negative structural elements of eRF1, limiting its recognition of one or two stop-codons.

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The scientific carrier of Lev L. Kisselev began in 1958, when as a student of the Department of Biochemistry, School of Biology and Soil Sciences (Moscow State University) he made a diploma project under the supervision of a PhD student at this Department, V. P. Skulachev. The results of this study on coupling between respiration and phosphorylation led to four publications [1-4].

The outstanding abilities of the student L. Kisselev were appreciated by Head of the Department of Biochemistry, S. E. Severin, and by R. B. Khesin, who was organizing his laboratory at the Radiobiology Department (RBD) of I. V. Kurchatov Institute of Atomic Energy. However, Kisselev could not enter PhD studentship at Moscow State University or join RBD due to certain political reasons typical for this period. The first reason was the Bureau of Communist Party at School of Biology and Soil Sciences disapproving high anti-Lysenko activity of student Kisselev. Party functionaries were actively working against his PhD studentship at Moscow State University. In a formal report made after graduation from the University Kisselev was labeled as a Mendelist–Morganist (i.e., a supporter of scientific ideas of Mendel and Morgan) who was fighting against Lysenko doctrine and would not "confess his delusions". The second reason was his life at the age of 5-8; during the Great Patriotic War (1941-1945) he lived on a territory occupied by Nazi troops, and he was liberated by the Red Army only in 1945 in Chemnitz (Germany). This fact made his

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working at the strictly controlled Atomic Energy Institute absolutely impossible.

A third invitation came from V. A. Engelhardt, a Professor of the Department of Biochemistry giving a lecture course on enzymology. In the beginning of 1959 the Academy of Sciences of the USSR started to organize a new Institute of Radiation and Physico-Chemical Biology within the Academy of Sciences of the USSR. (In reality the decision was made in 1957, but due to resistance of "Michurin biologists" its realization was postponed until 1959.) New vacancies were opened, and L. Kisselev together with other young graduates took a position of probationary researcher.

The first of Kisselev's studies in this Institute, which is now known as the V. A. Engelhardt Institute of Molecular Biology, Russian Academy of Sciences, was a bit unusual but at the same time typical for that period. In the very beginning of Russian Molecular Biology, many physicists switched their interests to investigation of biological macromolecules. N. A. Kisselev, a distinguished expert in electron microscopy, and his cousin Lev Kisselev decided to visualize soluble (transfer) RNA by means of electron microscopy. These are small molecules (from 75 to 90 nucleotides) and nobody had ideas of microscopy of such small objects. Nevertheless, the experimental skill of N. A. Kisselev and high quality of tRNA preparation isolated by L. Kisselev gave a good result not only in visualization of tRNA but also in evaluation of shape of these molecules [5]. This was the first study, which opened a series of studies on tRNAs and aminoacyl-tRNA-synthetases (aaRSases) which were carried out by Kisselev and his colleagues from the beginning of 1960s up to the end of 1990s.

STRUCTURE–FUNCTION ANALYSIS OF tRNAs AND aaRSases

In the middle of 1950s, F. Crick proposed an adaptor hypothesis predicting the existence of molecular adaptor between genetic information encoded in nucleic acids and proteins; this adaptor is crucial for transition of nucleotide alphabet into the amino acid alphabet. At the end of 1950s and the beginning of 60s the existence of such molecular adaptor was experimentally proven [6]. This is the tRNA (transfer RNA) molecule. Transfer RNA molecules exhibit two important and inseparable functions: (i) they can accept an amino acid residue at the 3′-end, this reaction involving aaRSases (EC 6.1.1); (ii) using nucleotide triplet (anticodon) they interact with corresponding nucleotide triplet (codon) of messenger RNA (mRNA) positioned on the ribosome. The function of tRNA as an "interpreter" occurs at the pre-ribosomal stage: interaction within the "triangle" amino acid–aaRSase–tRNA results in highly selective covalent attachment to cognate tRNA. Errors originating from attachment of "wrong" amino acid to tRNA cannot be corrected at the stage of codon–anticodon interaction and consequently errorless reproduction of genetic information is determined not only by the ribosomal stages of protein synthesis, but also by pre-ribosomal stages (tRNA loading with correct amino acid). So, studies of tRNAs and aaRSases were key basic problems of molecular biology. The importance of these problems has been underlined by the Nobel Prize award to R. Holley for determination of primary structure of alanine tRNA.

Kisselev's group was the first Soviet group specializing on the study of tRNA, and so they had to develop their own methodological basis and isolate enough quantities of highly purified tRNAs (both total and individual ones). The first problem was readily solved [7], whereas the latter required the development of their own original purification method [8]. This was the very first study, which was carried out by L. Kisselev in collaboration with D. Knorre and his colleagues.

Understanding the functioning of tRNA inside and outside of the ribosome (in cytoplasm) requires knowledge of its physical properties and macromolecular structure. L. Kisselev solved this problem using methods previously employed for studies of high molecular weight polymers. The difficulty consisted of the small sizes of tRNA molecules and their weak polymer properties. However, it was possible to apply a combination of physical methods for tRNA studies, which included: sedimentation, viscosity [9-12], flow birefringence [13], circular dichroism and optical rotatory dispersion, spectrophotometry, fluorescence (including polarization of fluorescence) [14-17], microcalorimetry [18], small angle X-ray scattering [19]. The physical methods were supplemented by chemical modification of tRNA bases [20-23]. These studies were carried out in tight contact with many (mainly physical) Russian laboratories.

These studies provided experimental evidence for the following conclusions:

1) in spite of rather small sizes, secondary structure of tRNA behaved in the same manner as high molecular weight viral or ribosomal RNAs investigated by other groups (P. Doty, J. Fresco, A. Spirin, etc.) and the ratio of double helical and single stranded regions was elucidated in tRNA structure;

2) tRNA molecule consists of two domains positioned at some angle to each other (this conclusion was later supported by X-ray analysis of phenylalanine tRNA by A. Rich, A. Klug, and others);

3) the tRNA molecule contains three exposed sites located outside the double-helical region; these are the anticodon, the CCA-end, and a site between two domains; this conclusion based on experiments with valine tRNA was confirmed by other authors for tRNAs of different amino acid specificity;

4) using phenylalanine tRNA and poly(U), specific codon–anticodon interaction was demonstrated in ribo-

some-free solution; these experiments [24] provided experimental evidence for the existence of exposed anticodon in the spatial structure of tRNA in solution and its ability for specific duplex formation with mRNA codon; five years later X-ray analysis of $tRNA^{Phe}$ confirmed the correctness of this conclusion;

5) studies of folding and unfolding of tRNA in solution revealed a role of Mg^{2+} in this process [25-27].

All these results together with data on primary structures of tRNAs obtained in many laboratories in the 1960s and 1970s created the structural background for investigation of functional properties of tRNAs during their interactions with aaRSases and functioning within the ribosomes.

L. Kisselev's laboratory paid special attention to eukaryotic aaRSases (see for review [28, 29]), as they were less studied compared with the bacterial enzymes. Using classical methods of molecular enzymology (isolation of individual enzymes, kinetic analysis, use of substrate analogs, etc.) and modern gene engineering, the following results were obtained.

The amino acid sequences of human and rabbit tryptophanyl-RSases were elucidated [30, 31].

Kisselev's team has characterized exon–intron organization of the human tryptophanyl-RSase gene and demonstrated that this is an interferon-dependent gene and the gene transcript undergoes alternative splicing [32-35].

They also elucidated the spatial organization of mammalian tryptophanyl-RSase: this enzyme is a homodimer (α_2) and each subunit consists of two nonequal domains. The N-terminal domain (representing about 1/3 of the subunit size) is not essential for catalytic synthesis of tryptophanyl-tRNA [36, 37].

Using monoclonal antibodies, Kisselev and his colleagues demonstrated the presence of aaRSases in nuclei of animal cells [38, 39]; later these results were confirmed in other laboratories. They explained early observations by V. A. Gvozdev, who found amino acid activation in mammalian cell nuclei.

Binding of substrates (amino acid, ATP, tRNA) and products (AMP, pyrophosphate, aminoacyl-tRNA) to aaRSases may follow two kinetic mechanisms [40-44]: ordered (for tryptophanyl-RSase) and random (for phenylalanyl-RSase). Later both kinetic mechanisms were also demonstrated for other aaRSases.

Tryptophanyl-RSase can form covalent intermediates. A tryptophanyl residue can be transferred from the enzyme onto $tRNA^{Trp}$ in the absence of ATP; the latter suggests macroergic mode of bonding between Trp and aaRSase [45-51].

Molecular mechanism of tryptophanyl-RSase functioning involves negative cooperativity between subunits [52-54], ordered substrate binding, and covalent enzyme–substrate complex formation (see for review [55, 56]).

Kisselev and his coworkers provided experimental evidence that in contrast to most mammalian aaRSases, tryptophanyl-RSase is a Zn^{2+}-dependent enzyme; Zn^{2+} ion is ultimately required for enzyme functioning and its absence alters catalytic properties of this enzyme [57, 58].

In the absence of tRNA, tryptophanyl-RSase can form Ap_3A dinucleotide, an important regulator of cell processes; this appears to be a characteristic feature of this enzyme as other aaRSases lack such property [59, 60].

Mammalian glycyl-RSase and *E. coli* lysyl-RSase demonstrate molecular polymorphism [61-63].

Using immobilized substrate, Kisselev's group obtained the enzyme–substrate complex between aaRSase and tRNA, and this approach allowed the development a new method for affinity purification of aaRSases and study of conditions required for complex formation [64].

Development of polyclonal and monoclonal antibodies to various domains of mammalian tryptophanyl-RSase and their subsequent use for enzymological and immunocytochemical studies provided important insight into the highly conservative structure of this enzyme in all kingdoms of living organisms; antigenic determinants are unequally distributed between domains, and abnormally high Trp-RSase content has been found in the ruminant pancreas [65-68].

Functionally essential histidine residues have been found in mammalian tryptophanyl-RSase [69].

Kisselev and his group found that mammalian tryptophanyl-RSase contains covalently bound carbohydrate [70].

They also synthesized selective covalent inhibitors of aaRSases and used them for selective blockade of one (of two) active sites of tryptophanyl-RSase [71-75].

Kisselev's team selected cell lines resistant to tryptophan analogs and characterized properties of tryptophanyl-RSase in these cells [76, 77].

The gene encoding tryptophanyl-RSase has been localized on the human and bovine chromosome [78].

The interaction between aaRSase and substrate tRNA (enzyme–substrate) is accompanied by mutual conformational changes [79].

Conditions of *in vitro* aminoacylation influence the behavior of iso-acceptor forms and transcripts of tRNA genes [80-82].

Kisselev's team employed computer analysis for comparative investigation of interaction of aaRSases with tRNA in prokaryotic and eukaryotic systems [83].

They also investigated the structure of 2-dimensional crystals formed by tryptophanyl-RSase [84].

Studies of aminoacyl-RSases have been accompanied by development of new methods for investigation of these enzymes, including analysis of catalytic activity and enzyme–substrate interactions [85-88].

Through high long-term research activity of Kisselev's laboratory and the use of wide ranges of ide-

ologies and methods mammalian tryptophanyl-RSase became one of the most studied eukaryotic aminoacyl tRNA synthetases (see reviews [89-92]).

Many of the abovementioned results were obtained in collaboration with other Russian laboratories. This is very typical of L. Kisselev, who has constant interest in collaboration.

In the process of genetic information decoding, the stage of amino acid attachment to cognate tRNA is especially important. It is clear that the specificity of this reaction is determined by mutual recognition of certain sites of tRNA and the corresponding aaRSase.

In 1964, a hypothesis explaining specificity of such interaction was originally suggested. L. Kisselev and L. Frolova proposed dual function of tRNA anticodon: (i) it is involved in tRNA–mRNA interaction on the ribosome by forming anticodon–codon duplex; (ii) the anticodon specifically interacts with aaRSase of the same amino acid specificity as tRNA [93-96]. The principal advantage of this hypothesis consisted in strict coupling between acceptor and adaptor functions of tRNAs, which is required for correct decoding of genetic information. This hypothesis that aaRSase recognizes tRNA anticodon as a specific element has experimental background. Chemical modification of $tRNA^{Val}$ and other tRNAs revealed correlation between nucleotide composition of tRNA anticodon and sensitivity of acceptor function of tRNA to chemical modification. In particular, the acceptor function of $tRNA^{Val}$, having C as the third anticodon letter, was highly sensitive to modification of this base by hydroxylamine or O-methyl-hydroxylamine. The tRNA lacking C in their anticodons were insensitive to this modification. Later it was demonstrated that anticodon C is indeed responsible for loss of $tRNA^{Val}$ activity after modification. In A. A. Baev's laboratory (Institute of Molecular Biology, Russian Academy of Sciences) use of the "dissected molecule" method demonstrated similar phenomenon: removal of two "root" nucleotides from $tRNA^{Val}$ anticodon was accompanied by total loss of acceptor activity. Later L. Kisselev's laboratory also demonstrated the crucial role of $tRNA^{Trp}$ anticodon for recognition by tryptophanyl-tRNA synthetase [97, 98].

It should be noted that in the very beginning of the appearance of this "anticodon hypothesis" its authors emphasized that in the tRNAs encoding amino acids with six codons (serine, leucine, arginine) anticodon plays secondary role (if any) and in these cases another recognition mechanism is involved.

Experiments with synthetic polynucleotides inhibiting aminoacylation of tRNAs, containing anticodons, which had the same nucleotide composition as the added polynucleotides provided independent evidence supporting the role of tRNA anticodons in recognition by aaRSases; this suggested competition between anticodons and polynucleotides for the same site on the enzyme molecule [99].

In the end of the last century, the hypothesis of the role of anticodon in determining acceptor function of tRNA obtained exhaustive experimental evidences by means of classical enzymological methods and also X-ray analysis of tRNA-aminoacyl-tRNA synthetase complexes [100-102]. This was strictly proven for at least half of all aminoacyl-tRNA synthetases; for the others this hypothesis was confirmed by various indirect methods. Nevertheless, three of 20 aminoacyl-tRNA synthetases employ other site(s) of tRNA molecules (acceptor stem, variable loop, etc.). It was also shown that together with anticodon, many aminoacyl-tRNA synthetases contain a second recognition site; this increases specificity of tRNA–enzyme interaction.

Accumulation of convincing evidence validating the correctness of the "anticodon hypothesis" took more than 30 years (1964-1995). Now the role of tRNA anticodon as the key element determining specific recognition by cognate amino acyl-tRNA synthetases is firmly recognized. This dogma has been included into textbooks on biochemistry and molecular biology, and L. Kisselev and his coworkers have unquestioned priority in this field.

The following scientists made important contributions to the series of studies on tRNA conducted by Kisselev's team: T. A. Avdonina (Akopian), R. Afasizhev, O. F. Borisova, H. Gross, N. G. Esipova, T. I. Zhilyaeva (Ponomareva), R. Giege, S. I. Klenin, S. Ya. Lyubina, T. D. Mashkova, L. S. Sandakhchiev, A. N. Surovaya, V. Serebrov, V. G. Tumanyan, L. Yu. Frolova, N. S. Kholod, V. N. Tsvetkov, V. Sh. Sheinker, S. V. Steinberg.

Studies on aaRSases are inseparable from the names of: V. Z. Akhverdyan, S. F. Beresten, A. Grigorieva, G. K. Kovaleva, L. L. Kochkina (Zavalova), D. G. Knorre, I. A. Madoyan, E. G. Malygin, T. I. Merkulova, O. D. Nelidova, E. L. Paley, A. V. Parin, V. I. Popenko, V. S. Prasolov, O. O. Favorova, F. Fasiolo, L. Yu. Frolova, V. A. Engelhardt.

TERMINATION OF TRANSLATION

In 1990 the distinguished American scientist C. T. Caskey, who made substantial contributions to translation termination studies in 1960-1970s, reported the decoding of primary structure of eukaryotic translation termination factor (eukaryotic release factor, eRF), which shares sequence homology with bacterial tryptophanyl-tRNA synthetase [103]. At that time, L. Kisselev's laboratory determined the primary structure of human tryptophanyl-tRNA synthetase [30], and B. and J. Labouesse and their coworkers determined the primary structure of bovine tryptophanyl-tRNA synthetase [104]. All the structures were almost identical, and Kisselev and coworkers suggested [30] that the amino acid sequence of the translation termination factor determined by Caskey's team was not correct. Joint study by L. Kisselev

in collaboration with A.-L. Haenni (Institut Jacques Monod, Paris) and W. P. Tate (University of Otago, Dunedin, New Zealand) provided convincing evidence that Caskey's team used preparation of the translation termination factor containing traces of rabbit tryptophanyl-tRNA synthetase; they wrongly attributed cloned rabbit cDNA to that factor resulting in serious error [31, 105]. This story has been described in detail by L. Kisselev [106].

These studies raised a question about the actual structure of eukaryotic translation termination factor. This problem was solved by L. Frolova and L. Kisselev in collaboration with researchers from other laboratories. Their efforts culminated in reliable determination of primary structure [107], and that report was accompanied by special comments published in *Nature* [108]. The authors demonstrated unique structure of eRF1, which did not share similarity with either tryptophanyl-tRNA synthetase, or bacterial termination factors RF1 and RF2 known at the time.

The authors [107] suggested that prokaryotic and eukaryotic termination factors have a different evolutionary origin and lack a common ancestor. Although this viewpoint had been questioned [109], subsequent analysis employing a representative number of amino acid sequences followed by their correct alignment confirmed the hypothesis of independent origin of eRF1 and RF1/RF2 [110]. Subsequent X-ray analysis of eRF1 [111], RF2 [112], and RF1 [113] also demonstrated principal differences of spatial structure of these factors.

Identification of eRF1 and decoding of its primary structure helped understanding of functions of some proteins with known primary structure (but with unknown functions at that time). These include yeast, *X. laevis*, and human proteins. Comparison of these proteins revealed high similarity of their primary structures; this suggested that amino-acid sequences of the eRF1 family are highly conserved [107].

In collaboration with colleagues from Novosibirsk, L. Kisselev's team identified tripeptide Gly-Gly-Gln (GGQ) as a common structural element of all class 1 translation termination factors; this includes eRF1, RF1, and RF2 families and also aRF1 family (archaea factors close to eRF1) [114]. This motif is located within the M-domain at one end of the eRF1 molecule [111]. Modification of its glycine residues is accompanied by loss of RF-activity *in vitro* and *in vivo*. This was reported for human eRF1 [114] and also yeast [111] and *E. coli* [115] RF1. According to a hypothesis proposed by Kisselev and his colleagues [114], GGQ motif is involved in peptidyl-tRNA hydrolysis in the ribosomal peptidyl-transferase center; possibly it opens water access to the ester bond. Biochemical [116] and X-ray [117] data obtained for prokaryotic ribosomes support this hypothesis.

However, it should be noted that a suggestion on direct involvement of the glutamine residue of this motif in orientation of water molecules near the hydrolyzed bond [111] was not experimentally confirmed [118, 119].

Experiments revealed methylation of GGQ motif glutamine residue both in eukaryotes and prokaryotes; this reaction requires a special methyl transferase, and methylation increases activity of eRF1 [120]. Interestingly, methylation of eRF1 required its complex formation with class 2 termination factor, eRF3 (see below).

L. Kisselev, L. Frolova, and their younger colleagues obtained the first biochemical evidence that eRF1 N-domain is responsible for decoding of mRNA stop-codons in the ribosome [121-124], as suggested earlier [111, 125].

In parallel with elucidation of the functional role of the M and N domains, Kisselev's team found that the C-domain of human eRF1 did bind to the other termination factor eRF3 both *in vitro* and *in vivo* [126-128]. This interaction also involved the C-terminus of eRF3 [128]. Similar results were obtained in Y. Nakamura's and M. Tuite's laboratories for yeast factors. Interestingly, after removal of the C-domain eRF1 was able to induce ribosomal peptidyl-tRNA hydrolysis in *in vitro* experiments (eRF1 was used in excess) [129]. Consequently, C-domain is not involved in decoding and hydrolysis of peptidyl-tRNA, but it is responsible for physical contact with eRF3 and this significantly influences the activity of both factors.

Since the shape of prokaryotic RF1 and RF2 molecules in crystals significantly differs from that of eRF1 crystal structure, a reasonable question on eRF1 behavior in solution has arisen. The shape and size of eRF1 did not differ from that of the crystal structure [130]. This emphasizes big differences between eukaryotic and prokaryotic class 1 RFs.

Summarizing results obtained in his laboratory, L. Kisselev came to the following two conclusions. In the eRF1 protein family, there is a clear correlation between domain organization and functions: N-domain is faced to the mRNA side; it is partially positioned on the small ribosomal subunit and provides direct interaction of eRF1 with one of three stop-codons. The M-domain is faced to the large ribosomal subunit; using GGQ motif it interacts with peptidyl-tRNA in the peptidyl-transferase center and induces hydrolytic reaction of peptidyl-tRNA cleavage into polypeptide and free tRNA. The C-domain binds to class 2 termination factor eRF3 and activates its GTPase activity within the ribosome; this interaction does not require the N-domain, and the MC-domain is fully competent for realization of this function. This concept has been widely accepted [131] and has good citation.

The second conclusion is related to resemblance between eRF1 and tRNA. Y. Nakamura underlined the structural similarity between tRNA and class 1 termination factors [109]. Based on detailed analysis, L. Kisselev

proposed a concept of functional similarity of tRNA and class 1 termination factors; he provided convincing arguments that these are true functional homologs [132]. He referred the proteins of class 1 termination factors to a special type of proteins defined as antiribozymes; being proteins in nature, these "antiribozymes" are functionally equivalent to nucleic acids. This idea may have intriguing consequences because besides class 1 termination factors other proteins functioning as nucleic acids may also exist. Thus, in spite of basic chemical differences proteins and nucleic acids do not have a functional gap.

During recent years, L. Kisselev and his laboratory have focused attention on a search for sites of eRF1 molecules responsible for specific decoding of mRNA stop-codons at the ribosome. This problem is a mirror reflection compared to that solved by L. Kisselev and L. Frolova studying tRNA and aminoacyl-tRNA synthetases: in that case the authors were looking for a tRNA site (anticodon) responsible for protein recognition, whereas in the case of eRF1 and mRNA they were looking for a codon-recognizing a protein site. Solution of a new problem required use of a different strategy. The results were quite interesting. First, the authors demonstrated that class 1 factor but not the ribosome is responsible for decoding specificity [133]. This was silently suggested earlier, but the first experimental evidence was obtained for eRF1. Experiments also revealed that archaea class 1 factors are characterized by the same spectrum of decoding stop-codons as eRF1; this followed from experiments in which aRF1 (archaea factor) also decoded all three stop-codons in the mammalian ribosome [134].

After localization of decoding specificity in the eRF1 N-domain [121-125, 135], a principally important fact was determined: two different sites of the N-domain are responsible for decoding of the first (U) nucleotide of stop-codon and of the second and third nucleotides. In 3D structure of the protein, these sites are closely positioned, but within the primary structure they are distantly located (positions 61-64 and 125-131 in human eRF1). This result has shown that in contrast to tRNA anticodon, which recognizes mRNA codon by forming a 2D codon–anticodon duplex, in the case of eRF1, this is 3D-recognition involving various fragments of the polypeptide chain. So, it is irrelevant to apply the term "protein anticodon" for eRF1; it is more accurate to employ a 3D-protein discriminator for characterization of this interaction.

Identification of two key conservative motifs of eRF1 (NIKS and YxCxxxF) involved in decoding made possible artificial *in vitro* simulation of the process, which happened a long time ago: point substitutions of two amino acids in the N-domain converted omnipotent human eRF1 into the unipotent factor recognizing only UGA stop-codon [122]. Such type of stop-codon recognition is typical for some ciliate infusoria (*Stylonychia*, *Tetrahymena*, etc.) possessing a variant genetic code. This experiment confirmed the hypothesis of molecular evolutionists suggesting that uni- and bi-potent factors originated from omnipotent ones [136]. Based on results of these experiments, L. Kisselev and colleagues proposed a new hypothesis that transition from omnipotent into unipotent or bi-potent states is achieved due to negative elements, which block some side chains of amino acids and therefore prevent their involvement in recognition of one or two stop-codons [122].

Indirect support for this hypothesis came from joint experiments with Japanese scientists [123]. This study demonstrated reverse conversion of unipotent factor into omnipotent one achieved by simple temperature increase. This effect may be attributed to the increased mobility of side chains of amino acids attenuating or abolishing their negative effect on recognition. The concept of "negative elements" responsible for loss of omnipotence in variant-code organisms has recently been confirmed in direct experiments. Using the method of inter- and intra-domain molecular chimeras developed in Kisselev's laboratory, the authors identified negative element in the N-domain of *Stylonychia* eRF1. In this infusorian eRF1 recognized only one stop codon, UGA. This negative element is positioned at 122-124 (using human eRF1 numeration) near conservative, functionally important motif YxCxxxF. It prevents contact of the second nucleotide of stop-codon, A, with eRF1 recognition site (the YxCxxxF loop). In this position of human eRF1 there is tripeptide TSL, lacking properties of negative element. Interestingly, in another ciliate *Euplotes*, recognizing stop-codons UAA and UAG, there is another mechanism limiting omnipotence and eRF1 lacks negative element positioned at 122-124 and fragments of the negative element are located in completely different sites of the eRF1 molecule.

L. Kisselev and his team made substantial contributions to discovery and study of class 2 termination factor eRF3. This factor was identified [126] soon after discovery of prokaryotic RF3. In collaboration with French scientists and colleagues from St. Petersburg, Kisselev demonstrated that eRF3 belongs to a class of GTPase enzymes. GTPase activity of human eRF3 was experimentally demonstrated [137] before demonstration of such activity in *E. coli* RF3. In contrast to RF3 and other GTPases, manifestation of this activity in eRF3 requires the presence of both ribosomes and eRF1 [137].

After discovery of eRF1-dependency of GTPase activity of eRF3, it was suggested that eRF1 may act as GAP (GTPase activating protein) or GEF (guanine nucleotide exchange factor, responsible for GTP/GDP exchange) [138, 139]. However, this suggestion still needs experimental validation.

eRF1 and eRF3 exhibit mutual influences: GTPase activity of eRF3 requires the presence of eRF1, whereas manifestation of eRF1 activity *in vitro* at low concentra-

tions of template oligonucleotides requires the presence of eRF3 [137].

A decisive contribution of L. Kisselev and L. Frolova in identification of eukaryotic eRF1 and eRF3 and elucidation of their basic biochemical properties has been accepted by the international scientific community. L. Kisselev was a speaker on this subject at recent symposia and conferences on protein biosynthesis, ribosomes, and tRNA, and he authored reviews on this subject as well [131, 139-141].

L. Kisselev and his colleagues were among the first biologists employing methods of bioinformatics for analysis of stop-codon contexts. Their results [142, 143] have been subsequently confirmed by other laboratories. For example, in prokaryotes and eukaryotes nonrandom distribution of some nucleotides at −1 and +4 to the stop codon was observed.

In joint study with M. Yarus's laboratory (USA) L. Kisselev and L. Frolova obtained RNA aptamers, which selectively bind to eRF1 and eRF3 and inhibit their activity [144]. In collaboration with a French group and using the method of selective covalent cross-links between mRNA and eRF1 [145], they found that eRF1 binding with the ribosome occurs in two steps, and the first one does not depend on stop-codon, whereas the second step depends on stop-codon [146].

Now L. Kisselev's laboratory very successfully continues studies of mechanism responsible for translation termination in eukaryotes. We hope that in the near future results of these studies, usually original and unexpected, will be published soon.

Among members of L. L. Kisselev's laboratory who have made the major contribution to translation termination studies, we should mention L. Yu. Frolova, the first author of most papers published on this subject, and also PhD students A. Seit-Nebi, A. Kononenko, P. Kolosov, and S. Lekomtsev, and staff-members N. Yu. Oparina, E. Z. Alkalaeva, and V. I. Dubovaya.

Several studies were carried out in collaboration with I. Arman's laboratory (Institute of Molecular Genetics, Russian Academy of Sciences), G. G. Karpova (Institute of Chemical Biology and Fundamental Medicine, Siberian Branch of the Russian Academy of Sciences), S. I. Tatkov (State Scientific Center for Virology and Biotechnology "Vector", Novosibirsk Region), Institute of Protein Research, Russian Academy of Sciences, Pushchino (E. Davydova, M. Garber, and A. S. Efimov), and V. V. Volkov (Institute of Crystallography, Russian Academy of Sciences).

One of the key studies was carried out in collaboration with G. Zhouravleva and S. Inge-Vechtomov (St. Petersburg University). Many foreign scientists were also involved in these studies: A.-L. Haenni, W. Tate, M. Philippe, R. Buckingham, A. Favre, J. Justesen, T. Merkulova, J. Celis, J. Camonis, Y. Nakamura, M. Yarus, M. Ehrenberg, O. Jean-Jean, and others.

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