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APPLICATIONS OF MOLECULAR GENETICS IN PERSONALIZED MEDICINE

Part 1: Organization of Human Genome:

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TRANSCRIPTION AND TRANSLATION

Pelin Pelit[1], Tayfun Acar[1], Mesut Karahan[2]

[1]Yildiz Technical University, Faculty of Chemical and Metallurgical Engineering, Department of Bioengineering, 34220 Esenler-Istanbul Turkey

[2]Üsküdar University, Faculty of Engineering and Natural Sciences, Department of Bioengineering, 34662 Uskudar-Istanbul TURKEY, E-mail: mesut.karahan@gmail.com
Fax: +90 216 474 1256 Phone: +90 216 400 2222

TRANSCRIPTION

Transcription means that the genetic informations stored in double-stranded DNA are copied or printed in the form of a single-stranded RNA molecule like mRNA, tRNA, rRNA [1]. The first stage of the flow of information from DNA to polypeptide is the transcription of DNA nucleotide sequence to a RNA nucleotide sequence. One of the latest developments related to transcription is marked by that Stanford University Biologist Roger Kornberg won the Nobel Prize for Chemistry in 2006 as a result of his work on eukaryotic transcription [2,3].

THE IMPORTANCE OF THE TRANSCRIPTION

The faundation of the Molecular Biology is based on formation of RNA from DNA and subsequently the conversion of that RNA into protein. When the DNA genetic information of each individual (geneotype) is converted to the proteins, it reveals individual's unique characters (phenotype). Therefore, the conversion of DNA into an RNA product is the first step [4-7].

STAGES OF TRANSCRIPTION

In transcription, there are three basic steps as initiation, extension and termination which occur in both eukaryotes and prokaryotes. Although the general process of transcription is very similar in prokaryotes and eukaryotes, there are also some significant differences.

Transcription is initiated from this region called as the promoter, that is firstly bound by relate proteins in both bacteria and eukaryotes [2,8].

Promoter: Promoter which serves as the control point in the regulation of gene transcription is a region of the DNA segment toward 5' prime of the gene. It compromises elements of specific DNA sequences that is recognized by transcription factor proteins. These promoter sequences lead RNA polymerase to the coding region of the gene and initiate the function of the RNA polymerase [9-11].

Eukaryotic Promoters: These promoters usually extends toward 5' of the gene and have various elements which are remote from the transcription start site. Many eukaryotic promoters contain a TATA box (the DNA sequence in the promoter region of the gene) (TATAAA sequence). This TATA box binds protein that helps the formation of the RNA polymerase transcriptional complex. TATA box is located in close proximity to the transcription start site (within 50 bases) [9,12-14].

Prokaryotic Promoters: The promoters of prokaryotes are comprised of two short sequences from the transcriptional start site which are located upstream at -10 and -35 bp (base pairs) position. Sequence at position -10 is called Pribnow box or the element of -10. This sequence usually contains 6 nucleotide as TATAAT. Pribnow box is required for the initiation of transcription in prokaryotes. The other sequence at position -35, is mostly composed of six nucleotide comprising TTGACA. The presence of this -35 sequence position ensures the higher rate of transcription [8,9,15].

- **Initiation:** RNA polymerase enzyme is responsible for RNA transcription. This enzyme is linked to specific portions called as promoter in DNA to start RNA synthesis [6].
- **Elongation:** RNA polymerase enzyme synthesizes RNA strand along the DNA chain. While the acting enzyme opens the front of double-stranded DNA, creates the helical structure after the reaction.
- **Termination:** RNA synthesis continues along the DNA strand until it encounters a signal representing termination of the polymerase enzyme. The termination process happens as the transcription complex separation takes place on the DNA sequence of terminator [6,16].

RNA (RIBONUCLEIC ACID)

RNA is a polymer composed of nucleotides. Each nucleotide within the RNA structure includes a nitrogenous base, a ribose sugar and a phosphate. RNA is involved in many important biological processes [7].

Genaral Features of RNA:

In nature, there are essentially two kinds of nucleic acid including DNA and RNA. RNA is different in many respects from DNA [7,17-19]:

1. RNA has a single-stranded nucleotide chain structure. It is not like the double-stranded structure of DNA. This allows more flexibility of RNA and formation of complexes in a much greater variety, in three-dimensons.
2. RNA comprises ribose sugar in its nucleotides instead of deoxyribose sugar present in DNA.
3. RNA nucleotides (ribonucleotides) comprises adenine, guanine, cytosine bases and uracil base instead of thymine base in DNA.
4. RNA can catalyze important biological reactions similar to proteins but DNA can not. RNA molecules functioning such as protein enzymes is called ribozyme.

Classification of RNA:

RNA is generally divided into two groups. One class of RNAs mediates gene decoding process of the polypeptide chain. This 'informative' RNAs are called messenger RNAs (mRNAs). These RNAs transmit genetic information in DNA to ribosome. For the rest of the genes in the minority, the RNA itself is the ultimate functional product. This kind of RNAs are functional RNAs [7, 20,21].

I. **The Messenger RNA (mRNA):** They are the RNAs which mediate the translation of genetic information in DNA into protein. They are protein-coding RNAs [7].
II. **Functional RNA (fRNA):** These RNAs' genes, which are also called non-coding RNAs, generate the functional RNA molecules instead of encoding proteins [7].
    1. **Transfer RNA (tRNA):** It is responsible for bringing amino acid toward mRNA in the process of translation. All kinds of tRNA are connected to a single kind of amino acid (20, in general) and carry it to the ribosome [7].
    2. **Ribosomal RNA (rRNAs):** They are essential components of ribosomes. They guides assembly of amino acid chain which is made by mRNA and tRNA with pretending to be large macromolecular machines [7].
    3. **Small nuclear RNA (snRNAs):** It is a part of RNA transcription system in eukaryotic cells. Some snRNAs provide guidance to the rRNAs modifications. Others are combined with various protein subunits to form ribonucleoprotein processing complex [7].
    4. **Small nucleolar RNA (snoRNAs):** Until 1995, more than 20 small nucleolar RNA was detected. Small nucleolar RNAs are responsible for making various modifications after transcription for rRNA, tRNA, or small nuclear RNAs [22-24].
    5. **MicroRNA (miRNA):** MicroRNAs, conserved in a high level, encoded from DNA regions but are translated to protein, are about 18-24 nucleotides in length. The miRNAs, carry out the regulation of gene expression after transcription binding to the target mRNA that is complementary to its nucleotide sequences and leads to translational inhibition or mRNA degradation. With this way miRNAs play an important role in homeostatic processes such as cell proliferation, cell differentiation, and cell death [2,7,25-28].

RNA Polymerase Enzyme:

RNA polymerases (RNAP or RNAPol) are enzymes which copy the information from a DNA or RNA molecule to an RNA molecule. There are RNA polymerase enzymes in all living things and many viruses. While bacteria and archaea have a single RNAP, in eukaryotes there are three types of a RNAP. Bacterial RNAP, archaeal RNAP, and eukaryotic RNAP I, RNAP II, RNAP III are members of conserved protein family called as multi-subunit RNAP family. Bacterial RNAP and eukaryotic RNAP II exhibits striking structural similarities [11,28-32].

- **RNA Polymerase I (Pol I):** RNA polymerase I enzyme found in eukaryotes is involved only in the transcription of rRNA. This kind of RNAs constitute half of the amount of total RNA synthesized in a cell. Pol I includes 8-14 protein subunits (polypeptide). There is exact or related subunits in Pol II and Pol III [33-35].
- **RNA Polymerase II (Pol II):** It is responsible for making transcription of genes which encode mRNA and some small nuclear RNAs. This enzyme is able to recognise thousands of different RNA regions. Pol II has 12 enzyme subunits and additional factors depending on the transcription stages (starting, elongation and termination). The first stage of the transcription starts with the formation of a closed promoter complex including 10 Pol II core subunits, Rpb4/7 Pool II sub-complex and (*TF) IID, TFIIB, TFIIE, TFIIF ve TFIIH transcription factors. (*TATA-box binding proteins containing TBP and TBP-related factors) [35-41].
- **RNA Polymerase III (Pol III):** RNA polymerase III is the largest and most complex ones of the eukaryotic RNA polymerase enzymes. It contains 14 subunits and has weight of 700,000 Da. All of its transcribed genes are small and all of them can not be translated into protein. The most important target for Pol III is the genes of all tRNAs and 5S ribosomal RNA. Like in large ribosomal RNA genes, this small genes are present in multiple copies. However, they are neither grouped together in successive sequences nor localized in a region of the core. On the contrary, they are distributed throughout on the genome and the core. Pol III synthesizes a basic assortment including tRNA, 5S rRNA and 7SL RNA that are necessary for protein synthesis. High rates of Pol III transcription are needed in order to sustain growth of the cells [2, 8, 28, 42-44].

PROKARYOTIC TRANSCRIPTION

I. **Start:** It needs a particular DNA sequence called as promoter in prokaryotes to find the right starting point of RNA polymerase enzyme transcription. This section is located close to the start of transcription. Promoters are important part of the regulatory region of a gene. In transcription start site, there is generally a purine base (G or A) and C and T bases which are located on both sides (CAT, CGT). The synthesis of RNA transcript starts 5' of the promoter and continues towards 3'. Typically, 5 prime is written on the left and 3 prime is written on the right. Because the promoter is near the end of the gene where transcription is initiated, in other word being in 5 prime of the gene, promoter region is also referred to regulator 5 (Figure 1). In figure 1b, it is shown promoter region of seven different genes in the E. coli

genome. Although there is a same RNA polymerase, different genes have promoter sequences. It is not surprising for the similarities between promoters. Especially great similarities of two regions are seen in almost all cases. These regions are known as -35 and -10 regions. The reason is that they are located respectively 35 and 10 base pairs. These portions are separated from each other by 15-17 base pair. -35 and -10 regions of different genes do not need to be the same. However, it is possible to arrive find a nucleotide sequence which is compatible with most sequence. This sequence is called as a consensus sequence. RNA polymerase holoenzyme binds to DNA from this point. After that, the double helix DNA is opened and a synthesis of RNA molecule is started. The first transcribed base always determines the initiatiıon site in the same position. Transcription begins before protein-encoding gene segment. Thus, a transcript has '5' untranslated region (5'UTR).

Bacterial RNA polymerase enzyme is also called as RNA polymerase holoenzyme. This enzyme scans DNA for a promoter sequence. This multisubunit enzyme complex consists of the four subunits of the basic enzyme (alpha (α) subunit, beta (β) subunit, beta prime (β') subunit and omega (ω) subunit) and sigma factor (σ) also called as a subunit. In holoenzyme, there are two alpha units and one from each units of the other four units (like $\alpha_2\beta\beta'\omega\sigma$). The alpha subunit is encoded by gene rpoA. It is required for association of basic complex but there is unclear whether it has a transcriptional activity or not. It is consider that the beta subunit encoded by gene rpoB is the catalytic subunit of the RNA polymerase enzyme. Furthermore, β' subunit is encoded by gene rpoC. It is known that this unit is responsible for binding to DNA. σ subunit is connected to -35 and -10 regions, so that it is positioned correct start site to initiate holoenzyme transcription. σ subunit has also a role to separate DNA strands around -10 region. In this way, the basic enzyme binds tightly to DNA in preparation process for RNA synthesis. While the basic enzyme is bound after initiation, transcription starts and σ subunit is separated from the rest of the complex.

As in many other bacteria, E. coli has many different sigma factors. One of them is σ70 (its mass 70 kDa). This primary sigma factor is used in the early stages of great majority of E. Coli genes transcription. Other sigma factors recognize different promoter sequence. Thus, facilitated different factors, the same basic enzyme recognizes different promoter sequences and transcribes different groups of genes [6,7, 45-49].

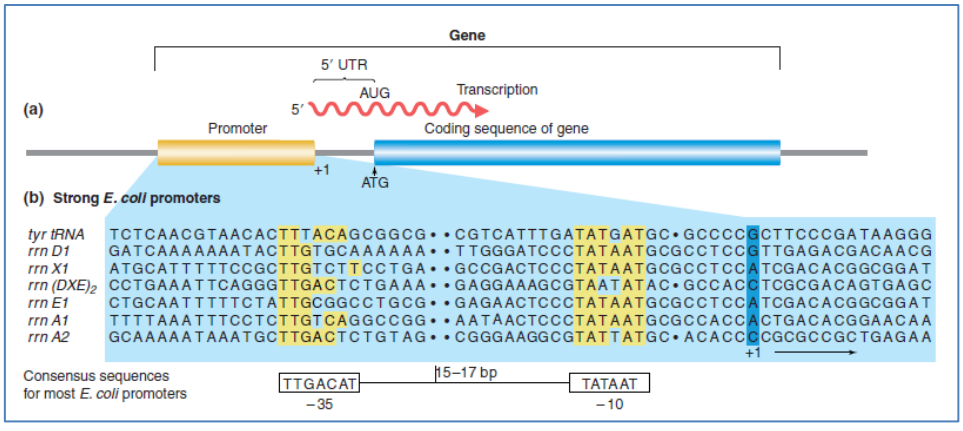

Figure 1 : Promoter sequence [7]

II. **Elongation:** When RNA polymerase moves along the DNA strand, enzyme wraps the upstream transcribed DNA helix back while opening the downstream DNA helix. In this way, enzyme holds a portion of single stranded DNA region. This region is called transcription bubble. Polymerase enzyme in bubble watches the bindng of free ribonucleoside triphosphate to the next open base in DNA template and if a complementary match is made, that base is added to the mRNA chain [7, 50,51].

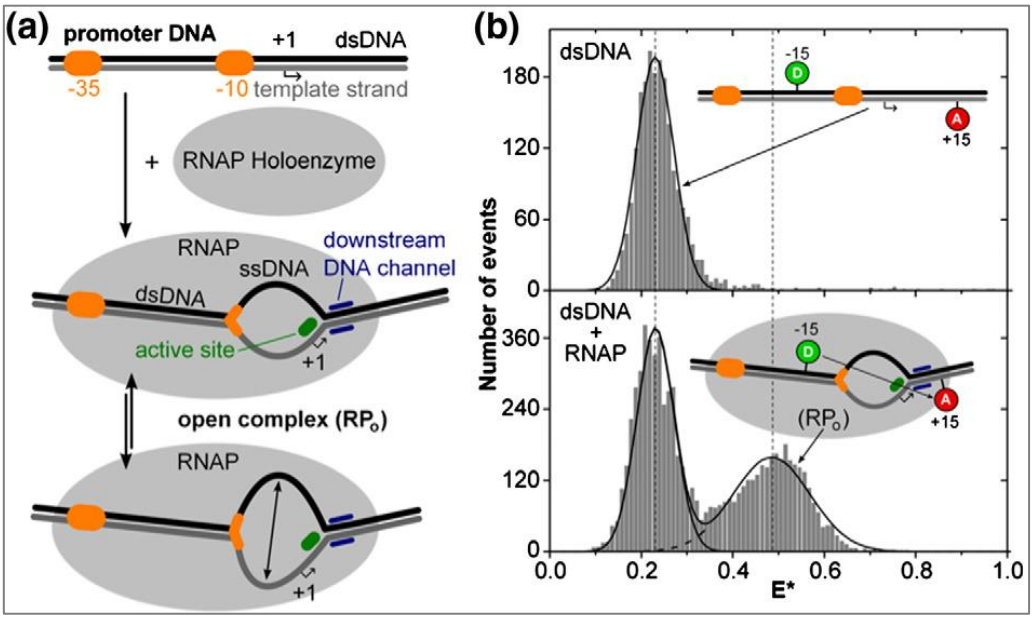

Figure 2: Blistering shape [50]

III. **Termination:** A single gene transcription is terminated out of the protein-coding segment of the gene at the end of the 3' untranscribed regions (3 UTR). For the termination of RNA polymerase chain, the elongation in transcription continues until it recognizes a specific nucleotide sequence acting as a signal. The signal initiates the oscillation of RNA newly formed RNA with its nucleotides and template from the enzyme. In prokaryotes (E. coli and other bacteria) in termination step of transcription, this signal can be from two different mechanisms. These are Rho-independent mechanism (the real mechanism) and Rho-dependent mechanism.

Rho-Independent Termination: Rho-independent terminator is the easier one when we compare the two systems. As a result of this, this mechanism is called as a simple termination. Rho-independent terminator sequence contains about 40 base pairs. These bases are terminated rich in GC. G and C in the template sequence will respectively give C and G in transcription and RNA will be rich for GC in this region. These C and G bases being complementary between them can form hydrogen bonds and end with a hairpin loops. G-C base pair is more stable compared to A-T base pair, because G-C is connected with triple bonds. While the A-T (or AU) is connected by two hydrogen bonds. Harpin loops consisting of G-C base pair are more stable than loops consisting of A-T base pairs. Cycle follows with eight U base, in accordance with the A residue that is on the DNA template. In this mechanism, it is believed that the polymerase enzyme stops after U bases are synthesized. Base pairings that consisted with

correspondance of A bases in template DNA strand to U residues, weakens the combination of DNA-RNA. This, facilitates the removal of RNA chain from enzyme complex and template DNA chain.

Rho-Dependent Termination: While RNA polymerase enzyme can terminate RNA transcription from the hairpain structure itself, sometimes termination regions may not create hairpin structure. In this case, it is required Rho-dependent termination mechanism. In this mechanism, it needs to have Rho co-factor for recognition of the termination signal by RNA polymerase enzyme. With the Rho-dependent termination signals, RNAs do not generally have U residue sequences and hairpin loops. Instead, they have 40-60 nucleotide sequences including an upper portion called as Rho bindly region which is rich in C residues but poor for G residues. When Rho binds to a single-stranded RNA, it is a hegzameric protein that can hydrolyze ATP. Consisting of six similar subunits, rho binds to the rho-binding region on the new RNA chain. After binding, Rho facilitates the oscillation of RNA from RNA polymerase. These regions are located upstream of sequences where RNA polymerase enzyme tends to stop [6, 7, 52-60].

EUKARYOTIC TRANSCRIPTION

Although eukaryotic and prokaryotic transcription are basically same, eukaryotic transcription has some distinctive differences from prokaryotic transcriptions. Eukaryotic transcription is more complicated. There are some reasons for this complexing. In eukaryotes, there are much more genes to be recognized and transcribed. Eukaryotes deal with these challanges with several ways. The first of them is that in transcription three types of RNA polymerase are involved. Secondly, before RNA polymerase II enzyme begins RNA synthesis, it requires the binding of many protein to the promoter. While some of these proteins known as general transcription factors bind DNA before the enzyme binds, some of them bind after enzyme binds. The other reason of having complicated structure of eukaryotic transcription is that in eukaryotic cells there is nucleus. The nucleus is a main decisive feature of eukaryotic cells. Genetic material of the cells is stored in the nucleus, RNA synthesis takes place in the nucleus and require to be processed before transfer from nucleus to cytoplasm for translation. The final reason is that for transcription the template genomic DNA is organized into chromatin in eukaryotics. Some of chromatin structures can prevent the access to DNA. This feature of chromatin makes eukaryotic gene regulation a very complex mechanism [7,60-62].

I. **Start:** As mentioned before, in prokaryotes, transcription begins with the subunit of RNA polymerase holoenzyme recognizes -10 and -35 promoter regions of a gene. After the start, subunit is decomposed and enzyme continues to synthesize RNA in a transcription bubble moving along the DNA. Similarly in eukaryotes, RNA polymerase II enzyme can not recognize promoter sequence itself. However, unlike bacteria, in eukaryotes polymerase is required to bind to the promoter region which is an integral part of holoenzyme. General transcription factors do not take place travel

with RNA polymerase during the RNA synthesis. They recognize promoter sequences and bind it and they have a duty to take RNA polymerase enzyme nucleus. They provide the right region to initiate transcription of enzyme. Six general transcription factors has been designed as TFIIA, TFIIB TFIID, TFIIE, TFIIF, and TFIIH.

RNA polymerase II is then separeted from general transcription factor and initiates transcription. Although the detailed studies of this process are continuing, a protein tail of RNA polymerase II subunit called carboxyl tail domain (CTD) is interesting. It is known that this section participates in many critical phases in the RNA synthesis and start phase in processing. CTD is located near the region of the new RNA synthesized from the polymerase. After the phosphorylation of CTD with one of the general transcription factors, the start phase ends up and the elongation phase begins. Here, it is thought that the phosphorylation weakens connection of RNA polymerase II with other proteins of starting complex and allows elongation [7, 63, 64].

II. **Elongation:** As described in prokaryotic RNA synthesis, eukaryotic elongation also takes place in transcription bubble. However, the newly formed RNA is different in prokaryotes and eukaryotes. The carboxyl tail domain of the large subunit of RNA polymerase II plays an important role in the process of elongation control. It was noticed that CTD phosphorylation occurs with the efficient elongation transition. An intact CTD is required for elongation control process. CTD is formed by repeating a series of seven amino acid many times. These repeating units act as binding site for some enzymes and some required proteins in coating, attaching and cleaving of RNA. Because of being close to occurance of new RNA from CTD polymerase, this region is an ideal place to control connecting and oscillation of proteins which are needed in the process of formation of new RNA transcription while RNA synthesis is continuing. RNA elongation continues until the conserved sequences close to 3’ prime (AAUAAA or AUUAAA) are recognized by the enzyme. Then enzyme cuts the RNA about more than 20 bases from the 3’ end. After cutting, 150-200 adenine (A) nucleotide portion [poly(A)] is added. Therefore, AAUAA sequence of protein-coding genes is called as polyadenylation signal [7, 64-66].

III. **Termination:** Although start and elongation stages have been well researched, the mechanism of termination stage especially for RNAP II transcription was unknown until recently. Termination is an important step for releasing RNAP from its own template. Termination also prevents the formation of antisense RNAs. Such RNAs may inhibit the formation of normal RNA. Thus, abnormal gene expression does not occur. The termination with RNA Pol II does not happen in conserved region or at a fixed distance from 3’ of mature RNAs. Termination step in mammals occurs in anywhere from several base pairs to several kilobases downstream of 3’ of mature RNA. Polymerase II termination can happen in different ways depending on the RNA 3’ prime processing signal and termination factors, which are located at the tip of the gene. Two ways have been well studies inducing poly (A)-dependent and Sen1-dependent ways.

Poly (A) dependent termination happens to many protein-coding genes, where RNAP II termination is engaged with a RNA maturation event. Here, 3' of newly synthesized transcript is exposed to cleavage and polyadenylation. This 3' processing reaction can be divided into two steps. Firstly, transcription of poly (A) region follows the suspension of RNAP II transcription and the endoribonucleolitic separation of newly synthesized transcript. Secondly, while upstream cleavage product is polyadenylated, downstream cleavage product is decomposed. Sen1 dependent termination is an alternative termination mostly for non-coding RNAs. It is firstly discovered in S. cerevisiae yeast. Unlike mRNA, endoribonucleolitic division and/or core exosome with exoribonucleolitic cutting at 3' of the yeast snRNA and snoRNA is created by TRAMP complex and they do not contain poly (A) tail in their mature form. RNAP I termination includes less factors compared to RNAP II, but it is still a complex process. In yeast, the most important three major termination regions have been identified in the sequence of intergenetic spacer region (IGS=intergenic spacer region). In 90% of the yeast RNAP I is terminated in the first terminator (T1). Sal box is the largest terminator in mammals. It is recognized by TTF-I (termination factor for polymerase I) for direct termination. In addition, in mammals the formation of 3' prime of rRNA and oscillation of RNAP I need a free factor. This factor called as PTRF (Polymerase I and transcription release factor) is associated with RNAP I and TTF I. Adding PTRF into in vitro assay is sufficient to release free transcript from mold DNA and RNAP I. RNAP III transcribes various short, nuclear and cytoplasmic non-coding genes (5S rRNA, U6 spliceosomal snRNA, tRNAs and RNAse P, RNAse MRP, adenovirus-associated (VA) and 7SK RNAs). RNAP III is a very effective polymerase not only because of there short transcription units but also because the enzyme gets reinstalled quickly on similar transcription unit. RNAP III is able to efficiently terminate without an apparent need to other factors. RNAP II has three classes, each of their transcribed genes use a specific promoter (tRNAs/VA RNAs, 5S rRNA and U6 snRNA). Although the use of different promoters, RNAP III terminates transcription in a simple common consensus sequence of 3' prime of gene. In in vitro transcription, the lack of specific subunits of RNAP III (C11, C37, ve C53 (RNAPIIID)) shows heterogenous termination in accordance. The addition of C37/C53 heterodimer subunit is sufficient to allow recognition of terminator and to fix flaws of termination. It is suggested that C37/C53 complex reduces the extension rate of RNAPIIID. This reduction provides an increasing lag time for terminator elements to cause oscillation of transcript and RNAP III. C11 is an essential subunit that also mediates RNA cutting activity of RNAP III [60,67-69].

COMPARISON OF PROKARYOTIC AND EUKARYOTIC TRANSCRIPTION

In the process of transcription in prokaryotes and eukaryotes, there are significant differences [70,71]:

- In prokaryotes, transcription is simplier than in eukaryote.
- In prokaryotes, transcription occurs in the cytoplasm. In eukaryotes, it occurs in the nucleus of cells.
- Comparing to the eukaryotes DNA, in prokaryotes DNA is more accesible to RNAP. Eukaryotic DNA is wrapped into proteins called as histone to form nucleosomes, there is further packaged to form chromatin. While prokaryotic RNAP interacts directly with DNA, in eukaryotes many proteins mediate the interaction of RNAP and DNA.
- The other difference is the promoter sequences. While prokaryotes have -10 and -35 sequences that serves as promoter, in eukaryotes there is a TATA box that is located -25 base pairs, upstream of the transcription start size.
- In prokaryotes, there are two ways of termination: rho-dependent and rho-independent. In eukaryotes, termination is based on two events: In the termination process, a poly (A) signal and a downstream terminator sequence.
- As a result of transcription, produced mRNA is not changed in prokaryotic cells. In eukaryotic cells, mRNA is modified with RNA cutting, 5’ prime closing and an addition of poly (A).

TRANSLATION

Translation means that genetic information copied into RNA with transcription is converted to a protein or polypeptide chain. In other words, it is the expression of genetic information in the form of protein molecules. Three important components of protein synthesis are messenger RNA (mRNA), transfer RNA (tRNA) and ribosomes [1,72,73].

mRNA includes a code (password) which determines the protein's amino acid sequence. The mRNA unit that encodes an amino acid and comprises three nucleotides is called codon. When the translation of mRNA starts, codons are read as successively without a space and hesitation. Each codon indicates either one aminoacid participating in protein synthesis or the termnation of protein synthesis [74,75]. Code defines three nucleotide sequences called as codon and the relationship between aminoacids [76]. After the discovery of the structure of DNA by James Watson, Francis Crick, Maurice Wilkins and Rosalind Franklin, during the works starting on the coding of proteins, George Gamow stated that to encode 20 different aminoacids, it is required to use a triliteral code. It is calculated mathematically that for 20 amino acids, at least 64 codon is necessary. Made in the accounts, it was calculated that if each nucleotide translates one amino acid, only 4 of 20 amino acids can be encoded; When it is concerned that two nucleotide encodes one amino acid it can be found the possibility of 16 possible arrangement (4^2) because of existing four different bases. Hereupon, an amino acid is encoded in mRNA with three consecutive nucleotides and for four possible nucletides there are nucleotide combinations that permits 4^3=64 possible codon. This is a sufficient number to identify all the amino acids. 3 of these codons are termination codons which shows the end of the translation. The 61 codons are codons encoding amino acids, they are also called sense codons [77-79]. Degeneracy of the genetic code gives the meaning that aminoacids can be determined by more than one codon. Only tryptophan and methionine are determined y a single codon. Almost all of the aminoacids are determined by 2, 3 or 4 different codons, leucine, serin and arginine are determined by six different codons. The degenerate term is a term taken from the quantum physics by Francis Crick and it has homonymous to tell multiple physical condition [79-82]. The genetic code is the same in almost all oganisms. For example, codon indicates aminoacid arginine in AGA bacteria, in humans and other organisms. The universality of the genetic code takes place in strongest evidences where all living things share a common evolutionary heritage. Except few small exceptions, all viruses, prokaryotes, archaea, and eukaryotes use the same password dictionary. The codons which do not code any aminoacid are called stop codons: [77, 83]

- UAG-amber codon
- UGA-opal codon
- UAA ochre codon

Transfer RNA; it is a small, about 80 nucleotide RNA chain which adds specific amino acids to the growing polypeptide chain in protein synthesis in the ribosome during translation [84]. 3 prime of tRNA has CCA nucleotide sequence and here is the region of amino acids connected [78]. tRNA is an 'adapter' molecule which mediates the recognition of codon

sequence in the mRNA, allows translation of codon to the suitable amino acid is hypothesized by Francis Crick. In Crick's hypothesis of adapter molecule, while adapter molecule at one prime connects amino acids while the other prime it establishes a connection with amino acid-related mRNA sequence. In tRNA structure there is an anticodon region [85,86]. On tRNA called as anticodon, there are nucleotide sequences of three bases which establish hydrogen bonds with them to recognize codons in the mRNA. For example, tRNA anticodon nucleotide sequence which matches a mRNA strand as UUU shaped, is in the form of AAA [1,87,88]. Anticodons are read in the direction of 3'->5', in mRNA codons are read in the direction of 5'->3'. For example, if the anticodon base sequence is 3'-AAG-5', codon in mRNA is shaped as 5'-UUC-3' [89]. If there was a specific tRNA for each amino acid codon in mRNA, there should be 61 kinds of tRNA. In 1966 Francis Crick observed degeneration in the third position and made a statement suggesting wobble hypothesis. He put forward that 5' base of the anticodon ("Wobble base") is not so constricted as much as the other two bases spatially and in this way it can make non-standard base pairing. The first two letters of codons that define the same amino acid are the same, only the third letter is different. The first two bases of a mRNA codon always makes powerful Watson-Crick base pairing with anticodon in tRNA. For the third position nucleotide between codon-anticodon there is a flexibility in the establishment of hydrogen bonds and there is no obligation to obey base-pairing rules tightly. In this regard, the most variable tRNA is the tRNAs containing inosine in the wobble position. Inosine, which do not bear amino group at the second Carbon atom, is a guanine analogue. In wobble position of tRNA anticodoninosine and adenine can match with cytosine or uracil. For example, a tRNA whose tRNA anticodon is CCI, fitting GGU, GGC and GGA shaped mRNA codons can add glycine amino acid into the growing protein chain. According to this hypothesis, 61 tRNA is not needed for 61 codons which determine the amino acid [90-93].

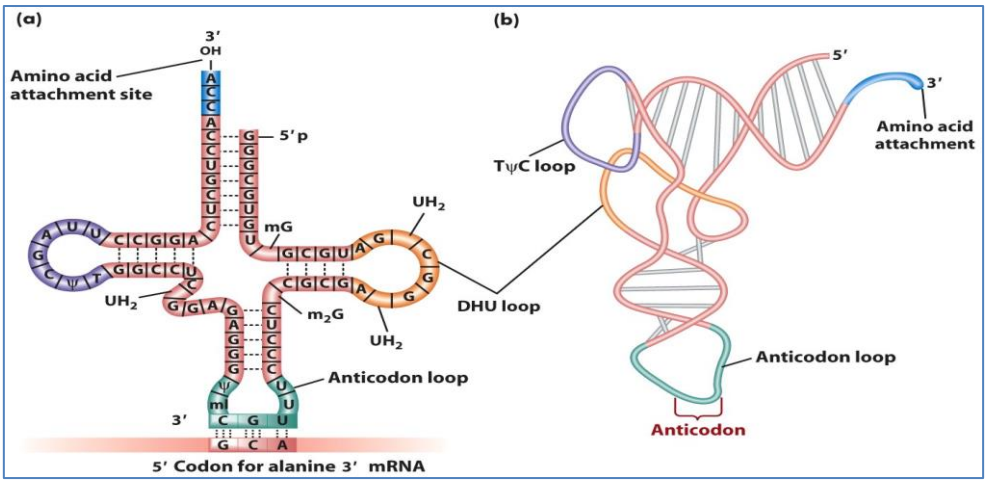

Figure 3: tRNA molecule [83]

Ribosomes, are found in all living cells and has primary importance in translation. About 65% of the ribosome is composed of rRNA, and 35% of the other part is composed of ribosomal proteins. They are cytosolic particles found in eukaryotic cells as 40S and 60S sedimantation coefficient of two subunits, a total of 80S sedimentation coefficient; and in prokaryotic cells, 30S and 50S sedimantation coefficient of two subunits, a total of 70S

sedimentation coefficient [1, 94, 95]. In 30S ribosomal subunit of prokaryotes, 16S ribosomal RNA is found. In 50S ribosomal subunit there are two types of rRNA, these are 5S and 23S rRNAs [96]. In eukaryotes, in small ribosomal subunit 18S is found; in large subunit there are three types of rRNA including 5S, 5.8S and 28S rRNAs [97]. During the translation of Messenger RNA (mRNA) by ribosome, mRNA is located between these two subunits [98]. During protein synthesis, many ribosomes on the same mRNA can form a polyribosome (polysome) [1]. Polysomes are observed in both eukaryotic and prokaryotic cells. Polysomes in eukaryotic cells with 7-8 ribosomes per polysomes, are smaller than polysomes in prokaryotic cells. A typical eukaryotic cell contains millions of ribosomes in its cytoplasm [99]. A ribosome contains 4 binding sites. One of them is for mRNA and three of them are for tRNA (called the A-site, the P-site, and the E-site) [100]:

- A-Site (Acceptor Site): It is the site where specific tRNA anticodons linked with amino acids matches the bases located on the mRNA.
- P-Site (Peptidyl Site): It is the site where amino acids which are connected with a specific tRNA get transfer to the A-site are transferred to empty this site.
- E-Site (Exit Site): It is the site where tRNA separated from P-Site before leaving subunit, peptidyl site.

There are similar designs and functions of eukaryotic and prokaryotic ribosomes [95, 101].

Activating Enzymes

Aminoacyl-tRNA synthetase enzymes (M.A.: 40 000-100 000) are highly conserved proteins. Each of them containing ten enzymes is divided into two groups. One of them accesses with minor groove of tRNA acceptor helix, the other accesses with major groove of the same helix. Amino acids in cytoplasm are activated as aminoacyl-tRNA with binding to their specific tRNAs in the presence of ATP (adenosine triphosphate) with the help of activating enzymes called as aminoacyl-tRNA synthetases (aaRS) which are required Mg^{2+}. A cell has 20 different aminoacyl-tRNA synthetases for each of 20 amino acids [1,77,79,95]. Amino-acyl tRNA synthetase enzyme use two step binds amino acids to tRNA molecule. In the first step, ATP and amino acid enter the reaction and amino acid with carboxyl group is connected to AMP (adenosine monophosphate), as a result, aminoacyl-AMP and pyrophosphate (PPi) are formed. In the second step, between amino acid and 3'OH group of adenosine ribose located in the 3 prime of tRNA molecule bind with water exit (ester bond) and AMP is separated. AMP is separated. In a conclusion, aminoacyl-tRNA is generated [1, 95,102,103].

1) Amino acid + ATP $\longrightarrow$ amino acyl-AMP+ PPi

2) Amino acyl-AMP + tRNA $\longrightarrow$ amino acyl-tRNA + AMP

Conclusion: Amino acid + ATP + tRNA $\longrightarrow$ amino acyl tRNA + AMP + PPi [95].

The translation can be divided into three stages [83]:

- Initiation
- Elongation
- Termination

1) The Initiation of Translation

For translation, mRNA, tRNA ribosomes, as well as some protein factors are also required. In prokaryotes, for the initiation of translation requires IF1, IF2, and IF3 (initiation factors) protein factors [104]. In eukaryotes, the number of protein factors are more than 12 (eIF1, eIF1A, elF2, eIF2B, eIF3, eIF4A, eIF4E, eIF4G, eIF5, eIF5B) and some of them play an important regulatory role [105-107].

The initial stage consists of three basic step. Firstly, mRNA is bound to the ribosome small subunit. Secondly, by connecting the initiator tRNA to the mRNA, codon-anticodon match occurs. In the third stage, it is added to the initiation complex with the large subunit of the ribosome and protein synthesis proceeds [77,79].

Protein synthesis is started with AUG codon which is at the beginning of the mRNA-carried code. To distinguish initiation codon and other methionines, prokaryotes contain specific sequence Shine-Dalgarno sequence (UAAGGAGG) which is located about 5-10 nucleotides before the initiation codon. Close to the 3' of 16S rRNA of 30S ribosomal subunit, there is a nucleotide sequence complementary to Shine-Dalgarno sequence, thus it accelerates the binding of mRNA to the 30S ribosomal subunit. In eukaryotes, the first codon located at the beginning of mRNA is 5'-AUG-3' and it is recognized by specific initiation tRNA. In prokaryotes, protein synthesis is initiated with N-formyl methionyl tRNA. In eukaryotes, protein synthesis is initiated with non-formylation of a special methionyl tRNA (tRNAi Met) [79,108-110].

5'- UAAGGAGG (5-10 base) AUG mRNA

3'--AUUCCUCC.....16S rRNA [103]

In prokaryotes, protein synthesis starts with the initiation complex. In prokaryotes when protein synthesis starts, the initial complex is formed in the presence of initiation factors (IF) and GTP near the 5' of the mRNA [1,77,79,110]. mRNA molecule is binded to small 30S ribosome subunit. During initiation, initiation factor (IF-3) provides binding to the small subunit and prevent the binding to the large subunit. The second step is the binding of initiator fMet-tRNA to the initiation codon. In this step IF2 plays a role by binding tRNA and control entry of tRNA into the ribosome. IF2 in GTP-bound form is connected to 30S P site. After the binding of IF2, fMet-tRNA binds to IF2 and IF2 transfers fMet-tRNA to the P site. IF1 is associated with 30S ribosomal subunit in A site and prevents entry of aminoacyl-tRNA to the A site, increases the seperation of small and large subunits. It prevents the binding of initiator tRNA in small subunit to A site. 30S initiation complex is formed by 30S ribosome subunit, mRNA, initiator tRNA, GTP and initiation factors [79,83,111,112].

In the final stage of initation, 30S is divided from IF3, small subunit and 50S large subunit is joined to the initiation complex. In this conformation, the required energy is provided with by the hydrolyzes of guanosine triphosphate (GTP), into GDP and Pi by IF2 and IF1, and IF2 are separated [79]. By the binding of the 50S large subunit, 70S initiation complex forms [112-117].

Thus, with the interaction of mRNA and fMet-tRNA, the initiation complex of protein synthesis have occured. The resulting of the initial stage is a 70S ribosome formation whose A site is empty, carrying initiator tRNA in P site and associating with mRNA [118].

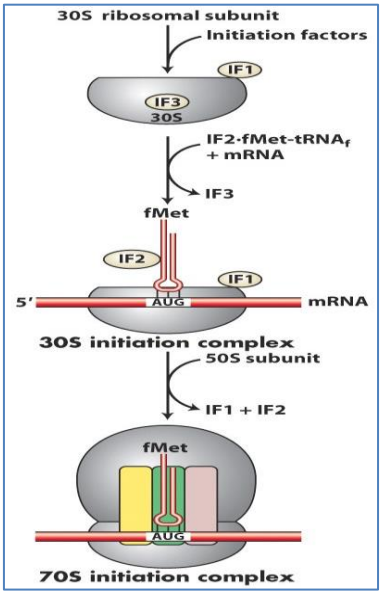

Figure 4: Formation of 70S initiation complex [83]

In eukaryotes, the initial stage looks like more complex. The initial phase is connected with 3' poly(A) tail of a typical mRNA, the cap at the 5' end of eukaryotic mRNA (the 5' cap) and at least 12 eukaryotic initiation factor (elFs) [107,119].

In eukaryotes, initiation starts with the binding of several elFs and other components to the small (40S) ribosomal subunit [120].

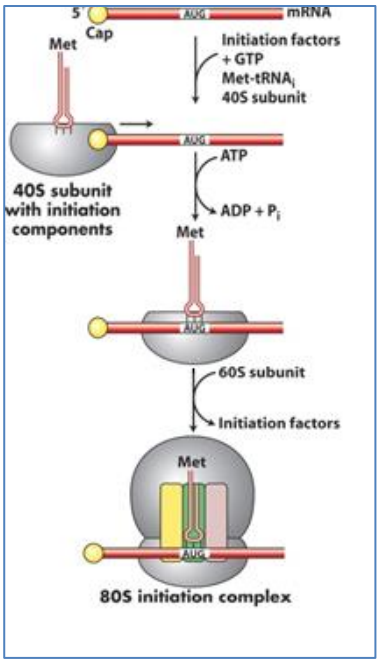

Figure 5: Formation of 80S initiation complex [83]

Eukaryotic mRNAs first interacts with ribosome with the 5’ cap structure; once ribosome recognize the cap structure, it moves to the 5’-AUG-3’ initiation codon. During movement, with the help of small subunit initiation factors, it finds the initiation codon in mRNA (AUG codon) with the base match with anticodon in initiator tRNA [83,121].

There are two other inducing translation of eukaryotic mRNA, one is in some mRNAs there is a purine three bases upstream of the initiation codon and a guanine downstairs (5’-G/ANNAUGG-3’) (Kozak sequence) It increases efficiency entering interaction with initiator tRNA [79].

Kozak sequence:

5’–ACCAUGG–3’ Start codon [79]

The second is poly-A tail of 3’ prime mRNA. It raises the translation level by supporting re-entering of ribosomes into the translation cycle. Shine-Dalgarno sequence is not available mRNA in eukaryotes unlike in prokaryotes [79,122].

IF1, IF2, IF3 factors and other additional proteins are replaced as equivalent initial factors in eukaryotes. elF3 is the initial factors as the equivalent of IF3 in prokaryotes. elF2 and elF5B, two proteins binding GTP help the binding of initiator tRNA. elf5B is the equivalent of IF2 in a dependent way of elF1A, the equivalent IF1, is connected to the small subunit; provides the binding of elf2 and initiator tRNA to the small subunit. The most important function of elF1A is to create 40 S preinitation complex by mediate the transfer of Met-tRNAf to the 40 S ribosomal subunits. Premise-initiation complex is formed (43S subunit, or the 40S and tRNA) [120,123].

elF4F enables recognizing of 43S preinitiation complex by mRNAs. Then, elF4B is bound to this complex. elF4B activates RNA helicase in elF4F. Helicase helps biding of 43S preinitiation complex to small subunit of mRNAs [118,124-127].

Correct base pairing of the small subunit and initiation factors triggers the separation of elF2 and elF3 during their movement along the mRNA and leads to the binding of large subunit to the small subunit. The connection of the large subunit results the separation of other initiation factors. Consequently, in the initial stage of translation in the eukaryotes 80S initiation complex is formed [83,118,124].

2) Elongation

The second stage in protein synthesis is the elongation stage, where amino acids are combined to form a polypeptide chain. It includes all occuring reactions from the first peptide bond formation to the last peptide bond formation in protein synthesis [79,118].

In prokaryotes, to fulfill the elongation, the initiation cmplex, tRNAs charged with amino acids, elongation factors EF-Ts (elongation factor thermo stable), EF-Tu (elongation factor thermo unstable) and EF-G (historically known as translocase) and GTP are required [79,128].

After the initial phase, ribosome bindly mRNA and fMet-tRNAfMet is positioned on the AUG initiation codon which is on the P site; A site is empty [130].

Elongation occurs in three steps [79,131]. The first step is the binding of aminoacyl-tRNA matching the codon in mRNA at ribosome A site. After formation of the initiation complex, thanks to hydrolysis of GTP and elongation factor (EF-Tu) for the A site of this complex, aminoacyl-tRNA comes to anticodon to recognize the codons of mRNA. Before that, EF-Tu firstly is bound with GTP and then to create a three-ternary complex binds to a charged-tRNA. By binding to 3'prime of EF-Tu tRNA, it protect amino acid and peptide bond formation. The occuring three-ternary complex the ribosome A site and here mask it codon on the mRNA and anticodon on the tRNA match. EF-Tu interacts with factor binding site in the large subunit (GTPase activity triggered), hydrolyzes the particular GTP and separates from EF-Tu–GDP complex and Pi ribosome released form of the Aminoacyl-tRNA [79,102,122,130-133].

EF-Tu-GDP is inactive and must be activated before the next elongation cycle. For this, EF-Ts is required, because affinity of EF-Tu for GDP is 40 times greater than its affinity for GTP. EF-Ts activates EF-Tu exchanging GDP with GTP. EF-Tu does not interact with fMet-tRNA because initiator fMet-tRNAis absent in the A site [1,130,132.134].

- EF-Tu·GTP + aminoacyl-tRNA ➔ EF-Tu·GTP- aminoacyl-tRNA [1]
- EF-Tu·GTP- aminoacyl-tRNA + ribosome ➔ ribozome·aminoacyl-tRNA + EF-Tu·GDP +Pi [2]
- EF-Tu·GDP + EF-Ts ➔ EF-Tu·Ts + GDP [3]
- EF-Tu·Ts +GTP ➔ EF-Tu·GTP + EF-Ts [4] [135]

Reactions are similar in eukaryotic cells. Instead of elongation factors EF-Tu and EF-Ts in prokaryotes; there is a stable ternary complex, shows similar features as ''eEF1-alpha-beta-gamma''. eEF1-alfa is eukaryotic equivalent of EF-Tu and eEF1-beta-gamma is eukaryotic equivalent of EF-Ts [132].

The second step in the elongation is hydrolysis of ester bond of COOH group in the amino acid found in the P site and the formation of a peptide bond with NH_2 group of the amino acid in A site. So, it is the transfer of extending polypeptide from tRNA in P site to amino acid of tRNA in A site. This reaction is called peptidyl transferase reaction. For the formation of peptide bond in ribosome, the responsible region is peptidyl transferase center [122,134,136].

The third step of the elongation phase is called as translocation. This step move positions ribosome on to the next codon and it is required the hydrolysis of elongation factor G(EF-G) and GTP into the GDP. After pepdidyl transferase reaction occurs, tRNA in P site breaks its bond with amino acid and extending polypeptide chain remains bound to tRNA in A site.

For the addition of a new amino acid into the extending polypeptide chain, there is a EF-G's role tRNA in A site moves to P site. The mRNA shift is accomplished by base pairings between a moving tRNA in A site and mRNA. mRNA is taken with moving tRNA from A site. At exactly the same time, tRNA in P site moves to E (output) site and from here tRNA being freed in E site leaves ribosome. The movement of tRNA in P site to the E site breaks base pairings between tRNA and mRNA [130,132, 137, 138].

EF-G factor is similar to EF-Tu but larger than it [133]. EF-G binding to ribosome secures translocation [95]. After peptidyl transfer reaction, with the separation of tRNA in A site, EF-G-GTP binds to A site. By hydrolysis of GTP, the three dimensional form of EF-G-GDP varies, triggers the translocation of tRNA from A site. When translocation is completed, the affinity of ribosome with EF-G-GDP reduces and allows it to be released [83,122].

Ribosomes can not interact with both EF-Tu and EF-G at the same time. These factors bind to ribosomes one by one. While the function of work one ends and leaves from complex, the other one is introduced to the ribozome. First, EF-Tu+GTP+amino acyl tRNA form ternary (triple) complex. After leaving of EF-Tu+GDP, EF-G+GTP is bound and then it is released as EF-G+GDP [95].

Elongation in eukaryotic cells occurs in a similar manner. EF-G in prokaryotes is equivalent to eEf2 (Eukaryotic elongation factor 2) in eukaryotes. eEF2 promotes GTP-dependent ribosome translocation. This protein is completely inactivated with EF2 kinase phosphorylation. As a result of the translocation, the A site of the ribosome is empty and ribosome is ready to accept the next aminoacyl tRNA (aa-tRNA) and repeat the cycle. Until reaching a termination codon, this cycle continues [79,132,139].

In summary, at this stage each of tRNA (except initiator tRNA) follows 6 steps as three : A site : P site : E site : released [79].

3)Termination

This step for release of the completed polypeptide includes necessary reactions. Aminoacyl tRNA binding in ribosome, formation of the peptide bond and translocation cycles continues until the arrival of one of the three termination codon (UAA, UAG, or UGA) to the A site. Because, there is no complementary tRNA of termination codon. When faced with a termination codon, no tRNA binds to the A site of the ribosome. Instead, proteins called as release factors (RF) correspond to the termination codons and terminate the translation. When a termination codon came to A site of the ribosome, a RF recognizes this codon and binds to it [77,79,83,122].

Releasing factors are divided into two classes as Class 1 RFs and Class 2 RFs. In prokaryotes, there are two types of Class 1 RFs: RF1 and RF2. In eukaryotic cells, Class 1 RF is the only kind: eRF1. In prokaryotes and eukaryotes there is only one Class II factor: RF3 and eRF3 [122,140].

In prokaryotes, there are three releasing factor totally (RF1, RF2 and RF3). Release factor 1 is responsible for the recognition of termination codons UAA and UAG and Release factor 2 is

responsible for the recognition of UAA or UGA. [141,142]. The other task of the RF1 and RF2 is to trigger polypeptide hydrolysis from tRNA in P site. RF1 and RF2 are similar in size and shape with tRNA and bind A site of the ribosome as it does during the elongation cycle of amino acid-tRNA-EF-Tu-GTP complex [79,143, 144].

Release factor 3 forms complex with GTP and binds ribosome. Release factor 3 structurally is similar to EF-G [132,143].

Then release factor promotes the bound of tRNA in P site from polypeptide chain, the link between the last amino acid in polypeptide chain and tRNA is then broken. In this process, RF3 bound GTP is hydrolized to GDP. With the help of release factors the last released tRNA molecule and polypeptide chain are separated from ribosome; the large subunit of the ribosome is separated from mRNA and the small subunit [79,122,143,144].

The termination of protein synthesis in eukaryotic cells is performed in a similar manner as of prokaryotes. However, 2 different release factors are located. The first one; eRF1; recognizes all three termination codons [143]. It can be said that it is the equivalent of RF1 and RF2 in prokaryotes. eRF3 binds with GTP and stimulates the separation of polypeptide from ribosome, with similar tasks with RF3 in prokaryotes. By providing termination, release factors enable protein synthesis cycle to end [140,143,144].

Ribosome Recycling

After release of polypeptide chain and RFs, ribosome (in its P and E site) is still connected to mRNA and uncharged tRNA. For ribosome enter a new cycle of polypeptide synthesis, it needs to release the mRNA and tRNA, to separate the large and small subunits of the ribosome. All of these events are called as the re-use of ribosome [122].

In prokaryotes, the activating of ribosome recyling after the release of polypeptide for recycling ribosomeis involves EF-G and IF3 [122,145,146].

RRF (ribosome recyling factor) binds to A site of the ribosome which is empty and imitates a tRNA; at the same time it allows the binding of EF-G to the ribosome; stimulates the release of uncharged tRNAs in P and E sites. IF3 (being initiation factor) leads release of mRNA and separation of the two subunits of the ribosome. These subunits can participate in a new cycle [122,146-148].

A COMPARISON OF PROKARYOTIC AND EUKARYOTIC TRANSLATION

In bacterial and eukaryotic cells, along the process of translation major similarities and differences are seen [1,79,149,150]:

First of all, although prokaryotes and eukaryotes have similar genetic codes, amino acid identified by initiation codon is different.

In bacteria, the modified form of methionine, N-formyl methionine (fMet) is the first amino acid which enters the structure of whole polypeptide and encrypted with 5'- AUG -3' codon. In eukaryotes, methionine is not formylated.

Other difference is the existence at the same time of transcription and translation in bacterial cells. But in eukaryotes there is a nuclear membrane, so that, transcription and translation are separated from each other. The physical separation of transcription and translation is important for the control of gene expression.

Another difference is that in eukaryotic cells, mRNA life (hours and days) is more long than mRNA life in prokaryotes (a few minutes). After transcription ended in eukaryotic cells, protein synthesis can persist for a long time, but it ends up very fast in prokaryotic cells.

In both bacterial and eukaryotic cells, aminoacyl-tRNA synthetases conjugate to amio acids to their cognate tRNAs. Chemical reactions are the same.

The differences include in the size and binding of bacterial and eukaryotic ribosomal subunits. For example, the large subunit of eukaryotic ribosome contains three rRNAs, but bacterial ribosome contains only two rRNA come for each subunit.

In the process of initiation, the number of initiation factors involved in eukaryotic cells is more than the number of initiation factors involved in prokaryotic cells. Also, in prokaryotic cells there is a Shine- Dalgarno consensus sequence while eukaryotic cells has a different ribosome binding sequence as Kozak sequence.

Although elongation and termination process in prokaryotic and eukaryotic cells are similar, different elongation factors and release factors are used.

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