# Chapter 2. Selenium metabolism in prokaryotes

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Summary: The biosynthesis and specific incorporation of selenocysteine into protein requires the function of a UGA codon determining the position of selenocysteine insertion and a secondary/tertiary structure within the mRNA, designated the SECIS element, following the UGA at its 3'side in bacteria and located in the 3'non-translated region in archaea. Biosynthesis of selenocysteine takes place on a unique tRNA species, tRNA<sup>Sec</sup>, which is charged by seryl-tRNA synthetase and serves as an adaptor for the conversion of the seryl moiety into the selenocysteyl product by Monoselenophosphate, selenocysteine synthase. provided bv selenophosphate synthetase, is the selenium donor. Selenocysteyl-tRNA<sup>Sec</sup> is bound by the special translation factor SelB, which in bacteria via its Cterminal extension interacts with the apical part of the SECIS stem-loop structure. Crystallographic and NMR structural analyses of this extension from *Moorella thermoacetica* SelB, either free or complexed with the SECIS element, showed that it is made up of four winged helix domains from which only the C-terminal one interacts with the RNA ligand. Structure of the entire SelB molecule from Methanococcus maripaludis in the apo- and GDP/GTP bound forms revealed that it is a chimera between elongation factor Tu and initiation factors. Comparison of the structures in the GDP and GTP forms and modelling of the interactions between selenocysteyl-tRNA and SelB provided information on how SelB may discriminate tRNA<sup>Sec</sup> from canonical tRNAs and may differentiate between the selenocystevl moiety and the servlresidue of the precursor. A scenario for the major steps in the decoding process is postulated and arguments are given why the interaction of SelB with the mRNA is crucial. Reasons are also presented for the necessity of a balanced ratio of the components of the selenocysteine insertion apparatus and how it is regulated in E. coli via translational repression implicating a SECIS-like element located at the ultimate 5'end of selAB mRNA.

### Introduction

When bacteria are challenged with low molecular weight selenium compounds in the medium, they can process selenium in a nonspecific or a specific manner. The nonspecific metabolism rests on the chemical similarity between selenium and its neighbor element in the periodic table, sulfur. When present above a critical concentration in *Escherichia coli*, i.e., at selenite concentrations higher than 1  $\mu$ M, selenium intrudes the sulfur pathways and is metabolized along the routes of sulfur metabolism [1,2] (Figure 1). Thus, selenium in the form of selenate is taken up by the sulfate transport system and reduced to selenide via the assimilatory sulfate reduction system. When offered as selenite, reduction appears to proceed chemically by interaction with thiol compounds like glutathione (see [3] for review).



Figure 1. Scheme for the specific and nonspecific metabolism and incorporation of selenium into macromolecules. The specific pathway is highlighted in bold.  $mnm^5s^2U$  is the abbreviation for 5-methylamino-methyl-2-thiouridine and  $mnm^5se^2U$  for 5-methylaminomethyl-2-selenouridine. O-Ac-Ser: O-acetylserine, [Se] designates the reactive selenium species used by the selenophosphate synthetase as a substrate for the synthesis of selenophosphate; its possible metabolic origin is indicated by dashed arrows (see Chapter 4).

The first organic selenium compound formed is free selenocysteine, which can be converted to selenocystathionine and eventually to selenomethionine. On the other hand, selenocysteine has been shown to be a substrate for cysteyl-tRNA synthetase, which forms selenocysteyl-tRNA<sup>Cys</sup> and in this way incorporates selenocysteine at cysteine positions in proteins [4-6]. The decision whether selenium is incorporated nonspecifically as either selenocysteine or selenomethionine, therefore, should be dependent on the relative catalytic efficiencies of cysteyl-tRNA synthetase and cystathionine synthetase for the substrate cysteine and its analog selenocysteine. Nonspecific incorporation into macromolecules is drastically reduced when the cysteine biosynthetic pathway is interrupted by mutations or when it is fully repressed [6].

When selenomethionine is provided in the medium, it is almost indiscriminately incorporated into protein in place of methionine. This replacement is frequently used in x-ray analysis of protein crystals by multiwavelength anomalous dispersion [7] or in NMR spectroscopy [8]. Selenomethionine as the major selenium compound has also been detected when bacteria were grown on excessive amounts of selenite [9,10]. Free selenocysteine, on the other hand, is highly toxic and therefore growth inhibitory. Its incorporation in place of cysteine requires an overexpression system like the promoter-polymerase system of phage T7 to circumvent toxicity [11,12].

The specific incorporation of selenocysteine, on the other hand, is effective at much lower concentrations of selenite in the medium. With the aid of a *fdhF-lacZ* fusion reporter gene, in which readthrough into *lacZ* is dependent on the availability of selenium (see below), saturation has already occurred by 0.1  $\mu$ M selenite [13]. Specific incorporation does not involve free, low molecular weight selenocysteine since the biosynthesis of the molecule takes place from a precursor amino acid esterified with tRNA. It should be emphasized that the capacity to synthesize selenoproteins by the specific pathway is not ubiquitous. Actually, it is absent in the majority of microorganisms [14]. In this chapter we will discuss the specific incorporation of selenocysteine by bacteria, mainly *E. coli* and by members of archaea.

Identification of the components involved in selenocysteine biosynthesis and specific insertion rests to a considerable degree on the early work of several groups studying the anaerobic formate metabolism of *E. coli* [15-20]. Genes had been analyzed which, when mutated, abolished the ability of *E. coli* to synthesize active isoenzymes of formate dehydrogenase known as formate dehydrogenase N and formate dehydrogenase H which couple formate oxidation to the reduction of nitrate or protons, respectively. Thus, some mechanism must have been affected in the mutants that is required for generating activity of both enzymes. The genes had been mapped on the

chromosome of *E. coli* and some of them (*fdhA fdhB and fdhC*) turned out to be involved in selenium metabolism [21]. Merits also go to two technical developments, namely the establishment of a plate overlay technique for screening large numbers of colonies for formate dehydrogenase activity [17] and the set-up of a procedure for specific incorporation of radioactive selenium into selenopolypeptides [22]. With the aid of these techniques, it was easy to differentiate between specific and nonspecific incorporation (see Figure 1).

# Specific incorporation of selenocysteine by bacteria

The first genes discovered to contain an in-frame UGA codon directing selenocysteine insertion were gpx, coding for glutathione peroxidase from mouse [23], and fdhF from *E. coli*, coding for the selenopolypeptide of formate dehydrogenase H [24]. Whereas an amino acid sequence was available for glutathione peroxidase showing colinearity between the UGA in the mRNA and selenocysteine in the protein, this was not the case for the bacterial enzyme. Evidence was obtained, however, by leading truncations from the 3'end into the gene and showing that removal of the segment containing the UGA also abolished selenium incorporation into the truncated gene product. Definite proof for the cotranslational insertion was then provided by fusion of the *lacZ* reporter gene upstream and downstream of the UGA in *fdhF* and the demonstration that readthrough of the UGA required the presence of selenium in the medium [13]. Analysis of mutations that affected readthrough led to the identification of the genetic elements involved in selenium metabolism in *E. coli* [21].

After the discovery that UGA also directs selenocysteine insertion into proteins in archaea [25], and with the results of the bioinformatic analysis of whole genome sequences from several hundred organisms, it has become an accepted notion that UGA is the universally conserved codon for selenocysteine [26].

# tRNA<sup>Sec</sup>

The key element for specific selenocysteine insertion in *E. coli* was identified as the product of the fdhC gene, now designated as the selC gene [27]. It codes for a tRNA with unusual sequence and structural properties (Figure 2A).

With 95 nucleotides, tRNA<sup>Sec</sup> is the largest tRNA in *E. coli* mainly because of an aminoacyl acceptor stem of eight possible base pairs and a 22 nucleotide long extra arm. There are also a number of deviations from the consensus structure characteristic of canonical elongator tRNAs, namely a G at position 8, an A at position 14, a Y-R pair at the 10-25 sites and an R-Y base pair at positions 11-24. Moreover, the R-Y Levitt pair between the positions 15-48 is missing. As expected, extensive enzymatic and chemical

probing of the solution structure of tRNA<sup>sec</sup> from E. coli, compared with that of canonical tRNA<sup>Ser</sup>, showed that these deviations, plus the fact that the D stem is closed to a six base pair helix minimizing the D loop to four nucleotides, also restrict the types of tertiary interactions within the molecule [28]. Whereas the canonical G19-C56 interaction is still present, there are new interactions between C16 of the D loop and C59 of the T loop and the canonical A21-(U8-A14) triple pair is substituted by a G8-(A21-U14) triple interaction. The extra arm is closed by a G45-A48 pair and connected to the anticodon coaxial helix only by interaction of A44 with U26. All these unusual sequence and structural properties are conserved in the sequences of other bacterial tRNA<sup>Sec</sup> species [29]. In view of the still open discussion on the structure of the eukaryal (see Chapter 3) and archaeal (Figure 2B) counterparts and of the lack of an x-ray structure, the conclusions can be concentrated on three characteristic features: (i) the acceptor-T stem stacked helix is extended to 13 base pairs made up of 8 plus 5 base pairs in bacteria and 9 plus 4 in archaea and eukarya, (ii) the closure of the D stem and the deviations from the sequence in canonical positions restrict the possibilities for tertiary interactions within the molecule, and (iii) the extra arm appears to be less well fixed to the body of the molecule than in classical elongator tRNAs.



**Figure 2.** Cloverleaf models of the *Escherichia coli* (A) and *Methanococcus jannaschii* (B)  $tRNA^{Sec}$  species. The modified bases are shaded. The bacterial  $tRNA^{Sec}$  is drawn in the 8 + 5 arrangement of the acceptor stem/T-stem helices and the archaeal one in the 9 + 4 structure.

## **Biosynthesis of selenocysteine**

Formally, the biosynthesis of selenocysteine as elucidated for E. coli takes place in the following three steps:

(a) L-Serine + ATP + tRNA<sup>Sec</sup>  $\rightarrow$  L-Seryl-tRNA<sup>Sec</sup> + AMP + PP<sub>i</sub>

(b) L-Seryl-tRNA<sup>Sec</sup> + SS  $\rightarrow$  Dehydroalanyl-tRNA<sup>Sec</sup> + SS + H<sub>2</sub>O

(c) Dehydroalanyl-tRNA<sup>Sec</sup> + SePO<sub>3</sub><sup>3-</sup>  $\rightarrow$  Selenocysteyl-tRNA<sup>Sec</sup> + PO<sub>4</sub><sup>3-</sup>

tRNA<sup>Sec</sup> is charged with L-serine by seryl-tRNA synthetase (equation a) [27] which is in accordance with the presence of the serine identity elements [28]. The overall catalytic efficiency of charging, however, is only about 1% of that measured for a cognate serine acceptor which reflects the limited requirement of serine carbon flux into the minor pathway [30]. Each of the structural properties differentiating tRNA<sup>Sec</sup> from cognate serine acceptors could be responsible for the reduced acceptor activity.

The conversion of seryl-tRNA<sup>Sec</sup> into selenocysteyl-tRNA<sup>Sec</sup> is catalysed by selenocysteine synthase (SS), which is the selA gene product. Selenocysteine synthase is a decameric protein made up of 50 kDa subunits which contain pyridoxal-5'phosphate as prosthetic group [31]. The amino group of serine forms an aldimine linkage with the carbonyl of pyridoxal phosphate and a water molecule is eliminated yielding dehydroalanyltRNA<sup>sec</sup> (equation b). Chemical proof for this intermediate was brought about via reduction by potassium borohydride, which yields alanyl-tRNA<sup>Sec</sup> [32]. Nucleophilic addition of selenide then gives rise to selenocysteyltRNA<sup>sec</sup> (equation c). The source of selenide is monoselenophosphate [33]. Since elevated levels of selenide can substitute for monoselenophosphate in the reaction, it has been speculated why free selenide is not used as the natural substrate. A possibility considered is that the phosphate serves as a specificity "handle" to discriminate selenide from the highly similar sulfide. Indeed, substituting selenophosphate by thiophosphate gave rise to cysteyltRNA<sup>Sec</sup> [34]. Moreover, selenium in the selenophosphate molecule is in an activated state, which also may contribute to the kinetics of selenide transfer to dehydroalanyl-tRNA<sup>Sec</sup> [35].

Biochemical and high-resolution electron microscopic analysis demonstrated that two subunits of the decameric enzyme bind one seryl-tRNA<sup>Sec</sup> molecule [31,36]. The fully loaded enzyme thus contains five molecules of charged tRNAs bound to it. Binding seems uncooperative, only depending on the stoichiometry between the protein and the substrate [36]. It appears that once the tRNA is charged with serine it is immediately bound to selenocysteine synthase and stays in the activated state until selenophosphate is available as the substrate molecule. The cellular numbers of tRNA<sup>Sec</sup> molecules (about 250) [37] and selenocysteine synthase decamers (about 150, which can bind five tRNA<sup>Sec</sup> molecules simultaneously) [31,32,36]

favor the assumption of the enzyme functioning as a sink for capturing the charged tRNA, which may be a good way to optimize the efficiency of utilization of the trace element.

All bacterial species capable of selenoprotein synthesis and whose genomes have been sequenced possess orthologs of *selA* and *selD* genes whose products share high sequence similarities with selenocysteine synthase and selenophosphate synthetase from *E. coli*, respectively. This suggests that the mechanism for the biosynthesis of selenocysteyl-tRNA<sup>Sec</sup> from seryl-tRNA<sup>Sec</sup> is identical in all prokaryotes [34]. On the other hand, genomes from archaea with the ability to form selenoproteins do not contain an obvious candidate of the bacterial *selA* gene. Although the derived amino acid sequence of the *selD* gene from archaea is very similar to its bacterial counterpart, the actual mechanism for the biosynthesis of selenocysteine in archaea remains to be determined [38].

#### **Translation factor SelB**

To participate in the decoding process, the 20 classical aminoacyl-tRNAs each have to enter a ternary complex with elongation factor Tu and GTP. When the affinity of EF-Tu to selenocysteyl-tRNA<sup>Sec</sup> was determined, it was found that it is about 200-fold lower than that of the standard aminoacyl-tRNAs [39]. Under competitive conditions, therefore, it cannot serve as a substrate for EF-Tu. This role is taken over by the specialized translation factor SelB [40]. SelB from *E. coli* (encoded by the *selB* gene, previously *fdhA*) is 69 kDa in size, and in its N-terminal part, it displays significant sequence similarity to EF-Tu (Figure 3).

Utilising the sequence signatures of the bacterial SelB protein as a lead, a homolog has been identified amongst the gene products of the archaeon *Methanococcus (M.) jannaschii* [41]. The product of this open reading frame (aSelB) was purified, shown to be a GTPase with guanosine nucleotide binding properties like bSelB, and demonstrated to bind selenocysteyl-tRNA<sup>Sec</sup> from the same organism, preferentially but not exclusively to seryl-tRNA<sup>Sec</sup>. aSelB contains a C-terminal extension of only 11 kDa compared to about 27 kDa of the bacterial SelB. Knowledge of the sequence of the archaeal SelB protein immediately prompted the identification of the eukaryal counterpart [42,43].

Recently, several independent crystallographic studies of bacterial and archaeal SelB proteins have provided first insights into the structral basis of selenocysteyl-tRNA<sup>Sec</sup> recognition and into the mode of SelB interaction with the SECIS element and the ribosome. The crystal structure of SelB from the archaeon *M. maripaludis* reveals a molecule with overall dimensions of 110 Å x 66 Å x 39 Å that consists of four distinct structural domains (domain



Figure 3. Domain structures of the bacterial SelB protein and its archaeal (aSelB) homolog, in comparison to the three structural domains of elongation factor Tu (EF-Tu). The G motifs involved in binding of the guanosine nucleotides are indicated by G1 to G4. Sequence segments absent in the SelB structures relative to that of EF-Tu are indicated by gaps. Note that domains IV of bSelB and aSelB are structurally unrelated (see figure 6).

I – IV), which adopt a "molecular chalice" arrangement [44] (Figure 4A). The first three domains form the cup of the chalice, whereas its base is formed by domain IV, which is linked to the cup via two long, anti-parallel  $\beta$  strands. The extended linker between the core of the factor formed by domains I-III and domain IV is flexible and allows domain IV to reach more than 50 Å from its attachment point (Figure 4B). Interestingly, the overall domain arrangement of archaeal SelB and the topology of its domain IV resemble the structure of IF2/eIF5B [45]. Furthermore, SelB has high sequence and structural homology to the  $\alpha$  subunit of the archaeal IF2, which is the other factor that specifically recognizes a non-canonical tRNA (initiator tRNA<sub>i</sub><sup>Met</sup>) [44,46,47]. Nevertheless, it is not clear if functional parallels between the initiation of protein synthesis and selenocysteine incorporation may exist.

Archaeal SelB adopts an EF-Tu:GTP-like overall domain arrangement in its apo-, GDP- and GppNHp-bound forms. Upon binding of a GTP analogue, small conformational changes are observed in the Switch 2 region in the GTPase domain that, based on the comparison with the EF-Tu:tRNA ternary complex, leads to the exposure of SelB residues involved in clamping the 5' phosphate of the tRNA. This mechanism may explain how under physiological conditions SelB binds selenocysteyl-tRNA<sup>Sec</sup> only in its GTP state although there are no major conformational changes at the domain level between this and the GDP-bound states.

The amino acid binding pocket of SelB is highly selective, in contrast to EF-Tu, and SelB has been observed to tightly bind selenocysteyl-tRNA<sup>Sec</sup> while discriminating against its precursor, seryl-tRNA<sup>Sec</sup> [39,40]. The combined structural and biochemical work confirmed the importance of

factors. The rate constant of the release of GDP from its complex with SelB was several orders of magnitude larger than that displayed by elongation factor EF-Tu, which explains why no guanosine nucleotide release factor is required for the function of SelB.

On the other hand, the rate constant for the release of GTP is two orders of magnitude lower and in the same range as that measured for elongation factor EF-Tu. When the interaction of SelB with the 17 nucleotide minihelix of the *fdhF* SECIS element which carried a fluorescent group was assessed, an affinity of 1 nM was observed which was even increased when selenocysteyl-tRNA<sup>Sec</sup> was present. Binding of the charged tRNA, therefore, maximizes the affinity of SelB for the RNA ligand; dissociation of the tRNA decreases the affinity, on the other hand, which leads to dissociation of SelB from the mRNA, a necessary requirement for the translation of codons downstream of UGA.

In conclusion, the following scenario can be visualized for decoding UGA as selenocysteine on the basis of the information presently available

- (i) A quaternary complex between SelB, selenocysteyl-tRNA<sup>Sec</sup>, the SECIS element of the mRNA and GTP is formed. Its formation is non-random; binding of the charged tRNA stabilizes the complex of SelB with the SECIS element.
- (ii) During translation, the complex is translocated towards the ribosome, the lower helical part of the SECIS element is melted, and when the UGA arrives at the A site, SelB makes contact with the ribosome, which induces GTP hydrolysis.
- (iii) The charged tRNA is released in the proximity of the A site; its release decreases the affinity of SelB for the mRNA and facilitates the dissociation of the SelB–SECIS complex.
- (iv) After translation of the SECIS sequence, the RNA can refold and serve as a target for the formation of a new quaternary complex to assist the next oncoming ribosome in decoding UGA.

The model can accommodate the results of the structure/function relation of the mutant SECIS variants, like the stringent requirement of a precise distance between the UGA and the loop region. Many issues, however, remain speculative. Examples are whether GTP hydrolysis precedes or succeeds the release of charged tRNA, how domain IV communicates with the EF-Tu like part of the SelB molecule and what effect domain IV exerts on the translation process when it contacts the ribosome at the mRNA entrance cleft.

# Involvement of the *E. coli* SECIS element in the control of gene expression

In *E. coli*, the genes for the components of the selenocysteine insertion machinery are organised in three transcriptional units on the chromosome, namely *selAB*, *selC* and *selD*. Transcription of these units is constitutive, thus independent of the physiological condition [79]. At the translational level, however, the expression of the *selAB* unit is subject to regulation. The crucial element involved is a SECIS-like structure located in the immediate 5'-end of the non-translated region, not overlapping with the ribosomal binding site [80]. The SECIS-like structure is the target for SelB binding, whereby the affinity is about 6-fold lower compared to binding by the inframe *fdhF* SECIS element. It also forms a quaternary complex with GTP, selenocysteyl-tRNA<sup>Sec</sup> and SelB, which results in repression of the *selAB* mRNA translation [80]. Since quaternary complex formation requires the presence of tRNA<sup>Sec</sup> charged with selenocysteine, translational repression affords the availability of an adequate supply of selenium in the medium.



**Figure 8.** Organisation of the *selAB* operon (A) and structure of the SECIS-like element (B). RBS: Ribosmal binding site; the ignition codon of the *selA* gene is indicated by an asterisk.

What is the rational for the necessity to control *selAB* mRNA translation? A possible reason may exist in the requirement for a balanced ratio of the components of selenocysteine insertion machinery. Under wild-type and balanced growth conditions the supply of tRNA<sup>sec</sup> is limiting as judged by

the effect of its overexpression, which results in an about 2-fold stimulation of UGA readthrough [81]. On the other hand, overproduction of SelB is detrimental to UGA readthrough because the statistics for formation of the complex with both the SECIS and selenocysteyl-tRNA<sup>Sec</sup> ligands is disturbed [81]. Translational repression of *selAB* expression thus adjusts the level of SelB to the amount required. Thus, under low mRNA levels, selenocysteine synthase and SelB formation are reduced but the readthrough of the UGA is still sufficient due to the higher affinity of its SECIS structure for SelB compared to that of the SECIS-like element. At high selenoprotein mRNA levels, such as under fermentative conditions, translational repression is relieved thus supplying the required increased amount of SelB.

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