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Selenoprotein synthesis: UGA does not end the story

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Abstract

It is well established that the beneficial effects of the trace element selenium are mediated by its major biological product, the amino acid selenocysteine, present in the active site of selenoproteins. These fulfill different functions, as varied as oxidation-reduction of metabolites in bacteria, reduction of reactive oxygen species, control of the redox status of the cell or thyroid hormone maturation. This review will focus on the singularities of the selenocysteine biosynthesis pathway and its unique incorporation mechanism into eukaryal selenoproteins. Selenocysteine biosynthesis from serine is achieved on $tRNA^{Sec}$ and requires four proteins. As this amino acid is encoded by an in-frame UGA codon, otherwise signaling termination of translation, ribosomes must be told not to stop at this position in the mRNA. Several molecular partners acting in c*is* or in *trans* have been identified, but their knowledge has not enabled yet to firmly establish the molecular events underlying this mechanism. Data suggest that other, so far uncharacterized factors might exist. In this survey, we attempted to compile all the data available in the literature and to describe the latest developments in the field.
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1. Introduction

The element selenium was discovered by the Swedish chemist Berzelius in 1817 and named after Sêlenê, the goddess of moon. This non-metal was long considered as a potent toxic substance, especially to grazing animals that would eat selenium accumulator plants of the genus *Astragalus* during periods of drought in arid or desert regions of western USA and China. Between 1930 and the mid-1950s, selenium attracted the attention of animal nutritionists who eventually defined it as an essential micronutrient endowed with a number of significant health benefits [reviewed in 1,2]. In the 1970s, the biological activity of selenium could be attributed to selenocysteine, a then novel amino acid found in selenoproteins. The majority of selenoproteins whose function is known are oxidation-reduction enzymes using selenocysteine in the active site. The chemical structure of selenocysteine differs from cysteine only by the selenium instead of the sulfur atom; however, the electronic structure of the selenium atom renders the selenolate anion, the conjugated base of selenocysteine, more stable than the corresponding cysteine thiolate. The selenol proton is thus more acidic than in the cysteine thiol (pKa of 5.2 versus 8.5 for the thiol), hence ionization of selenocysteine at physiological pH.

A further breakthrough appeared in the mid-1980s with the discovery that selenocysteine is encoded by UGA, a codon otherwise specifying termination of protein synthesis. Immediately, this finding aroused the interest of the scientific community who aimed at challenging this novel alternate reading of the genetic code. It is largely the pioneering work in *E. coli*, by the group of August Böck, that helped solve how selenocysteine is biosynthesized and specifically incorporated into selenoproteins in response to UGA [reviewed in 3]. Selenoproteins have been found in the three kingdoms of life, but not in all species of bacteria, archaea and eukarya. For example, neither fungi nor higher plants can incorporate selenocysteine at specific locations. How ribosomes are told not to stop at UGA Sec codons results from the combined action of several partners, acting in *cis* or in *trans*. The underlying mechanisms in archaea and eukarya present similarities but also dissimilarities to bacteria that will be discussed in this review. Focus will be put

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primarily on eukarya with comparisons to the bacterial and archaeal systems wherever needed. Two aspects will be addressed, biosynthesis of selenocysteine in the first place, followed by its co-translational incorporation into selenoproteins.

2. Biosynthesis of selenocysteine

Selenocysteine does not occur as a free amino acid. Thus, the first step of its biosynthesis consists in the charge of serine on the specific $tRNA^{Sec}$ by the conventional seryl-tRNA synthetase. The Ser-$tRNA^{Sec}$ is next converted into Sec-$tRNA^{Sec}$ by selenocysteine synthase that utilizes monoselenophosphate as the substrate. This compound is produced from sodium selenite or more likely selenide by a reaction catalyzed by selenophosphate synthetase. We will describe in this paragraph the characteristic features of $tRNA^{Sec}$ and the selenocysteine biosynthesis pathway.

2.1. Structure-function of the $tRNA^{Sec}$

Secondary structure models for $tRNAs^{Sec}$ are shown in Fig. 1, arising from experimental determination in bacteria and eukarya [4–6], or structure-based sequence alignments in archaea [6]. Two main characteristic features distinguish $tRNAs^{Sec}$ from canonical tRNAs. First, they share the hallmark of having a 6 bp D-stem, instead of 3–4 bp in other tRNAs. This extended D-stem was shown to be a major identity determinant for serine phosphorylation [7], a likely intermediate in selenocysteine biosynthesis in eukarya (see below). Second, the amino acid acceptor arm (A-T), resulting from coaxial stacking of the A and T-stems, is longer in $tRNAs^{Sec}$ (13 bp) than in canonical tRNAs where it is 12 bp long (7 + 5 bp). In bacteria, the 13 bp A-T arm is formed by coaxial stacking of the 8 bp A-stem and 5 bp T-stem whereas the same length is obtained in archaea and eukarya by stacking of the longer A-stem (9 bp) and shorter T-stem (4 bp) [5,6,8–14]. This evolutionary conservation is obviously a signal for one or more ligand(s). In bacteria, the extra length of the A-T arm is a determinant for binding to the specialized translation elongation factor SelB whereas it is required for serine to selenocysteine conversion in eukarya [15,16].

The position and nature of post-transcriptional modifications have been investigated in the vertebrate $tRNA^{Sec}$ [17, 18]. It contains only four modified bases, thus fewer than canonical tRNAs. Apart from pseudo-U55 and m^1A58 in the T-loop, mass spectrometry identified 6-isopentenyl-A37 (i^6A37) and mcm^5Um34, the 5-methylcarboxymethyl-2′-O-methyluridine modification, in the anticodon loop. The 2′ O-ribose modification, associated to mcm^5U, has been found so far in $tRNA^{Sec}$ only and its yield is a function of the dietary selenium status [17]. Formation of mcm^5U34 depends on the $tRNA^{Sec}$ tertiary structure and completion of all the other base modifications [19]. Interestingly, protein SECp43 identified earlier in a complex with the $tRNA^{Sec}$ [20], might be involved directly or indirectly in the 2′-O-methylation of mcm^5U34 [21]. Modification of i^6A37 has also a great importance as its absence produced a severe down effect on selenoprotein synthesis [22]. However, as conversion of A37 to i^6A37 occurs before U34 is modified to mcm^5Um and is indeed required for obtaining the latter, it was difficult to assign the observed effect to the lack of one or the other modification. To address the issue, knock-out transgenic mice were obtained wherein the $tRNA^{Sec}$ was replaced by the wt or a mutant transgene producing a tRNA that lacked both the U34 and A37 modified bases [23]. This study concluded that U34 modification has a greater influence than i^6A37 in regulating the expression of various mammalian selenoproteins.

2.2. The Ser-$tRNA^{Sec}$ to Sec-$tRNA^{Sec}$ conversion step

Neither in eukarya nor in archaea has been isolated monoselenophosphate, the biological donor of selenium in bacteria. Two enzymes catalyzing formation of this compound have however been described. A human cDNA of selenophosphate

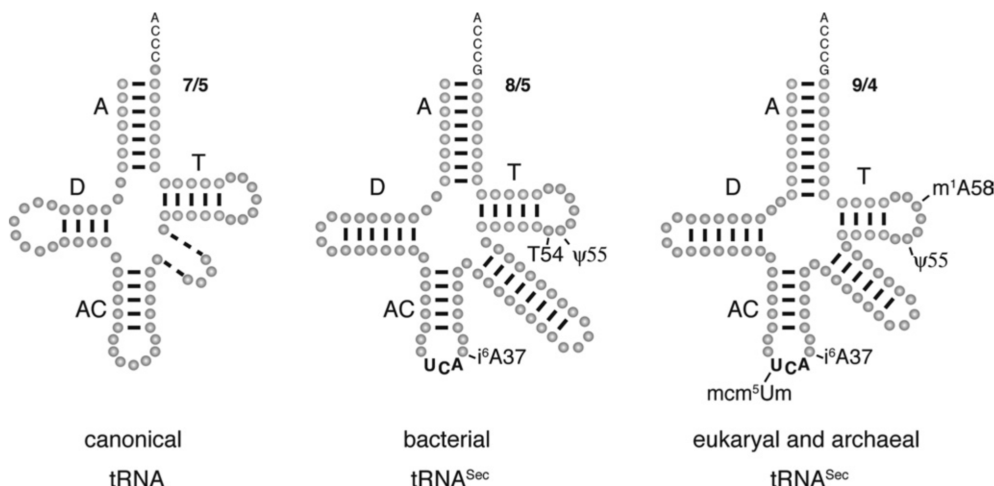

Fig. 1. Secondary structure comparisons of canonical tRNAs versus selenocysteine $tRNAs^{Sec}$. The various secondary structure elements are indicated: A, D, AC, and T stand for the amino acid, D, anticodon and T stems, respectively. 7/5, 8/5, 9/4 indicate the number of base pairs forming the coaxial A-T arm in the tRNAs shown. Dashes in the canonical tRNA structure signify that the extra arm is of variable length in different tRNAs. Modified bases are indicated where identified in the bacterial and eukaryal $tRNAs^{Sec}$. They were omitted in the canonical tRNA. The archaeal $tRNA^{Sec}$ was not investigated for its base modification content.

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