BBA - General Subjects xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

BBA - General Subjects

journal homepage: www.elsevier.com/locate/bbagen

Translation regulation of mammalian selenoproteins☆

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ARTICLE INFO

Keywords:
Selenocysteine
Selenoprotein
UGA recoding
Translational control
SECIS
Sec-tRNA$^{[Ser]Sec}$

ABSTRACT

Background: Interest in selenium research has considerably grown over the last decades owing to the association of selenium deficiencies with an increased risk of several human diseases, including cancers, cardiovascular disorders and infectious diseases. The discovery of a genetically encoded 21st amino acid, selenocysteine, is a fascinating breakthrough in molecular biology as it is the first addition to the genetic code deciphered in the 1960s. Selenocysteine is a structural and functional analog of cysteine, where selenium replaces sulfur, and its presence is critical for the catalytic activity of selenoproteins.

Scope of review: The insertion of selenocysteine is a non-canonical translational event, based on the recoding of a UGA codon in selenoprotein mRNAs, normally used as a stop codon in other cellular mRNAs. Two RNA molecules and associated partners are crucial components of the selenocysteine insertion machinery, the Sec-tRNA$^{[Ser]Sec}$ devoted to UGA codon recognition and the SECIS elements located in the 3′UTR of selenoprotein mRNAs.

Major conclusions: The translational UGA recoding event is a limiting stage of selenoprotein expression and its efficiency is regulated by several factors.

General significance: The control of selenoproteome expression is crucial for redox homeostasis and antioxidant defense of mammalian organisms. In this review, we summarize current knowledge on the co-translational insertion of selenocysteine into selenoproteins, and its layers of regulation.

1. Introduction

The genetic code, deciphered in the 1960s, establishes how the genetic information (DNA and mRNA sequences) is translated into a protein sequence by living cells, using a three letter code of 4 different nucleotides. The original rule of this genetic code states that among the 64 triplets or codons, 61 specify the insertion of an amino acid (sense codons) and 3 notify the end of protein synthesis and the release of neosynthesized polypeptide (stop codons). In eukaryotes, these stop codons – UAA, UAG and UGA – are recognized by one translation termination factor, eRF1, also called polypeptide chain release factor 1, while all sense codons are recognized by one, or more, specific tRNAs [1,2]. Yet, this universal genetic code is now referred to as canonical or standard genetic code, due to the discovery of variant codes and exceptions (Fig. 1A). The discovery of selenocysteine is one of the most fascinating exceptions. Indeed, in selenoprotein mRNAs, the co-translational insertion of selenocysteine occurs when the ribosome encounters an UGA codon, which is normally used as a stop codon in other cellular mRNAs [3–10]. Selenocysteine insertion in a group of proteins named selenoproteins occurs in archaebacteria, eubacteria, and eukaryotes, and is therefore called the 21st amino acid. This was the first addition to the genetic code.

In the human genome, twenty-five selenoprotein genes are found in which the UGA codons specify the insertion of selenocysteine [11–13]. In most genes, only one selenocysteine insertion event occurs, except for SelenoP gene in which ten in-frame UGA codons are recoded into selenocysteine (Fig. 1B–C). Remarkably, the mechanism of UGA/Sec recoding relies on two pivotal RNA molecules and their interacting factors [3–10,14–16]. The first one is the selenocysteine insertion sequence (SECIS), present in the 3′-UTR of all selenoprotein mRNAs. This

☆ This article is part of a Special Issue entitled Selenium research in biochemistry and biophysics - 200 year anniversary issue, edited by Dr. Elias Arnér and Dr. Regina Brigelius-Flohe

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https://doi.org/10.1016/j.bbagen.2018.05.010
Received 26 February 2018; Received in revised form 28 April 2018; Accepted 4 May 2018

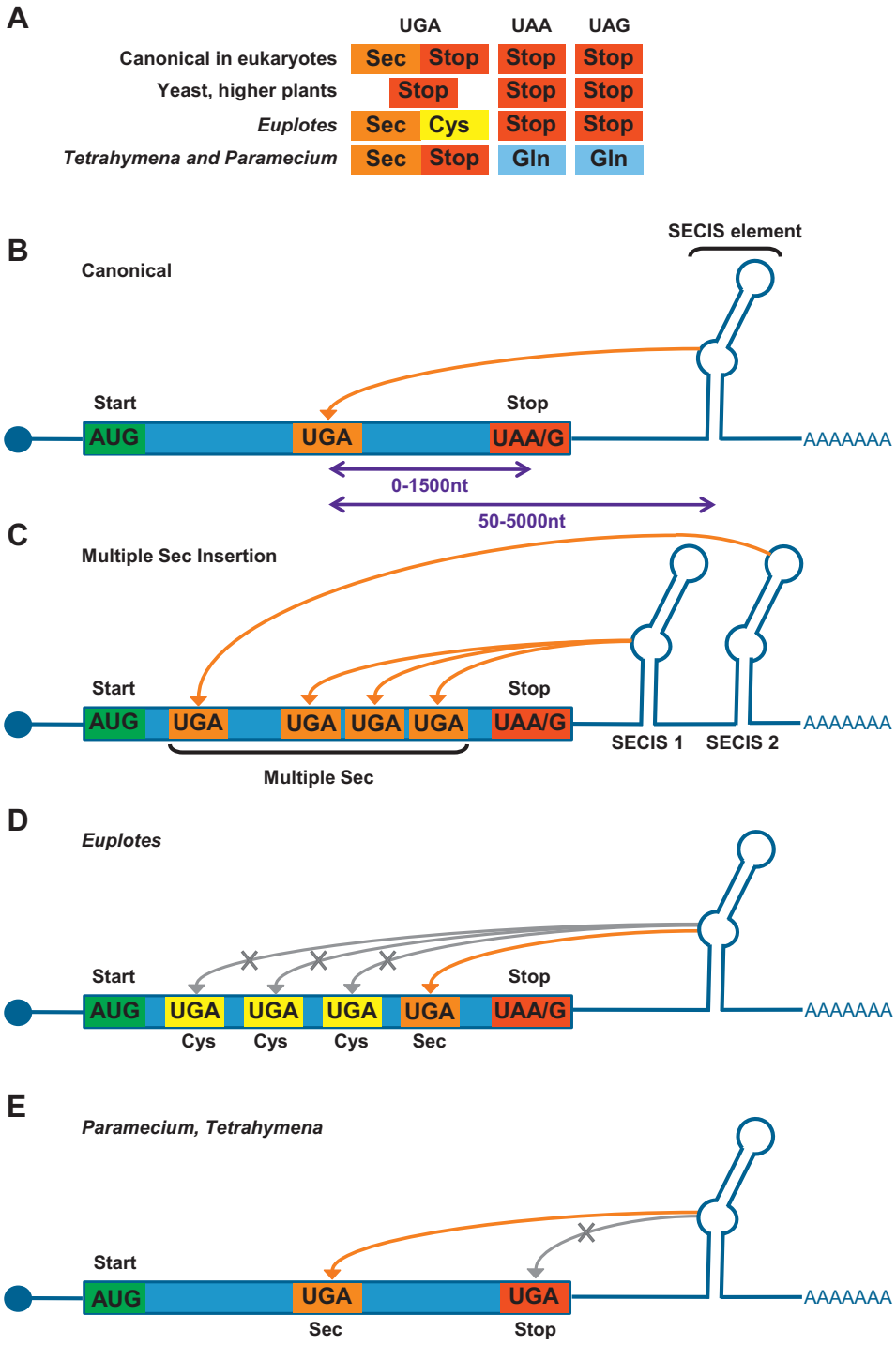

Fig. 1. Representation of selenoprotein mRNAs in eukaryotes.
A. Representation of the stop codon use, recoding as selenocysteine or reassignment in eukaryotes. Orange, selenocysteine; red, stop; yellow, cysteine; blue, glutamine, green, AUG start codon. B. The consensus structure of selenoprotein mRNAs contains one in frame UGA codon and one SECIS. C. In a few examples, multiple in-frame UGA codon are present in the open reading frame and recoded as Sec. In these mRNAs two SECIS elements are located in the 3′UTR, with different role: SECIS2 controls the translational rate of the first UGA codon decoding while SECIS 1 is in charge of the multiple consecutive UGA recoding. Variations of the canonical mechanism in ciliate organisms: *Euplotes* (**D**) or *Paramecium* and *Tetrahymena* (**E**) with reassigned stop codon and selenoproteins.

stem-loop-stem-loop RNA structure recruits the selenocysteine insertion machinery onto the 3′UTR of mRNAs [17–22]. The SECIS element is necessary and sufficient for UGA recoding and can be functional when inserted in heterologous reporter genes [23]. The second essential RNA player is the Sec-tRNA$^{[Ser]Sec}$, which displays several features that make it unique compared to other cellular tRNAs [3,24–26]. This tRNA gene is present in one copy per genome and is essential for the expression of all 25 selenoproteins. Initially viewed as a simple mechanism, the insertion of selenocysteine turns out to be an important regulatory point of control for the expression of selenoproteins. The fine-tuning of its efficiency is crucial for the proper use of selenium by the cell in response to various stimuli [8,27–38].

In addition to the components of the UGA-selenocysteine recoding machinery, multiple layers of control have been discovered in the past decades [3–9,39,40]. This review aims at describing this translational control of selenoprotein expression in eukaryotes with a particular emphasis on mammalian mechanism.

2. The selenocysteine-tRNA$^{[Ser]Sec}$

2.1. Sec-tRNA$^{[Ser]Sec}$ gene and animal models

The Sec-tRNA$^{[Ser]Sec}$ is dedicated to the translational insertion of selenocysteine as the ribosome encounters an UGA codon in