How selenium is incorporated into proteins: structural view of selenocysteine ‘recoding’

Selenium is an essential micronutrient for human health. It is present in proteins as a special amino acid, selenocysteine, which is the so-called 21st amino acid. Selenocysteine resembles serine and cysteine, where the selenium atom (Se) replaces the sulfur atom (S) of cysteine (Figure 1A). Most proteins are composed of only the 20 canonical amino acids, and very few proteins have selenocysteine in addition to them. Actually, only 25 out of ~22,000 human proteins contain selenocysteine. Although selenocysteine-containing proteins (selenoproteins) are rare, they are essential for brain and testis generation. Moreover, selenocysteine is utilized in many organisms in all three domains of life, Bacteria, Archaea, and Eukarya.

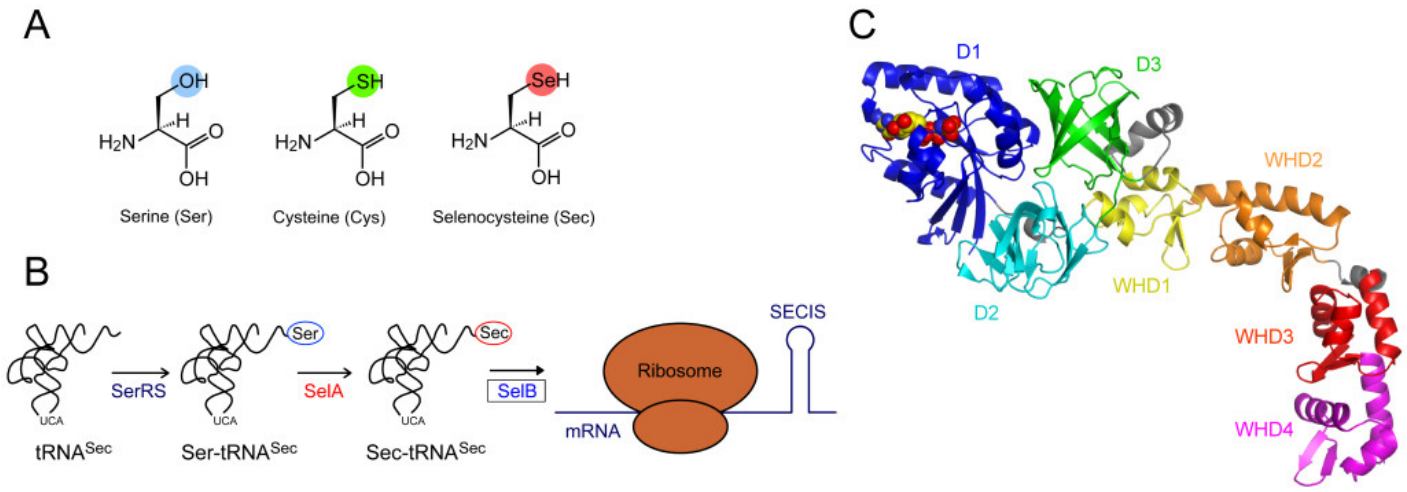

Fig. 1.

Proteins are chains of tandemly arranged amino acids, with lengths ranging from several tens to thousands. The amino-acid sequence information of each protein is encoded in the corresponding gene located in the genomic DNA. Genes are transcribed as messenger RNAs (mRNAs), which are translated into proteins by ribosomes. mRNA is also a long chain of tandemly arranged nucleotides, although it consists of only 4 types of nucleotides, A, U, G, and C. Therefore, a triplet of nucleotides, called the codon, is translated into one amino acid. There are 64 codons in total, and each of them encodes one corresponding amino acid, except for the UAA, UAG, and UGA codons, which encode stop signals. Selenocysteine is encoded by the UGA codon, one of the stop codons. The mRNA of a selenoprotein has a special sequence, the selenocysteine-insertion sequence (SECIS), downstream of the UGA codon, which is ‘recoded’ as selenocysteine in response to the SECIS.

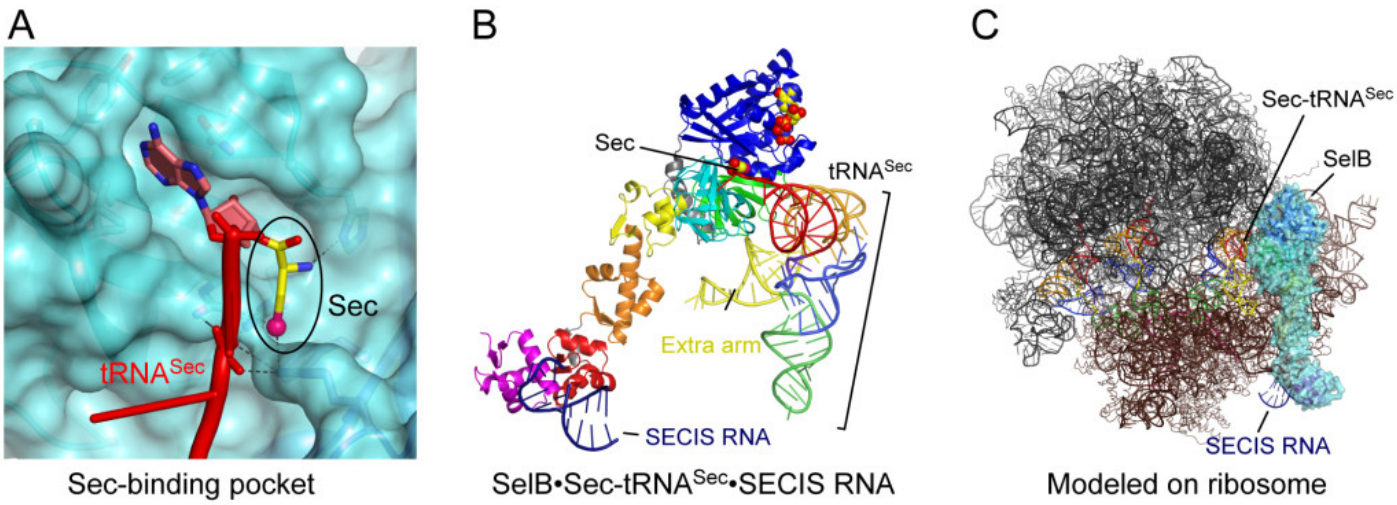

Fig. 2.

During translation, the canonical amino acids are transported to the ribosome with the assistance of two factors, transfer RNA (tRNA) and elongation factor Tu (EF-Tu). tRNA is an adapter molecule that binds covalently to amino acid, and EF-Tu carries the amino-acid ligated tRNA (aa-tRNA) to the ribosome. Each canonical amino acid has its corresponding tRNA species, whereas EF-Tu carries all canonical aa-tRNAs. Selenocysteine is synthesized from serine linked to its tRNA ($tRNA^{Sec}$), and the selenocysteine-specific elongation factor SelB, instead of EF-Tu, carries the selenocysteine-ligated $tRNA^{Sec}$ ($Sec\text{-}tRNA^{Sec}$) to the ribosome (Fig. 1B). Unlike EF-Tu, SelB also interacts with the mRNA to recognize the SECIS.

We determined the 3D structure of bacterial SelB at atomic resolution, by X-ray crystallography. SelB has three EF-Tu-like domains (D1–3) and four winged-helix domains (WHD1–4) (Fig. 1C). The EF-Tu-like domains bind to $Sec\text{-}tRNA^{Sec}$, while the winged-helix domains bind to the SECIS in the mRNA.

SelB was co-crystallized with free cysteine, which mimics selenocysteine. Cysteine was observed within the binding pocket for the selenocysteinyl (Sec) moiety of $Sec\text{-}tRNA^{Sec}$ in SelB (Fig. 2A). This Sec-binding pocket is smaller and more exposed than the corresponding site of EF-Tu. Based on the bound cysteine, $Sec\text{-}tRNA^{Sec}$ was modeled on SelB to visualize their interactions (Fig. 2B). The selenol group of Sec moiety forms ionic interactions with the arginine residues of SelB, while the long extra arm of $tRNA^{Sec}$ interacts with D3 of SelB (Fig. 2B). These interactions achieve the specificity for $Sec\text{-}tRNA^{Sec}$, since SelB only carries $Sec\text{-}tRNA^{Sec}$ and does not bind to the other aa-tRNAs.

We also modeled SelB and $Sec\text{-}tRNA^{Sec}$ bound to the ribosome, where $Sec\text{-}tRNA^{Sec}$ accommodates the aa-tRNA binding site (A site) of the ribosome and the SECIS is located in front

of the mRNA entrance channel (Fig. 2C). SelB bridges Sec-tRNA^{Sec} and SECIS by interacting with the ribosome, indicating the structural basis of the Sec incorporation mechanism.

Publication

Crystal structure of the full-length bacterial selenocysteine-specific elongation factor SelB.
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