

## Scientists clarify structural basis for biosynthesis of mysterious 21<sup>st</sup> amino acid

Researchers at the RIKEN Systems and Structural Biology Center and the University of Tokyo have clarified the structural basis for the biosynthesis of selenocysteine (Sec), an amino acid whose encoding mechanism offers clues about the origins of the genetic alphabet. The findings deepen our understanding of protein synthesis and lay the groundwork for advances in protein design.

One of the most remarkable aspects of translation, the process whereby genetic information is converted into proteins in cells, is its universality: nucleotide triplets (“codons”) encode a set of twenty amino acids that form the building blocks for all living organisms. Selenocysteine, the “21<sup>st</sup> amino acid” whose antioxidant properties help prevent cellular damage, is a rare exception to this rule. Structurally similar to the amino acid serine (Ser) but with an oxygen atom replaced by the micronutrient selenium (Se), selenocysteine is synthesized through a complex juggling of the cell’s translational machinery whose mechanisms remain poorly understood.

Central to this multi-step process is a Sec-specific transfer RNA (tRNA<sup>Sec</sup>) with an unusual structure that enables it to hijack the “stop codon” UGA to allow incorporation of selenocysteine during protein synthesis. In earlier work, the researchers identified features of tRNA<sup>Sec</sup> that differentiate it from other tRNA, notably the peculiar structure of a domain called the D-arm, which appeared to act as an identification marker for recognition by the selenocysteine synthesis machinery. This time, the team analyzed the D-arm’s role in the interaction of tRNA<sup>Sec</sup> with *O*-phosphoseryl-tRNA kinase (PSTK), a protein whose selective phosphorylation is essential for selenocysteine encoding.

Using X-ray crystallography, the team showed for the first time that it is the unique structure of the tRNA<sup>Sec</sup> D-arm which enables PSTK to distinguish tRNA<sup>Sec</sup> from other tRNA. Reported in the August 13<sup>th</sup> issue of *Molecular Cell* (online August 12<sup>th</sup>), the discovery clarifies a pivotal step in selenocysteine biosynthesis, shedding new light on the mysterious 21<sup>st</sup> amino acid and the elaborate process by which it is created.

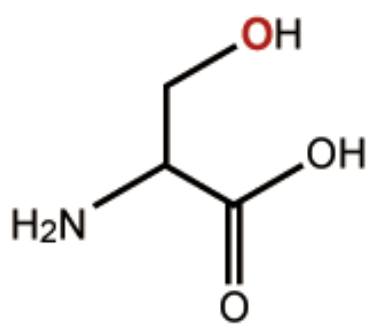
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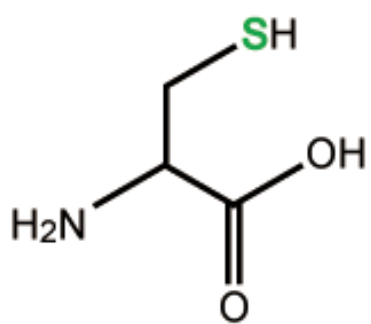
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**Reference:**

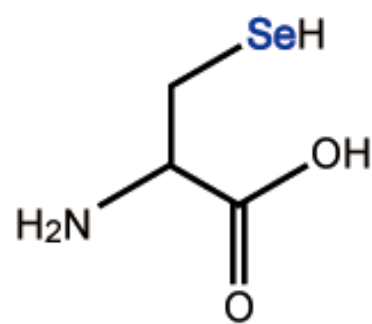
Shiho Chiba, Yuzuru Itoh, Shun-ichi Sekine and Shigeyuki Yokoyama. Structural Basis for the Major Role of O-Phosphoseryl-tRNA Kinase in the UGA-Specific Encoding of Selenocysteine. *Molecular Cell* 39: 1-11. August 13, 2010. DOI: [10.1016/j.molcel.2010.07.018](https://doi.org/10.1016/j.molcel.2010.07.018)



Serine (Ser)



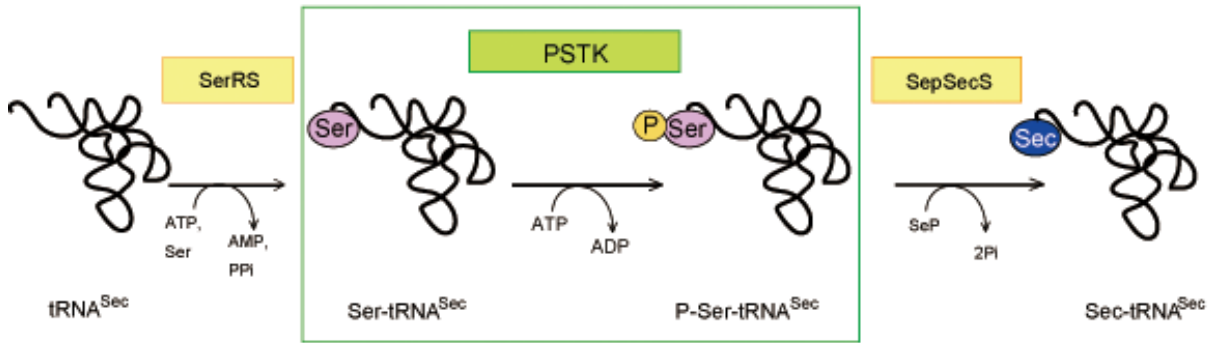
Cysteine (Cys)



Selenocysteine (Sec)

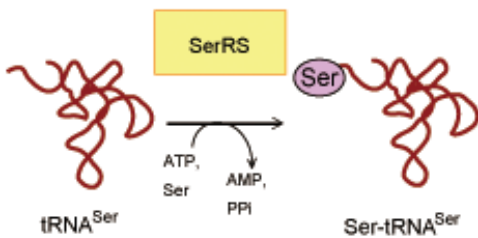
**Figure 1:** Comparison of selenocysteine (Sec) to the structurally similar amino acids serine (Ser) and cysteine (Cys).

## Selenocysteine biosynthesis



→ Sec is inserted into a specific site of a nascent polypeptide of selenoprotein by decoding the UGA codon.

## Standard amino acids (the case of serine)



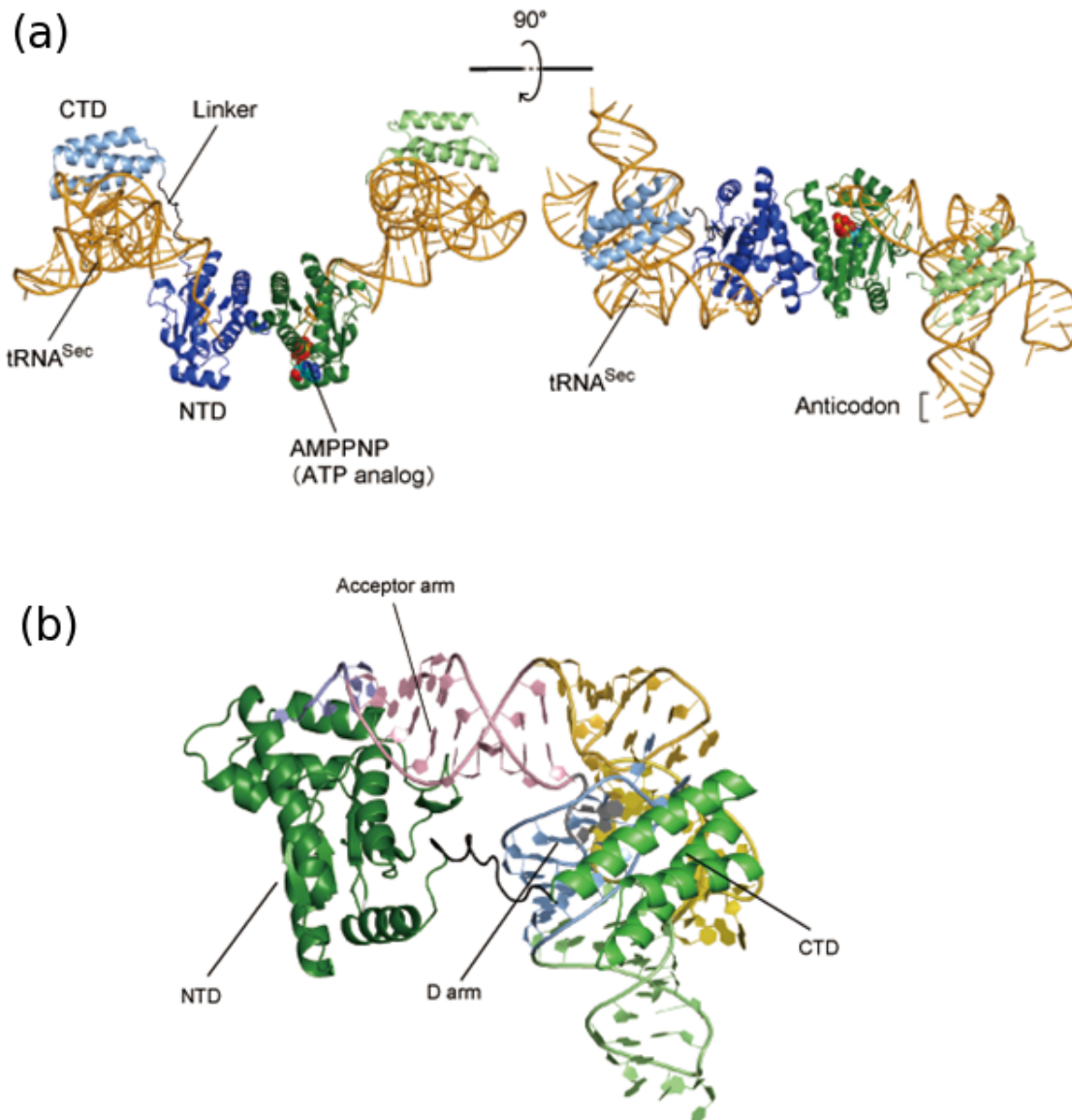
→ Ser is inserted into a nascent polypeptide by decoding the Ser codons.

PSTK does not work

**Figure 2:** Selenocysteine biosynthesis.

(Top)  $tRNA^{Sec}$  is first ligated with serine to form  $Ser-tRNA^{Sec}$ . The seryl moiety of  $Ser-tRNA^{Sec}$  is then phosphorylated by PSTK to yield  $P-Ser-tRNA^{Sec}$ , which is converted to  $Sec-tRNA^{Sec}$  and used on the ribosome to insert Sec into a specific site in a nascent polypeptide of selenoproteins.

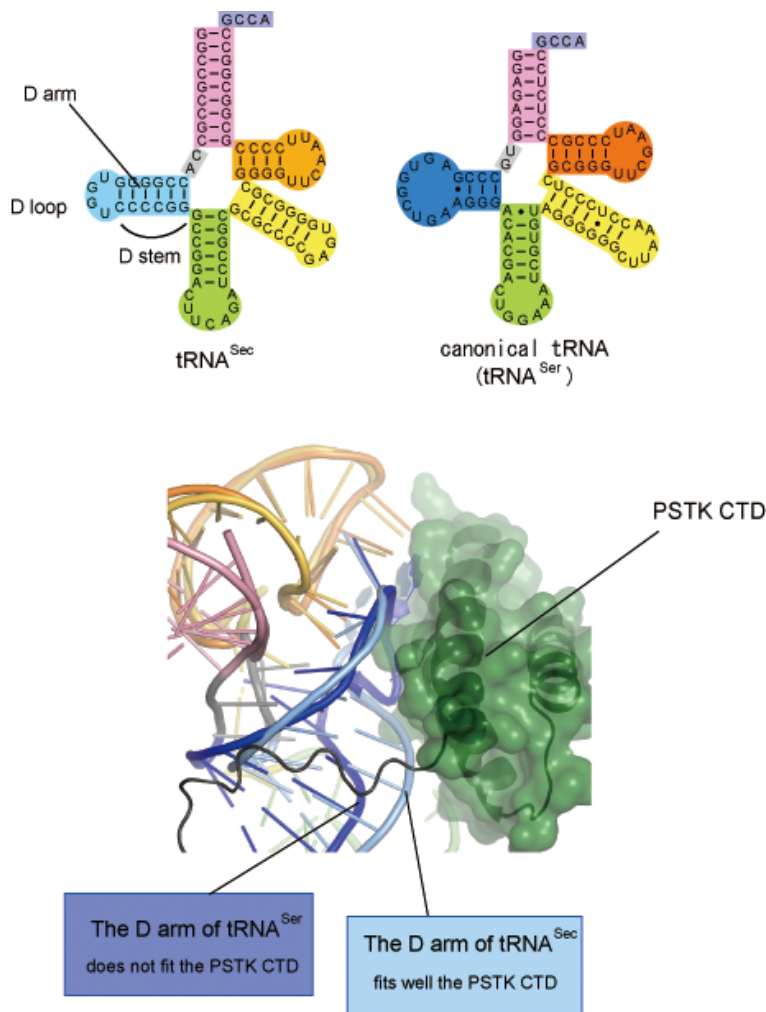
(Bottom) In the case of the standard amino acid serine,  $tRNA^{Ser}$  is ligated with serine and directly used for translation.  $Ser-tRNA^{Ser}$  is not a substrate of PSTK.



**Figure 3:** Structure of the tRNA<sup>Sec</sup> · PSTK complex.

(a) Two PSTK molecules (colored blue and green) interact with each other to form a homodimer. Each PSTK molecule binds a tRNA<sup>Sec</sup> molecule. PSTK consists of two independent, linker-connected domains, the N-terminal catalytic domain (NTD) and the C-terminal domain (CTD). These domains independently bind tRNA<sup>Sec</sup>.

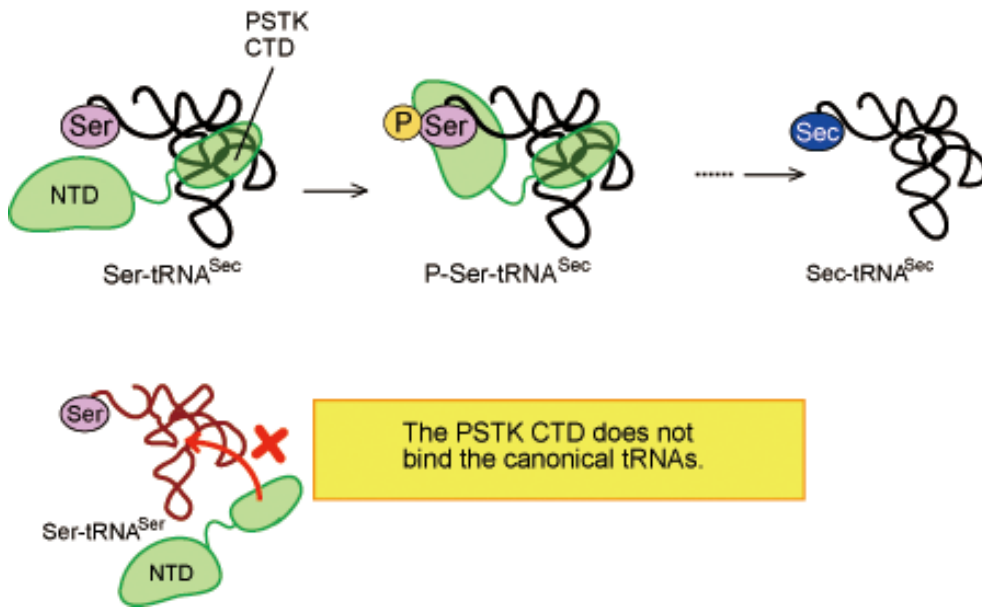
(b) A close-up view of one of the PSTK molecules bound to tRNA<sup>Sec</sup>. The N-terminal domain (NTD) and the C-terminal domain (CTD) of PSTK interact with the acceptor arm (colored pink) and the D arm (light blue), respectively. PSTK does not interact with the tRNA<sup>Sec</sup> anticodon complementary to the UGA codon.



**Figure 4:** Interaction between the unique D arm of tRNA<sup>Sec</sup> and the PSTK CTD.

(Top) Comparison of the secondary structure of tRNA<sup>Sec</sup> to that of a canonical tRNA. The tRNA<sup>Sec</sup> D arm consists of a six base-pair stem (D stem) and a four-nucleotide loop (D loop), in contrast with the 3–4 base-pair D stem and the 7–11 nucleotide D loop of the canonical tRNA.

(Bottom) The D arm of tRNA<sup>Sec</sup> (colored light blue) snugly interacts with the PSTK CTD (green), whereas the D arm of the standard tRNA (blue) does not fit the PSTK CTD.



**Figure 5:** tRNA<sup>Sec</sup> recognition by PSTK. The enzymatic activity of PSTK is governed by the specific interaction between its CTD and the unique D arm of tRNA<sup>Sec</sup>. The tight binding of the CTD to the D arm ensures that the N-terminal catalytic domain binds to the end of the acceptor arm, where the phosphorylation reaction occurs. In contrast, the CTD does not fit the D arm of canonical tRNAs, and thus PSTK does not act on them, segregating the Sec insertion pathway from the normal amino-acid translation process.