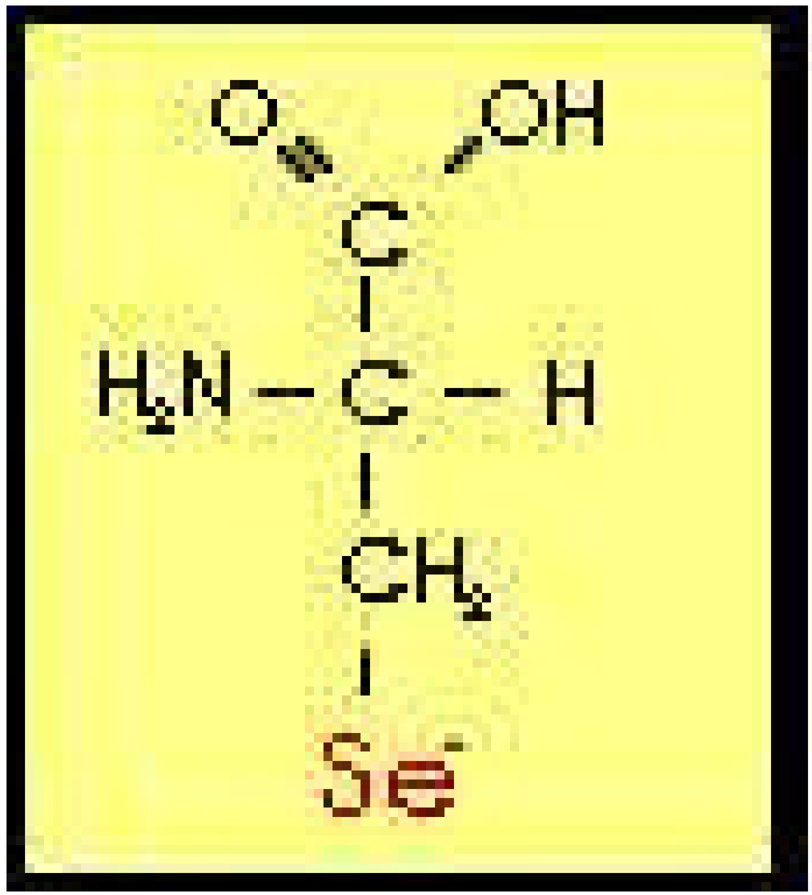
Selenocysteine:
The 21st Amino Acid

By:

M. Gill, S. Gupta, L. Zichittella

Selenocysteine (SeC) Structure:



Selenocysteine is found in every domain of life on Earth.

While there are many more amino acids than those twenty which are part of the standard genetic code, only selenocysteine has been discovered to be coded genetically.

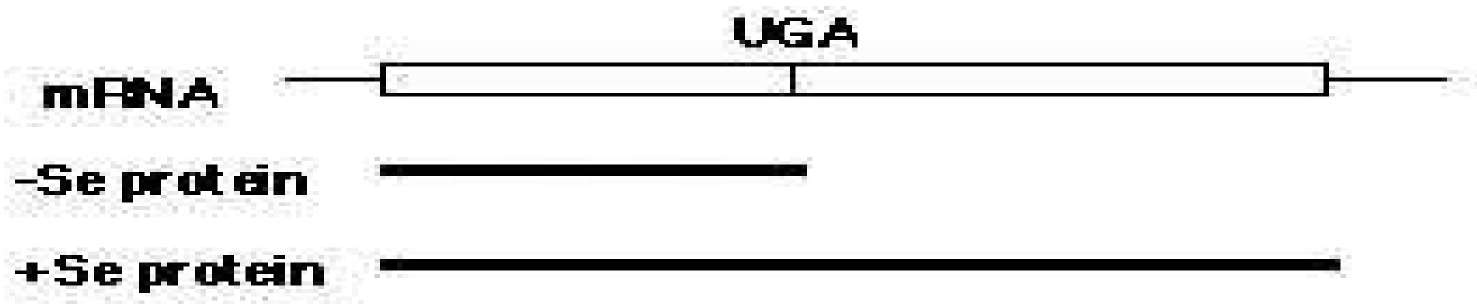
But there are only 64 possibilities for a triplet code, and each has been assigned an amino acid already so how can Selenocysteine be encoded?

Answer:

One of the codons must encode for two functions.

In fact Selenocysteine is encoded by the UGA codon, the umber codon, which is normally a termination codon.

There must however be something which tells the translational machinery of the cells that it should continue translation and to not terminate as normal at the UGA codon.



This process occurs by two different mechanisms in prokaryotes and eukaryotes.

In Prokaryotes:

One element must be found on the mRNA for the UGA codon to be read as a selenocysteine insertion element as opposed to a termination element. This element is a stem-loop structure found in the 3' untranslated region of the mRNA.

An operon consisting of four genes known as the *sel* operon is also necessary for the incorporation of selenocysteine into proteins.

Genes of the *sel* operon

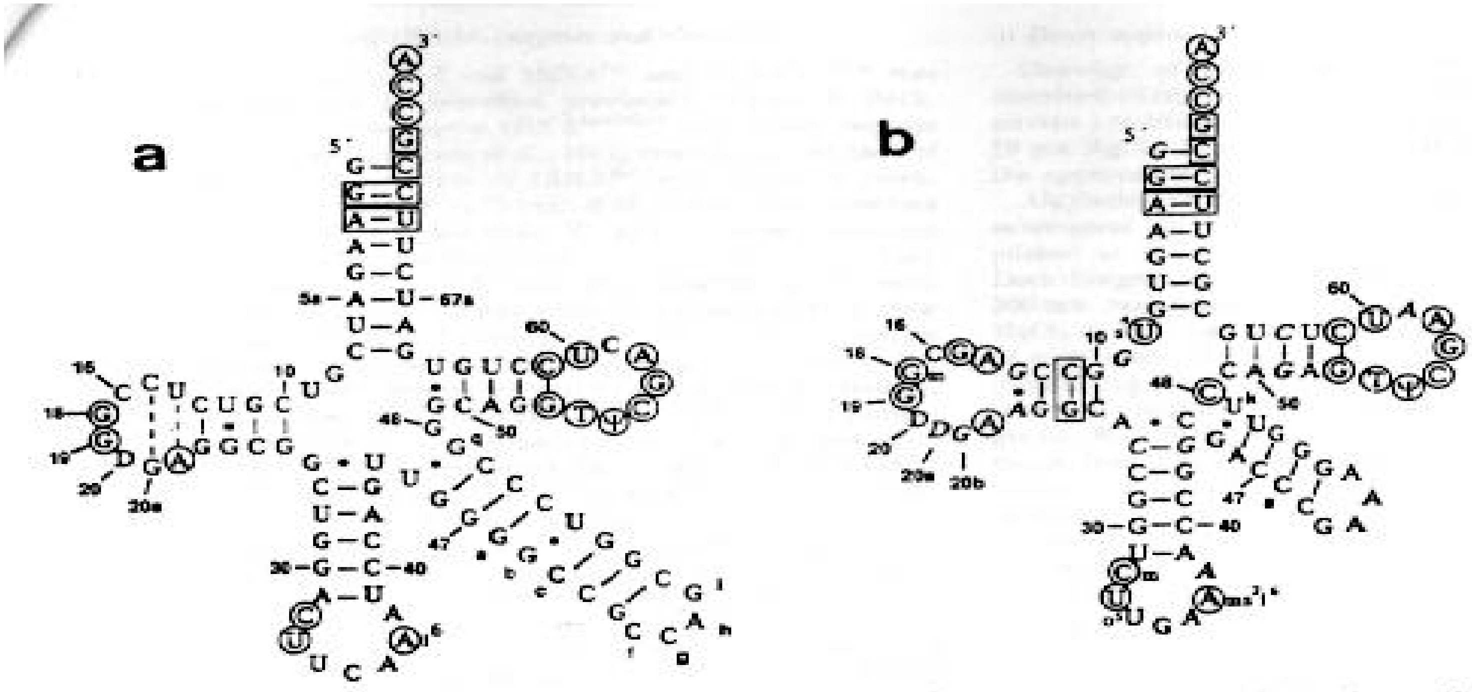
sel A- converts serine to dehydroalanine

sel B - codes for an EF-Tu like translation factor

sel C - codes for the specific selenocysteine tRNA

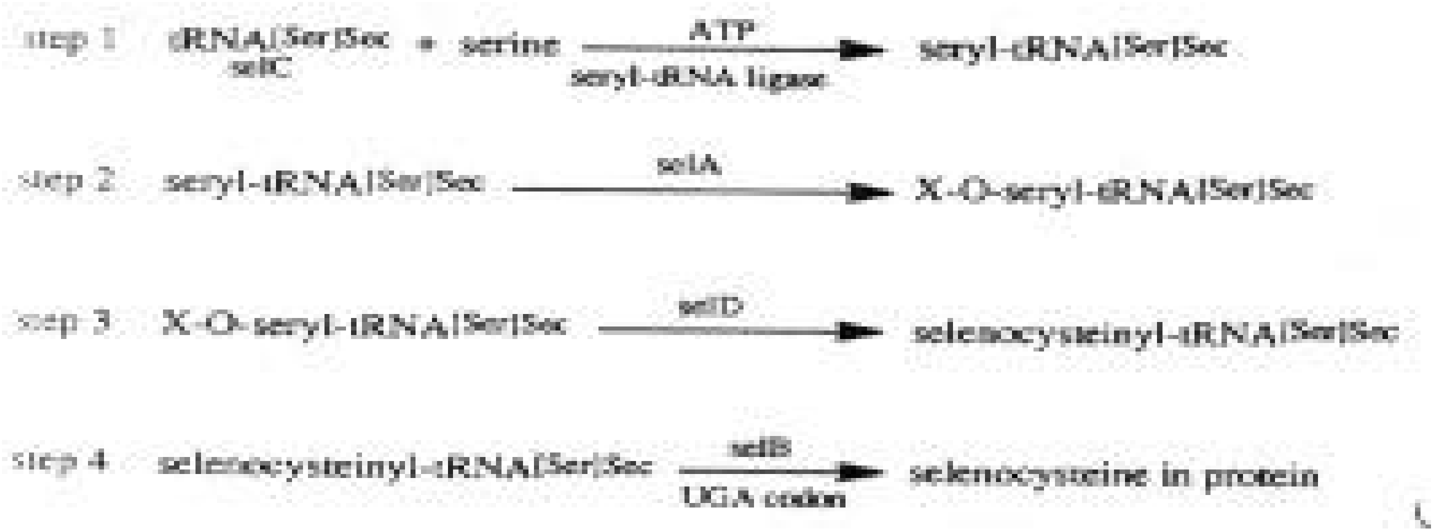
sel D - "activates" HSe^-

The first step in SeC insertion occurs with the product of *sel C*, this gene codes for the tRNA which carries SeC into the protein. SeC itself is highly toxic to cells in high doses so the cell must only use it when it is necessary for selenoproteins particulary.



In order to accomplish this the cell regulates the *sel* operon. However the tRNA itself is constitutively expressed under normal circumstances. This tRNA however cannot be charged without the presence of the other gene products. The tRNA itself is initially charged with Serine even though its anticodon can base pair with the UGA codon.

When the *sel* operon is expressed however the charged serinyl-tRNA^{Sec} is converted to selenocysteinyl-tRNA^{Sec} by the genes *sel A* and *sel D*. The gene *sel D* requires the presence of selenium which it converts to selenophosphate at the cost of one ATP molecule. Selenophosphate contains a high energy bond and is thus considered "activated." The product of *sel A* converts the charged serine residue to a more activated compound and these two compounds react and form selenocysteinyl-tRNA^{Sec}.



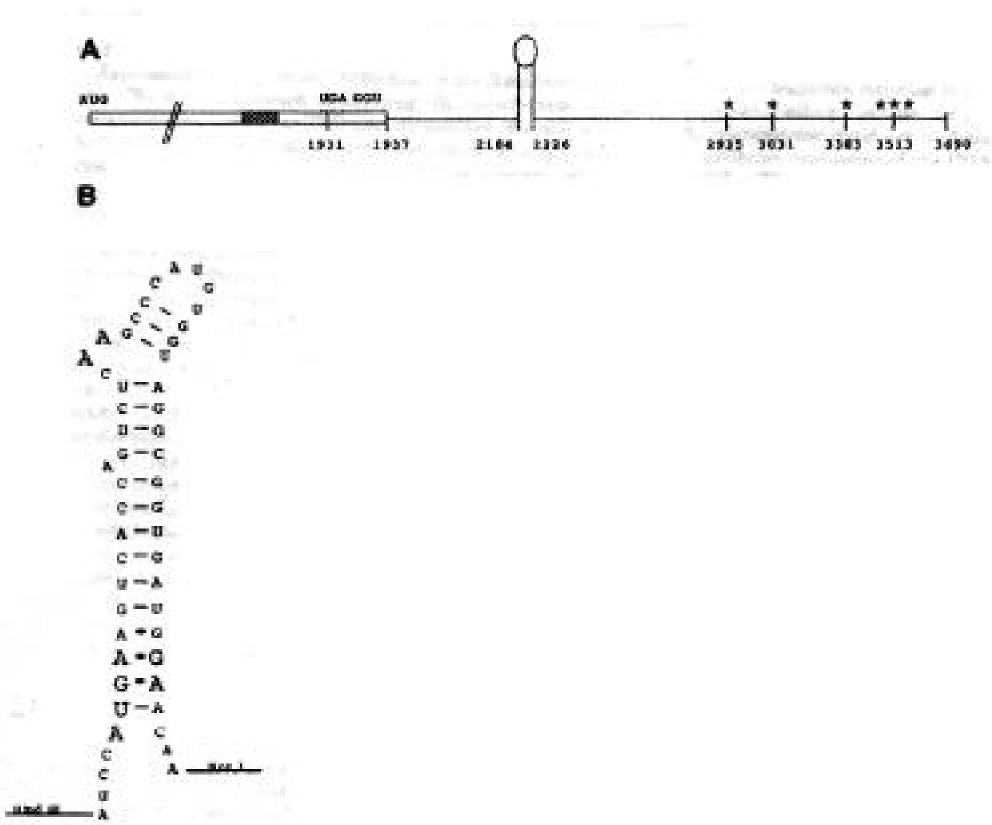
The Sel B protein functions to prevent EF-Tu from terminating translation. Its structure was found to be a analog of EF-Tu. A quaternary structure of Sel B, GTP, selenocystyl-tRNA and mRNA has been detected which is similar to the structure of EF-Tu, GTP, tRNA and mRNA.

In Eukaryotes:

Eukaryotes also contain a stem-loop structure. However they do not contain the *sel* operon.

The stem-loop structure is known as the SeC Insertion Sequence (SECIS) element. It is regulated by the presence of several factors. The factors which function similarly to Sel B consist of two different factors. One of these proteins is a SECIS binding protein called SBP2, and the other is the translation factor which helps in binding to the ribosome known as eEFsec.

Mammalian SECIS element:

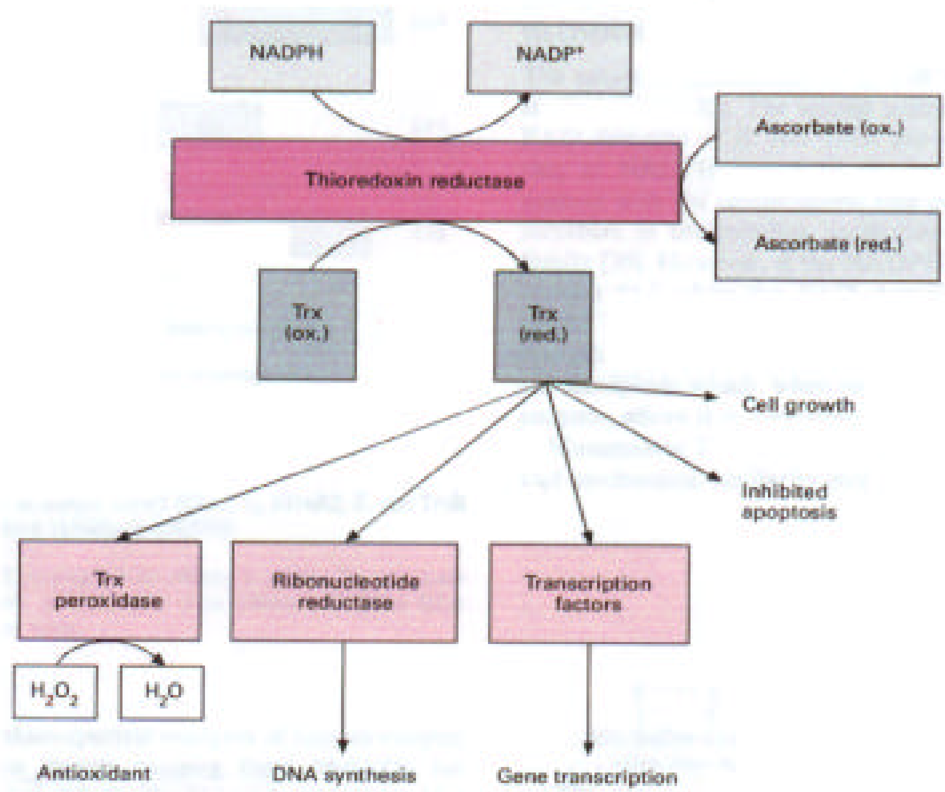


A baseline level of translation occurs with just a SECIS element, but SBP2 and eEFsec have both been found to be essential for significant translation of selenoproteins.

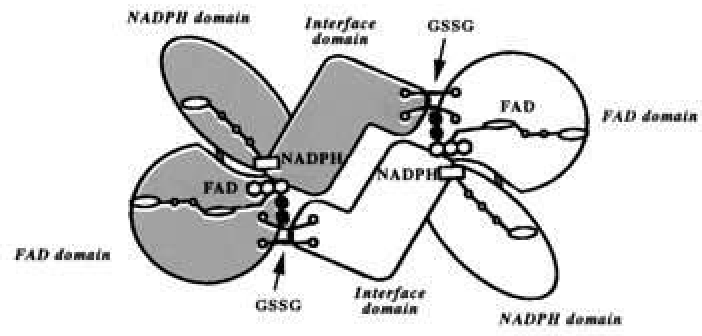
Thioredoxin Reductase

All known selenoproteins have redox activities. Among the most widely found selenoproteins in mammals are Thioredoxin Reductase and Glutathione Peroxidase.

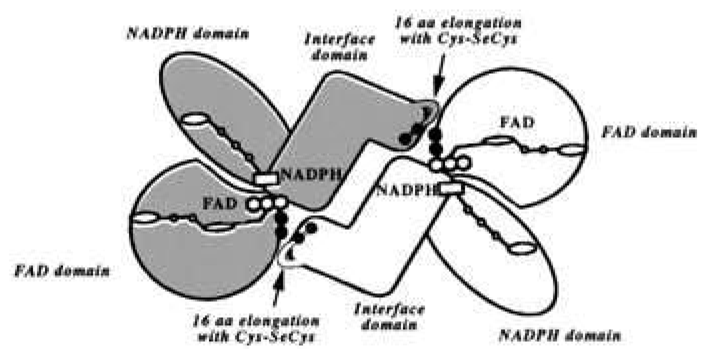
Mechanism of Thioredoxin Reductase (TR)



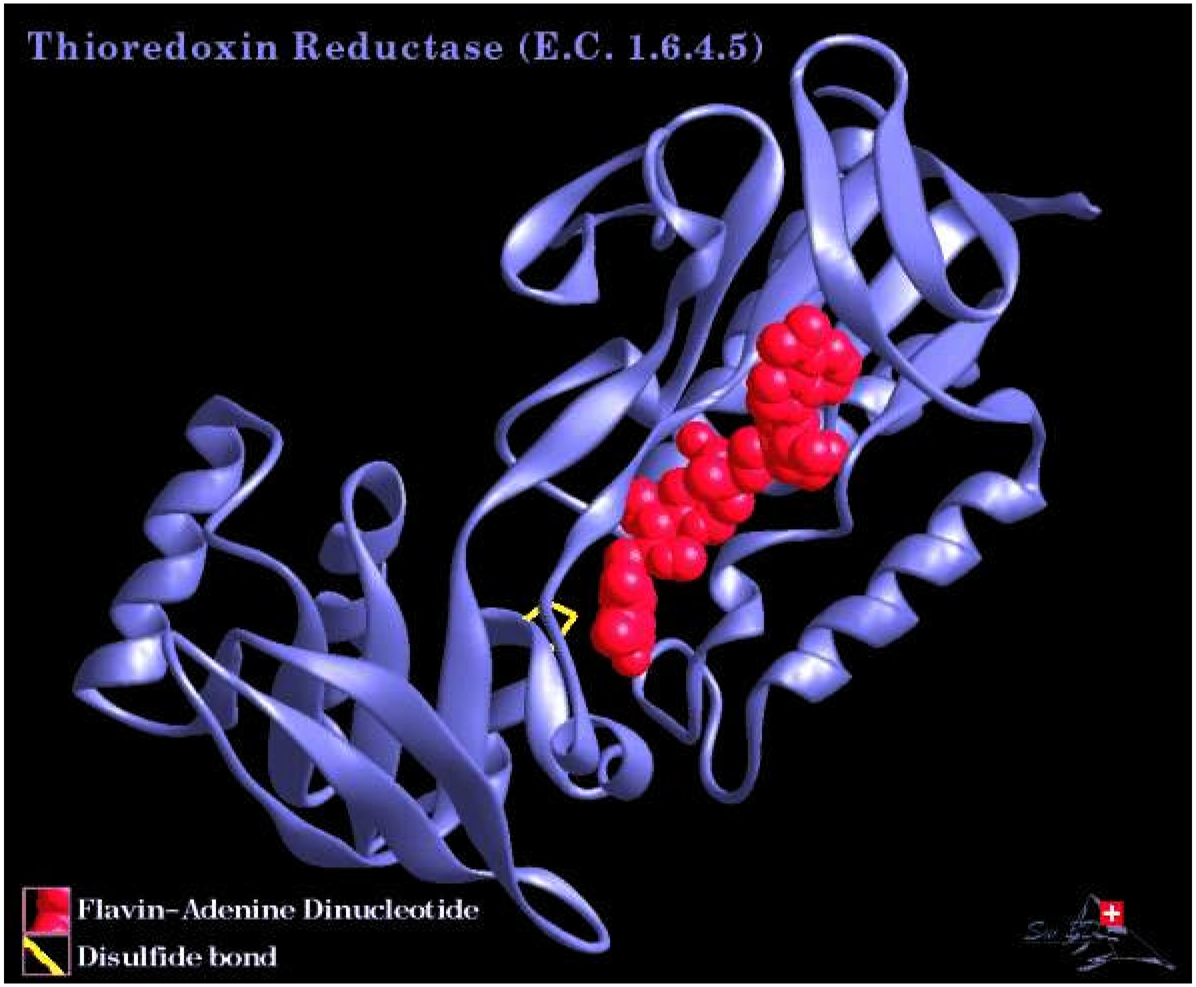
Both yeast and bacterial TR do not contain selenocysteine residues but mammalian TR’s are characterized by a SeC residue at second to last Carboxy-terminus.

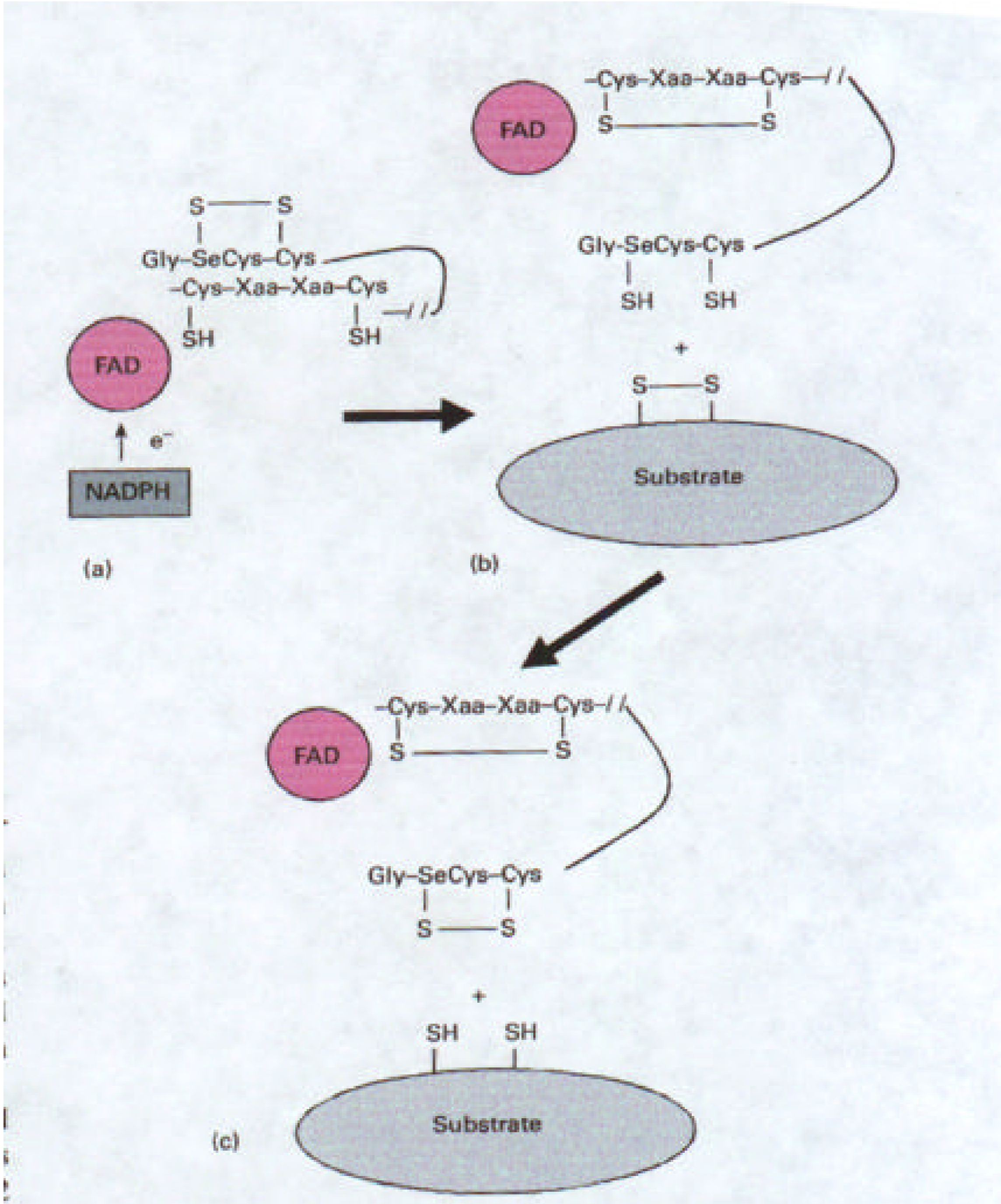


Glutathione Reductase



Thioredoxin Reductase


Thioredoxin Reductase (E.C. 1.6.4.5)
Flavin-Adenine Dinucleotide
Disulfide bond



S—S
Gly–SeCys–Cys
–Cys–Xaa–Xaa–Cys
SH
SH
FAD
e⁻
NADPH
(a)
FAD
–Cys–Xaa–Xaa–Cys–//
S—S
Gly–SeCys–Cys
SH
SH
+
S—S
Substrate
(b)
FAD
–Cys–Xaa–Xaa–Cys–//
S—S
Gly–SeCys–Cys
S—S
+
SH
SH
Substrate
(c)

Importance of Selenocysteine for Health

It has been discovered that HIV-1 encodes a functional selenoprotein. Patients with HIV have been shown to have a lower than average blood plasma selenium level. These individuals are also more succeptible to certain symptoms such as cardiac myopathy. They are also found to contain several low molecular mass selenium compounds. These compounds are thought to be a 7-9 kD selenoprotein which is encoded by the HIV genome. This protein is in fact a glutathione peroxidase. Patients with HIV often exhibit low selenoprotein concentrations in their cells. Thus AIDS patients are reccommended to take selenium supplements to allow their cells to continue to produce these valuable redox proteins.