An Unusual Shape Change to Deliver Selenocysteine to Proteins

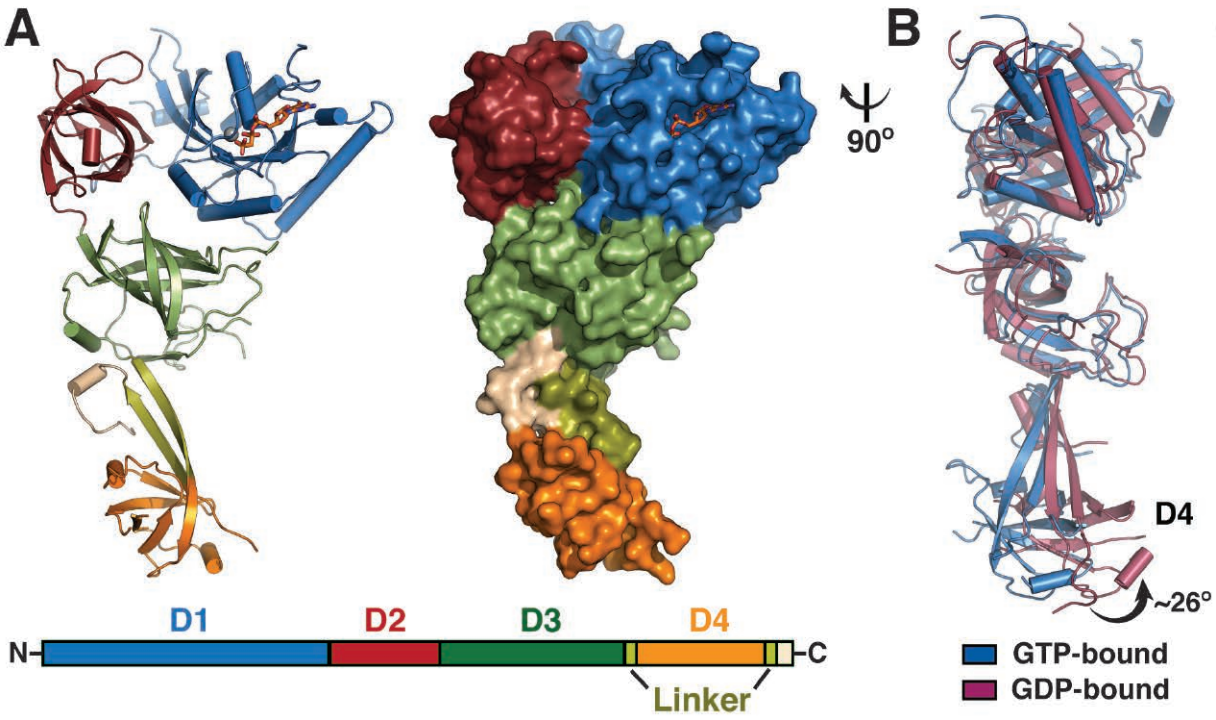

Fig. 1. (A) Cartoon (left) and surface diagram (right) of the overall structure and domain organization of human eEFSec. The color-coding is according to the scheme shown below. (B) The GTP-to-GDP exchange on human eEFSec induces an unexpected conformational change in D4, but not in D1. A comparison of the GTP- (light blue) and GDP-bound states (light red) reveals a lack of the canonical conformational change in the EF-Tu-like domain (D1-3). Instead, D4 swings ~26° towards the dorsal face of the molecule and away from the tRNA-binding site. The view is rotated ~90° clockwise relative to that in (A).

18-ID-D • Bio-CAT • Life sciences • Fiber diffraction, microdiffraction, small-angle x-ray scattering, time-resolved x-ray scattering • 3.5-35 keV • On-site • Accepting general users •

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The element selenium is incorporated into proteins through the 21st amino acid selenocysteine (Sec). Such selenoproteins are critically important to all types of life, suggesting that being able to accurately decode the Sec codon and correctly placing this amino acid in proteins is biologically fundamental. However, little is known about biosynthesis of selenoproteins in eukaryotic cells. To better understand this process, a team of researchers used data gathered at two APS sectors to determine the crystal structure of the human translational elongation factor responsible for recognizing and delivering the transfer RNA (tRNA) carrying Sec to the ribosome. They produced some surprising findings, which suggest that the mechanism for elongation factor to incorporate selenium into growing protein chains is different from that of elongation factors associated with every other type of amino acid.

Standard amino acids rely on the elongation factors eEF1A and EF-Tu. EF-Tu in particular is made of three sections, known as domains 1, 2, and 3. To perform its job, EF-Tu utilizes a molecule called guanosine triphosphate. Previous research has shown that during the process of delivering an amino acid-carrying (or aminoacyl) tRNA into a lengthening protein, one of the phosphates on the GTP molecule EF-Tu carries is cleaved off, or hydrolyzed, which turns it into guanosine diphosphate (GDP). This triggers a major conformational change: domain 1 rotates about 90 degrees away from domains 2 and 3, which helps the tRNA release EF-Tu and subsequent positioning at the appropriate site on the ribosome.

However, the tRNA associated with Sec requires a different elongation factor. In prokaryotic cells, that factor is SelB, and in eukaryotes, it's eEFSec. Both of these elongation factors are made of four domains. Some studies have shown that SelB doesn't undergo a conformational change after the GTP-to-GDP exchange, but little was known about the behavior of eEFSec.

To learn more about this process, investigators from the University of Illinois at Chicago, the Rutgers-Robert Wood Johnson Medical School, the University of Texas Southwestern Medical Center, the Illinois Institute of Technology, and Yale University used the Bio-CAT 18-ID-D, SBC-CAT 19-ID-D, and LS-CAT 21-ID beamlines at the APS to determine the crystal structure of eEFSec while it's complexed with non-hydrolyzable analogs of GTP, as well as GDP.

Their findings show that eEFSec has a structure shaped like a chalice: domains 1, 2, and 3 represent the cup, a linker region represents the stem, and domain 4 represents the base (Fig. 1). Further investigation showed the presence of a hydrogen bond between amino acid residues in domain 3 and the linker that seemed to act like a hinge—a clue that something unusual might take place at this region during hydrolysis.

Sure enough, when the researchers determined the crystal structure of eEFSec complexed with GDP, they found that domain 4 swung 26 degrees away from the other three domains. Domains 1 and 2 also underwent small shifts, with domain 1 moving slightly toward the predicted tRNA binding face and domain 2 toward the opposite direction.

Although the movement of domains 1 and 2 seem to tighten the Sec-binding pocket, which could help lower the binding affinity of the Sec tRNA, the movement of domain 4 is more mysterious. The authors speculate that the swing of domain 4 might help eject the tRNA and dissociate eEFSec from the ribosome.

More research will be necessary to better define the reasons behind this conformational change, the researchers say. Either way, it differs significantly from the mechanisms that eEF1A and EF-Tu use to deliver their aminoacyl-tRNAs to growing protein chains. The authors note that another research team recently revealed that some microorganisms use different codons to encode Sec, suggesting that more surprises about this amino acid are in store.

— Christen Brownlee

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