tion alters the accessibility of specific genetic loci (see the figure). The targets of the acetyltransferase enzyme are lysine residues in the amino-terminal tails of histones, particularly H3 and H4. The crystal structure of the nucleosome core has revealed that these tails extend out from the central disk of the nucleosome around which DNA is twice wrapped (*7*). Acetylation of these histone tails will alter their charge and change their contribution to chromatin structure. These tails are capable of folding back and contacting DNA on the surface of the nucleosome core but can also interact with the DNA or histone proteins of an adjacent core. This adjacent interaction might affect higher orders of chromatin structure such as its assembly into a compact array of supercoiled nucleosomes known as the 30-nm fiber. In addition, the histone tails are available for interaction with other proteins.

First, it is possible that histone acetylation alters the structure of the nucleosome in such a way as to allow binding of the recombinase to the recombination signal sequences. In the absence of acetylation, the RAG recombinases may be unable to recognize a recombination signal sequence on the surface of a nucleosome. Two recent studies have shown that packaging of a DNA substrate containing a recombination signal sequence into a single nucleosome inhibits recognition and cleavage by RAG1 and RAG2 (*8*, *9*). Close contact between the core histones and the wrapped DNA block other proteins from binding to these sequences. But, apparently this inhibition is not relieved when the nucleosome contains hyperacetylated histones (*9*). A second possibility is that histone acetylation causes the localized disassembly of higher order chromatin structure (*10*). This decondensed chromatin might be responsible for the observed deoxyribonuclease sensitivity of accessible loci and might contribute to better access for the recombinase as well. Finally, it is possible that acetylated histones recruit additional chromatin remodeling complexes (Swi/Snf homologs, for example). These remodeling activities might either displace nucleosomes from recombination signal sequences entirely or promote the sliding of nucleosomes, allowing occasional access of the recombinase to the recombination signal sequences (*2*).

The McMurry and Krangel study and the work of other groups suggest that enhancer-binding transcription factors that are developmentally regulated recruit histone acetyltransferase activity to a gene locus destined to undergo rearrangement. However, important questions remain (see the figure). How do these transcription factors gain access to their binding sites in unacetylated chromatin? What determines the boundaries of local histone acetylation? Although histone acetylation clearly correlates with recombinase accessibility, is it necessary? Are additional chromatin structural changes required for the recombinase to gain access to the chromatin? Do the modified histones recruit chromatin remodeling proteins, and if so, what is their role in regulating accessibility? And finally, is overcoming histone-mediated inhibition sufficient to target the recombinase, or are there accessory proteins that specifically recruit the recombinase to accessible loci? The resurgence of interest in how chromatin structure regulates gene expression is sure to lead to a heightened understanding of the regulation of both transcription and V(D)J recombination.

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PERSPECTIVES: PROTEIN SYNTHESIS

Unraveling the Riddle of ProCys tRNA Synthetase

Michael Yarus

Sometimes facts suddenly spin and settle into a more promising arrangement. Partisans of such lovely moments will want to look carefully at a report on page 479 of this issue concerning cysteinyl–tRNA synthetase (CysRS) (*1*). This enzyme is one of 20 aminoacyl–tRNA synthetases—the essential keepers of the genetic code's dictionary. All organisms use these catalysts (which are usually distinct proteins) to covalently connect one of the 20 standard amino acids to its corresponding triplet anticodon within the correct transfer RNA (tRNA) molecule. Thus, these enzymes ensure the subsequent proper alignment of amino acids carried by tRNAs when they pair with complementary triplet codons in mRNA.

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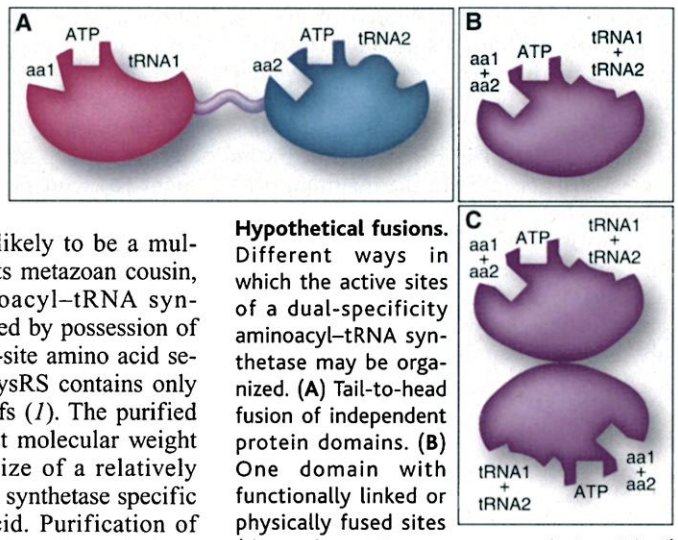
So, it came as something of a surprise to find that the full genome sequences of the archaea *Methanococcus jannaschii* (*2*) and *Methanobacterium thermoautotrophicum* (*3*) lacked an identifiable gene for CysRS. How can such creatures, which have proteins containing cysteines, translate the cysteine codons of mRNA? Apparently, this question has a simple answer: The enzyme was missed during genomic analysis. Extracts of *M. jannaschii* in fact can be shown to have an activity which, given ATP and cysteine, makes Cys-tRNA^{Cys} (*4*). The only unusual quality of this apparent CysRS is that it is "finicky," requiring modified nucleotides in the tRNA^{Cys}; it will not add cysteine to unmodified tRNA^{Cys}.

Stathopoulos *et al.* (*1*) have now followed up on the biochemical identification of the elusive CysRS, purifying the catalyst using a standard biochemical and cloning regimen. CysRS is not elusive for a simple or predictable reason. Instead, it turns out that the missing enzyme is the same protein as prolyl–tRNA synthetase (ProRS), identified in *M. jannaschii* during earlier analyses. Instead of only synthesizing either Pro-tRNA^{Pro} or Cys-tRNA^{Cys}, the purified ProCysRS protein catalyzes both reactions. It does not make the misacylated cross products (Pro-tRNA^{Cys} and Cys-tRNA^{Pro}), and ignores the other 18 amino acids. However, proline inhibits Cys-tRNA synthesis and cysteine inhibits Pro-tRNA synthesis.

Fusions of these two enzymic activities within the same catalyst might conceivably occur with all degrees of intimacy (see the figure). At one end of the scale (panel A), two domains each performing one activity could be simply linked head-to-tail with perhaps a linker peptide in between. Such a dual synthetase, GluProRS, has already been identified in metazoans, such as *Drosophila* (*5*). This 163-kD protein—in which the internal linker is suspected of being necessary for targeting or quaternary structure—has two discrete active sites. It can be cut apart into two separate domains, each fully functional as a GluRS (amino-terminal fragment) or ProRS (carboxyl-terminal fragment).

In contrast, early results on the archaeal ProCysRS suggest that it has a much more intricate fusion of enzymic activities (see the figure, panels B and C). The new archaeal molecule is unlikely to be a multidomain peptide like its metazoan cousin, GluProRS. All aminoacyl–tRNA synthetases are characterized by possession of type I or type II active-site amino acid sequences (*6*). But ProCysRS contains only one set of type II motifs (*1*). The purified protein has an apparent molecular weight of about 53 kD, the size of a relatively small aminoacyl–tRNA synthetase specific for only one amino acid. Purification of ProCysRS from an *Escherichia coli* clone makes it clear that a single subunit supports both activities. Thus, sites for two amino acids and two tRNAs must exist in close proximity or overlap within this unique small protein.



Hypothetical fusions. Different ways in which the active sites of a dual-specificity aminoacyl–tRNA synthetase may be organized. **(A)** Tail-to-head fusion of independent protein domains. **(B)** One domain with functionally linked or physically fused sites (these alternatives are not yet distinguished). **(C)** An oligomer of identical subunits with fused sites. The substrate (amino acid, aa; ATP; tRNA) for each site is shown. The notation a + b indicates that a site binds two substrates.

Cross inhibition between the specific proline and cysteine substrates also suggests linkage or overlap between their active sites. The relationship between the amino acid sites in the ProCysRS is presently not understood in detail. Envisioning an amino acid binding site with two specificities at first seems laborious. Perhaps cysteine could bind via catalyzed disulfide bond formation, thereby making minimal demands on remodeling the initial amino acid site. Any interactions between $tRNA^{Cys}$ and $tRNA^{Pro}$ sites within ProCysRS, if they exist, have not yet been studied. One intriguing observation (*1*), however, is that the presence of $tRNA^{Cys}$ is required for activation of cysteine. A few other synthetases, such as GlnRS (*7*), also have tRNA and amino acid activation sites that are strongly linked. Nonetheless, $tRNA^{Pro}$ is not required for proline activation and does not stimulate cysteine activation. So, experiments suggest that the sites in ProCysRS for activation of proline and cysteine are closely connected, and that the sites for $tRNA^{Cys}$ and cysteine are also linked. Site number, placement, and interaction are crucial because the ProCysRS must make both types of aminoacylated tRNAs in the presence of substrates that mutually inhibit each other's reactions. Perhaps a switch that minimizes interference is the binding of $tRNA^{Cys}$ to its site, with consequent conversion of the protein to a specific CysRS.

These collected properties are most easily understood if ProCysRS is a monomer (see the figure, panel B). Competition for one set of overlapping active sites then explains how the aminoacyl–tRNA synthetase activities mutually inhibit eachother. However, aminoacyl–tRNA synthetases are frequently oligomers. If ProCysRS is a homooligomer, then cross-inhibition implies communication between identical amino acid sites on different oligomers. In this case (see the figure, panel C), the extensive aminoacyl–tRNA synthetase literature offers many other possibilities for how the dual activities of ProCysRS could be coordinated. For example, one set of sites in an oligomeric enzyme can be active despite apparently identical inactive sites elsewhere in the oligomer (half-of-the-sites reactivity) (*8*). Either simple inhibition is transmitted between sites or, more surprisingly, a change in specificity to that matching the first-occupied site could be transmitted. The spreading effect of $tRNA^{Cys}$ on the activation of cysteine, and the dramatic effect of nucleotide modifications on the formation of Cys-tRNA (*4*) might conceivably be other symptoms of such allosteric variations.

The resolution of these mechanistic possibilities will be of interest to a group broader than aminoacyl–tRNA synthetase mavens. Consider that the molecule could arise by straightforward fusion between a ProRS and a CysRS (see the figure, panel A). Such a fusion might be selected when coordination of different synthetase activities becomes adaptive. On the other hand, if there are intimately fused bispecific sites (see the figure, panel B), or exquisitely communicating bispecific sites (see the figure, panel C), then there may exist molecular routes for fusion and evolutionary forces for the selection of specificity that have not yet been imagined.

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PERSPECTIVES: QUANTUM COMPUTING

Quantum Information Processing Without Entanglement

Peter Knight

Suppose you had a really stupid friend, who can remember your phone number but not your name. How long would it take him to search the phone book database, comprised of n entries, before he found you? If he were really unlucky, it would take $n - 1$ queries. But on average, it would take him $n/2$ queries, which is clearly still a demanding task. Of course, I have assumed that the search was done with classical devices. But what would happen if you exploited a quantum device to make the search? Grover of AT&T showed in 1997 (*1*) that, if you took advantage of the massive parallelism within quantum mechanics, you could reduce the search to on the order of $n^{1/2}$ queries on average. The Grover algorithm, along with remarkably few other algorithms—including Shor's famous algorithm for factoring numbers (*2*)—is what has attracted so much attention to the newly emerging field of quantum computing.

There have been a few pilot experimental studies of the Grover search algorithm, using nuclear magnetic resonance (NMR) (*3*) and interferometry (*4*). On page 463 of this issue, Ahn *et al.* report on a realization of Grover's search algorithm using a single atom as a quantum processor (*5*). In doing so,

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