Jekyll & Hyde: Evolution of a Superfamily

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Aminoacyl-tRNA synthetase mutations have been linked to neurological diseases, but aminoacylation may be unaffected. This protein superfamily also performs many other diverse functions. Yang et al. insightfully engineer a single mutation to unmask a cell signaling activity of tyrosyl-tRNA synthetase [1].

To begin with, this is fiction—and with all powerful fictitious stories, we start with a disclaimer: "*Characters, places, and incidents are either the product of the author's imagination or are used fictitiously, and any resemblance to actual entities, events, or locales is entirely coincidental.*" However, when a story is truly compelling, we become convinced that the disclaimer is merely masking the identity of real characters and their environment.

The story is reminiscent of the tale of Dr. Jekyll and Mr. Hyde [2], but is set in the theater of proteins. In essence, the leading character, Dr. Jekyll has a well-defined and respected role in a quite orderly intracellular environment. The rules, for all practical purposes, are understood. Yet much beyond his control, Dr. Jekyll can be transformed into Mr. Hyde, who doesn't honor precedent or adhere to the rules and can even turn violent to wreak havoc within the cell. Such is the case for a series of neuropathies, where genetic mutations have been identified in tRNA synthetase genes (Figure 1). Paradoxically, despite the disease-causing mutation, Dr. Jekyll may continue to faithfully supply aminoacylated tRNAs for protein synthesis. Thus, we ask as the plot develops, where is Mr. Hyde and what is his role?

The leading character in this work is played by tyrosyl-tRNA synthetase (TyrRS). TyrRS is well recognized as a conscripted component of protein synthesis. However, TyrRS has adapted to perform very different functions in certain species. For example, in addition to its housekeeping role in translation in the lower eukaryote *Neurospora crassa*, TyrRS is an essential RNA splicing factor [3]. In humans, TyrRS plays a dual role in cell signaling as a cytokine [4]. Its cytokine activity is dependent on exposure of a buried "ELR" tripeptide motif that occurs upon a specific proteolytic cleavage event. So, if Mr. Hyde does not emerge during protein synthesis, can he be found lurking in any of these alternate roles (Figure 2)?

The research group of Xiang-Lei Yang and Paul Schimmel at The Scripps Research Institute has introduced a single mutation into human TyrRS to unleash Mr. Hyde. Using X-ray crystal structures and models of human TyrRS, the mutation was rationally designed to expose the critical "ELR" motif that initiates a cascade of signals within the cell. This single mutation has little effect on the overall protein structure. Its aminoacylation activity is decreased, but remains robust for protein synthesis. In essence, Dr. Jekyll is transformed into Mr. Hyde and the mutant TyrRS cell signaling behavior goes awry because the ELR motif is now continuously exposed. Within the cell, the mutant TyrRS triggers uncontrolled endothelial cell proliferation and migration. In animal models, the mutant TyrRS becomes proangiogenic. In short, a single mutation has uncoupled regulation that balances the TyrRS's secondary roles in cell signaling.

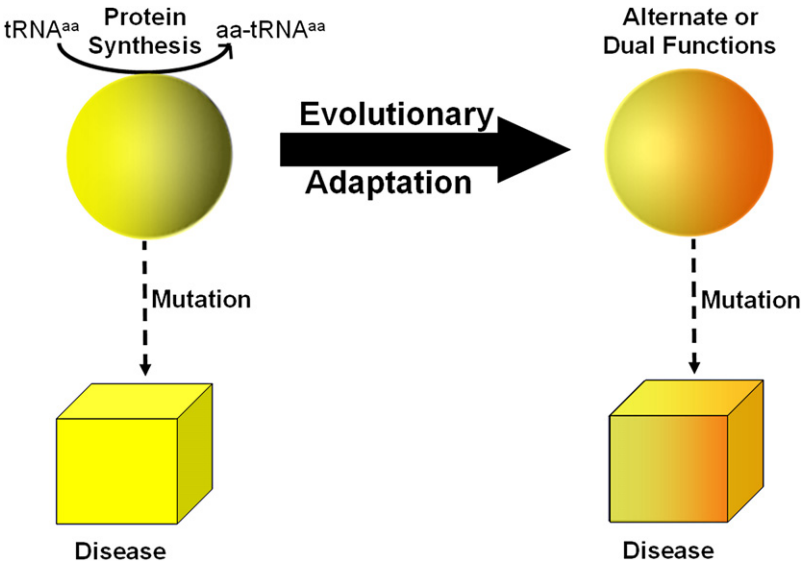

Figure 1. Evolution of the tRNA Synthetase Superfamily
Mutations confer new functions to a tRNA synthetase. Disease-causing mutations may affect either the protein synthesis activity of the tRNA synthetase or its alternate functions.

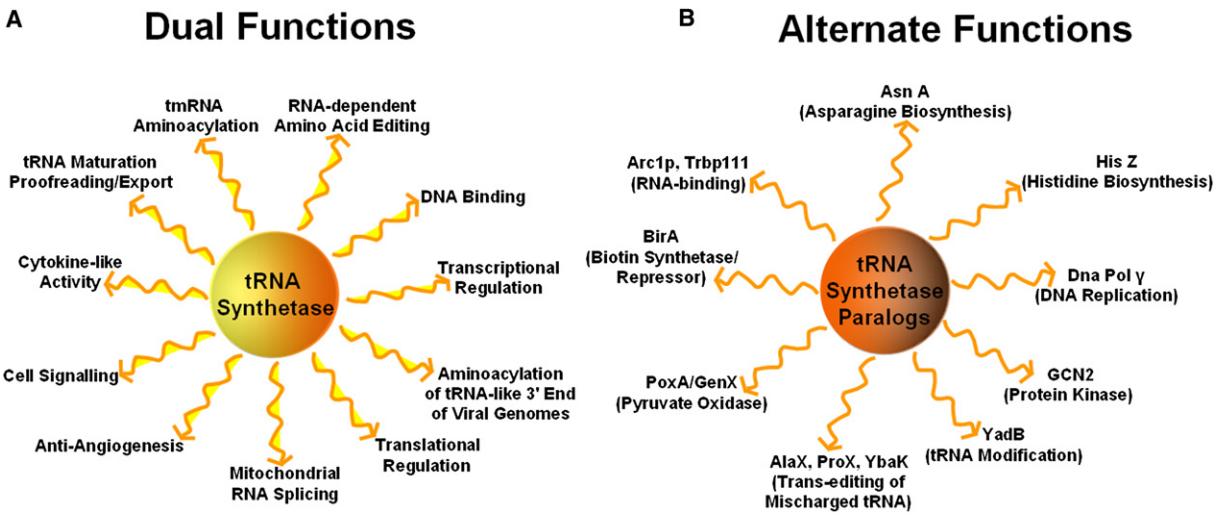

Figure 2. Non-canonical activities of tRNA synthetases
(A) The tRNA synthetases may be adapted for dual roles that coexist with their aminoacylation activity.
(B) Paralogs of tRNA synthetases and their domains can provide important nonaminoacylation functions within the cell.

Now, this is a theoretical mutation and thus the disclaimer at the beginning. However, it represents a powerful example that is reminiscent of a cast of disease-causing tRNA synthetase mutations which are poorly understood. The mechanism of this "virtual" disease-inducing mutation will likely foreshadow many authentic genetic mutations that are localized in the tRNA synthetases. A number of these genetic mutations have little impact on aminoacylation activity, yet they profoundly affect human health. These include mutations in TyrRS [5], as well as GlyRS [6] in different versions of Charcot-Marie-Tooth disease. As another example, a mutation in the amino acid editing domain of mouse alanyl-tRNA synthetase caused late onset of neurological disease [7].

The family of tRNA synthetases has adapted in very idiosyncratic ways to perform many other roles in the cell that extend well beyond tRNA aminoacylation (Figure 2). In some scenarios, the tRNA synthetase moonlights in the cell and maintains two jobs [8]. In other cases, a tRNA synthetase paralog has wholly adapted for a new role in this superfamily of proteins [9]. As Yang et al. have shown, it is the nonaminoacylation roles that many of these poorly understood tRNA synthetase mutations may affect. Indeed, in a twist of fate, Mr. Hyde will likely define and characterize new activities of tRNA synthetases to add to a growing list of diverse functions that have already emerged.

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