

Aminoacyl-tRNA synthetases and tRNAs in human disease: an introduction to the JBC Reviews thematic series

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Aminoacyl-tRNA synthetases (ARSs) catalyze the attachment of specific amino acids to cognate tRNAs for use in protein synthesis. This historical function of ARSs and tRNAs is fairly well understood. However, ARSs and tRNAs also perform noncanonical functions that are continuing to be unveiled at a rapid pace. The expanded functions of these essential molecules of life range from roles in retroviral replication to stimulation of mammalian target of rapamycin (mTOR) activity; DNA repair, splicing, and transcriptional and translational regulation; and other aspects of cellular homeostasis. Furthermore, mutations in tRNAs and synthetases are known to drive human maladies, such as the neurodegenerative disorder Charcot-Marie-Tooth disease along with other central nervous system dysfunctions and cancer. This series of reviews focuses on the diseases that result from natural variations in human cytoplasmic tRNAs, as well as from mutations in mitochondrial tRNAs and ARSs. Ultimately, the exciting work in this rapidly emerging area may lead to new therapies for microbial and parasitic infections, cancer, and neurodegenerative diseases.

Scientific fields sometimes expand in unanticipated directions. This is certainly the case for aminoacyl-tRNA synthetases (ARSs)² and tRNAs. ARSs have long been known to catalyze the attachment of specific amino acids to the 3'-adenosine (A76) of cognate tRNAs, the adaptor molecules in protein synthesis (1). Perhaps because of this early assignment of their functional roles, additional activities for these ancient and essential players in the translation of the genetic code were not sought. However, they are now known to play emerging roles in a variety of areas far outside the arena of protein synthesis and translation. This thematic issue explores these expanded functions, particularly in the context of new opportunities for therapeutic development. The reviews cover the role of natural tRNA variants, cytoplasmic and mitochondrial ARSs in specific diseases and viral infections, progress and challenges in ARS-based therapeutics, and emerging ideas about ARS complex function.

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² The abbreviations used are: ARS, aminoacyl-tRNA synthetase; mTOR, mammalian target of rapamycin; CMT, Charcot-Marie-Tooth disease; MSC, multisynthetase complex.

The 1000 genomes project, which “aims to provide a deep characterization of human genome sequence variation as a foundation for investigating the relationship between genotype and phenotype” (2), provides an important resource for the research community. O'Donoghue and co-workers (3) mined the tRNA sequence data from this database and summarize their (in many cases) surprising findings. No position in human tRNA is immune to variation, with common and rare variants distributed across nearly all sites. This review highlights the unexpected prevalence of mistranslating cytoplasmic tRNA variants in the human population. Many of the tRNA variants are linked to disease phenotypes, including genetic disorders, cancer, and neurodegeneration, providing new impetus for further studies to investigate the role of cytoplasmic tRNAs in human disease.

Mitochondrial tRNAs have a longer history of being linked to disease phenotypes than their cytoplasmic counterparts (4). Whereas mammalian mitochondrial DNA encodes all of the RNA components of the translational machinery, the ARSs are encoded by the nuclear genome and imported into mitochondria. In recent years, it has become clear that mitochondrial disease phenotypes are also linked to mitochondrial ARS mutations. As reviewed by González-Serrano *et al.* (5), disorders correlated with these mutations span a broad range and differ in disease severity, with the majority leading to clinical manifestations in the central nervous system. Whether the ARS-linked diseases are caused by defects in mitochondrial translation or alternative roles is an active area of investigation.

The most common ARS-associated disorder is Charcot-Marie-Tooth (CMT) disease, an incurable neurodegenerative disease that specifically affects the peripheral nervous system. The disease is caused by dominant mono-allelic mutations in any of five cytoplasmic ARSs or glycyl-tRNA synthetase, which is dual-localized to the cytoplasm and mitochondria, making this the largest protein family implicated in CMT etiology. Although still a matter of some debate, as discussed by Wei *et al.* (6), the field has progressed to the point where loss of tRNA charging is generally believed unlikely to serve as the main cause of the disease. Whereas some of the mutations do impact tRNA aminoacylation capability, progress in understanding the mechanisms of ARS-linked CMT includes the discovery of toxic gain-of-function effects.

Interestingly, nine cytoplasmic ARSs together with three nonenzymatic factors form a multisynthetase complex (MSC) in higher eukaryotes (from flies to humans). Many of the pro-

teins associated with this complex have been implicated in disease phenotypes. The functional significance of the MSC is still unclear, but Kim and co-workers (7) discuss two possible roles. The first is related to ARS function in protein synthesis. Here, the MSC is proposed to provide a channel through which tRNAs and amino acids transit, interacting with their cognate ARS and subsequently with other components of the protein translation machinery. The second proposed function of the MSC relates to the noncatalytic expanded functions of ARSs. Here, the macromolecular complex serves as a “depot” wherein a subset of ARSs is poised for rapid response to incoming stresses and stimuli. Kim and co-workers (7) focus on the link between ARSs and cancer, as well as the functional expansion of MSC-associated synthetases, which links them to diverse cellular processes, including mTOR signaling and DNA repair.

Together with my co-author D. Jin (8), I was happy to provide an update on the nontranslational roles of tRNAs and ARSs in retroviral and retrotransposon replication. The hallmark of all retroviruses, including HIV-1, is the requirement for a reverse transcription step, wherein the RNA genome is converted to DNA before it can be integrated into the host genome. It has long been known that host cell tRNAs serve as primers for reverse transcriptase, which catalyzes this step of the viral life-cycle. In recent years, nonpriming functions of tRNAs and tRNA-derived fragments have also been discovered, and tRNA-binding proteins, including ARSs, are believed to play important roles in the retroviral life-cycle. These discoveries open up new opportunities for antiviral strategies aimed at viral–host cell factor interactions.

Finally, progress and challenges in the development of ARS-based therapeutics are reviewed by Francklyn and Mullen (9). This comprehensive review covers early and more recently discovered lead compounds for antibiotic development that target the classical role of ARSs as essential components of the translational machinery, including strategies for combating bacterial, fungal, and parasitic pathogens. In addition, novel approaches that target the roles of ARSs in human diseases, such as cancer and neurological disorders described above, are also discussed.

The ARS/tRNA field is often referred to as “mature.” While the historical function of these essential players in protein synthesis is indeed reasonably well-understood, the exciting

reviews in this series highlight the fact that our understanding of the nontranslational function of ARSs, tRNAs, and tRNA-derived fragments is in its infancy. There are many unanswered questions and future directions to pursue, especially with regard to understanding ARS mutations linked to diseases such as cancer, CMT, and other neurological disorders. Why does the human genome encode >600 tRNA genes? This is a fascinating question that is only beginning to be explored. The 3D structure of the MSC is unknown, and a greater understanding of its function and dynamic nature is needed. Future studies investigating how the MSC-associated and free ARSs interact with each other and with other factors in the control of a variety of nontranslational cellular pathways are also needed. We hope you enjoy this glimpse into the exciting and rapidly expanding world of tRNA/ARS research and that it stimulates you to learn more about these amazing translation factors.

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