An Ancient Structural Bridge Joins Editing to Aminoacylation to Prevent Mistranslation

The translation of the genetic code into proteins relies on accurate ligation of amino acids to their matching tRNAs, by a group of enzymes known as aminoacyl-tRNA synthetases. Mistranslation from confusing (by alanyl-tRNA synthetase (AlaRS)) the amino acids serine or glycine for alanine has profound pathological consequences, both in mammals[1] and bacteria[2]. To achieve accurate translation, AlaRSs in all species have an aminoacylation site and an editing site that work collaboratively to hydrolyze the misacylated Ser/Gly-tRNA^{Ala}. A third domain, C-Ala domain, is universally tethered to the end of the editing domain in AlaRSs throughout the 3 kingdoms of life, but heretofore had no known function. In a work recently published in *Science*, a research team led by Profs. Paul Schimmel and Xiang-Lei Yang at The Scripps Research Institute determined the 3-D structure and the function of C-Ala and showed how these results, in turn, shed light on the early evolution of the apparatus for accurately translating the genetic code [3].

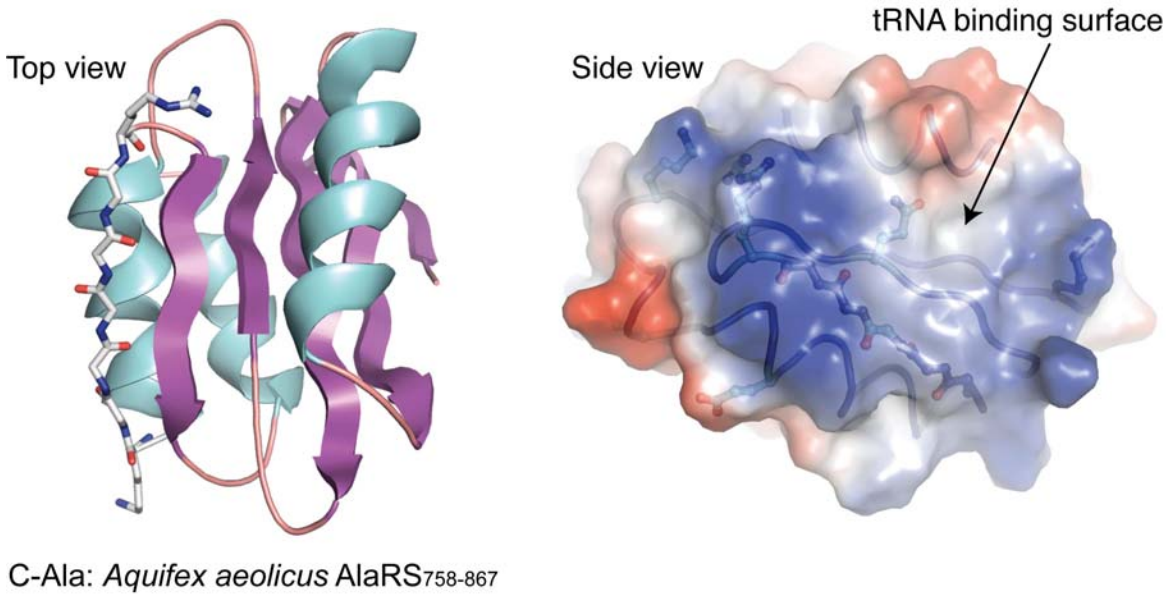

Figure 1. Structure of the C-Ala domain of *Aquifex aeolicus* AlaRS indicates it has a single-stranded nucleic acid binding fold with a tRNA binding surface located at one side.

Distinct from all the other aminoacyl-tRNA synthetases, AlaRSs have a group of free-standing partners—AlaXps—that are wide-spread in the three kingdoms[4]. AlaXps specifically hydrolyze the tRNA^{Ala}'s that has been mischarged with serine instead of alanine. This activity provides functional redundancy to the editing activity that is imbedded in AlaRSs[5,6,7]. The AlaXps are homologous to the editing domains of AlaRSs and some of them are also fused to C-Ala.

Using data collected at SSRL Beam line 11-1, the team quickly determined the three dimensional structure of C-Ala by the method of single anomalous diffraction. The automatic crystal-mounting at SSRL enabled the efficient screening and data-collecting of the crystals, just weeks after the cloning of this domain. The x-ray structure of C-Ala at 1.85 angstroms revealed a single-stranded nucleic acid binding fold, which was seen in some DNA exonucleases (such as RecJ) (Fig. 1). Site-specific footprinting showed that C-Ala binds to

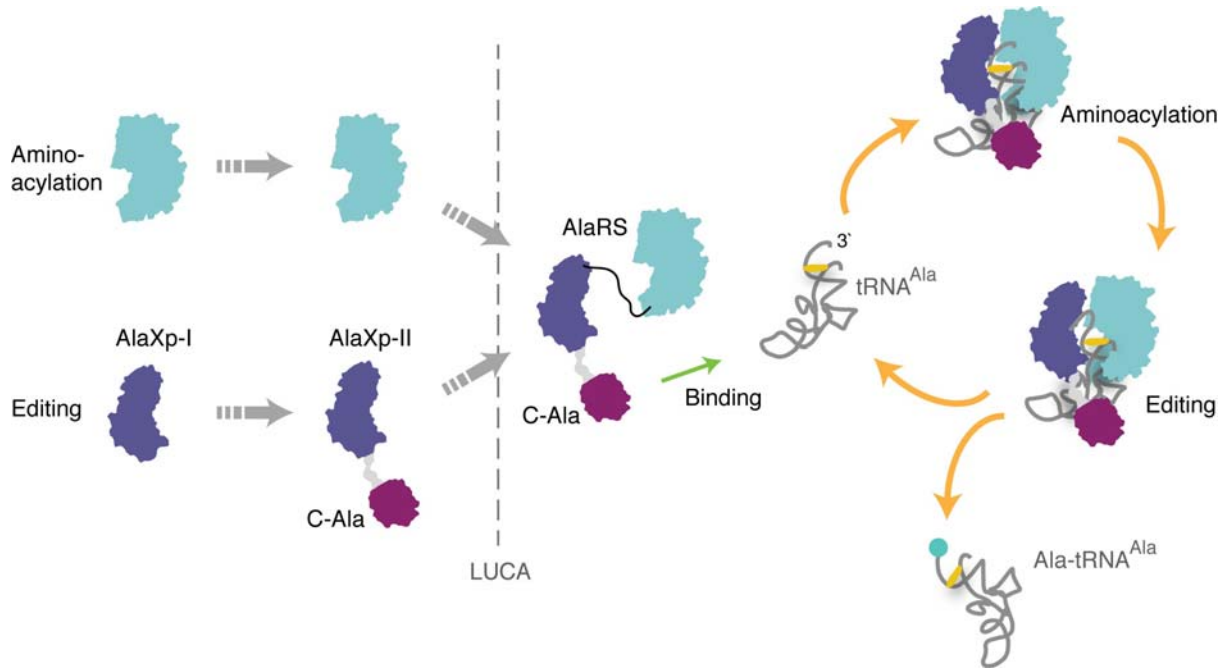

Figure 2. Proposed assembly of AlaRS in evolution. The shorter free-standing editing protein (AlaXp-I) is proposed to have coexisted in trans with the free-standing aminoacylation domain of AlaRS. The longer AlaXp-II formed by combining AlaXp-I with the C-Ala domain, which was able to bring together editing and aminoacylation centers to create the present-day AlaRS.

the elbow region of $tRNA^{Ala}$. Other experimental data, including binding and kinetic analysis, showed that C-Ala is a major tRNA-binding module of AlaRS, and serves as a bridge to collaboratively join editing with aminoacylation on one tRNA[3]. Separately, phylogenetic analysis showed that AlaXp evolved in the ancient community and that the imbedded editing domain of AlaRS originated from AlaXp (Fig. 2). Thus, C-Ala may have also had the historical role of being the bridge that first joined editing with aminoacylation.

Primary Citation

Min Guo, Yeeting E. Chong, Kirk Beebe, Ryan Shapiro, Xiang-Lei Yang and Paul Schimmel "The C-Ala domain brings together editing and aminoacylation functions on one tRNA". *Science*, **325**, 744-747 (2009).

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This work was supported by NIH grant GM 15539 and by a fellowship from the National Foundation for Cancer Research.

SSRL is primarily supported by the DOE Offices of Basic Energy Sciences and Biological and Environmental Research, with additional support from the National Institutes of Health, National Center for Research Resources, Biomedical Technology Program, and the National Institute of General Medical Sciences.