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Functional Activities between Protein Arginylation and Arginyltransferase

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Editorial

The post-translational modification of protein arginylation, carried out by arginyltransferase ATE1, involves the transfer of the amino acid Arg to substrate proteins and peptides. Charged tRNAArg is used by ATE1 as the donor of the arginyl group, which is also used in translation and is dependent on the activity of Arg-tRNA synthetases (RARS). Unknown processes control the functional harmony between ATE1, RARS, and translation. Here, we investigated how an intracellular arginylation sensor may be used to partition Arg-tRNAArg to functionally different routes in cell lines with overexpression or deletion of the ATE1 and RARS isoforms. We discovered that whereas translation activity and the availability of RARS isoforms do not directly alter arginylation levels, they are dependent on the physiological state of the cells. However, independent of RARS enzymatic activity, the removal of RARS from the multi-synthetase complex causes an increase in intracellular arginylation. The redistribution of ATE1 into the cytosol goes hand in hand with this outcome. Our findings offer the first thorough examination of the relationships between translation, arginyl-tRNA production, and arginylation.

A biological regulation mechanism called protein arginylation adds the amino acid Arg to proteins and peptides through the action of arginyltransferase ATE1 [1]. ATE1 is implicated in the control of numerous cellular and organismal processes, including cell migration, nucleotide biosynthesis, neurodegeneration [2], and cancer. More than 100 in vivo arginylation targets have been discovered [2-5]. In fungi and animals, ATE1 is encoded by a single gene, while in plants, ATE1 is encoded by two genes. The Ate1 gene in higher vertebrates produces four alternatively spliced isoforms. It is not known how these four very similar enzymes can carry out so many different in vivo tasks or what intracellular components are involved in this regulation. Relatively little is understood about the intracellular processes that balance arginylation with other pathways that use the same molecules as substrates, like protein synthesis, and very few ATE1 functional partners have been found to far.

Since arginylation is dependent on the activity of arginyl-tRNA synthetases, ATE1 needs Arg attached to tRNAArg as the donor of the arginyl group (RARS). In theory, this dependency puts translation-which also depends on RARS and other aminoacyl-tRNA synthetases (AARSs) to produce aminoacyl-tRNA (aa-tRNA) for the expanding polypeptide chains-in direct competition with arginylation. Prior research from our lab demonstrated that ATE1 can use Arg-conjugated tRNAArg-derived fragments (tRFArg), which are translation-incompetent and may therefore function to tip the scales in favour of arginylation rather than translation. RARS availability and activity, however, are also necessary for the initial step in the synthesis of Arg-tRFArg, and as a result, they may be rate-limiting for arginylation.

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RARS is translated from one mature mRNA into two isoforms in mammalian cells using two different start codons. As a result, these two RARS isoforms are identical downstream of the second start codon. However, the "long" RARS has an extra N-terminal stretch of sequence that contains a leucine zipper (LZ), which scaffolds it into the multi-tRNA synthetase complex (MSC, which also contains IARS, LARS, MARS, QARS, RARS, KARS, DARS, EPRS, and three scaffold proteins: AIMP-1,-2, The majority of this facility is devoted to translation. The "short" RARS, which is devoid of this domain, is soluble and cytosolic in contrast. It has been suggested that the MSC will direct aa-tRNAs to ribosomes to enable effective translation. Long RARS' LZ interacts with AIMP-1, which is necessary for RARS assembly in the MSC. This interaction also creates a foundation for QARS to be connected to the MSC. Even while eukaryotic cells only have AARSs in the cytoplasm to facilitate protein synthesis, multiple investigations have shown that MSC-bound AARSs have also been discovered in the nucleus. On the basis of this scaffolding, it has previously been proposed that the long RARS is primarily involved in translation, whereas the short RARS may be partially or entirely devoted to translation-independent functions, such as arginylation. Despite this, this hypothesis has never been put to the test. Recent research has shown that global translation levels and tRNAArg aminoacylation are unaffected by the displacement of the long RARS from the MSC by deletion of the leucine zipper domain responsible for this scaffolding, indicating that a more complex balance between translation and potential translation-independent RARS functions may exist.

Here, we investigated the ability of these two enzymes to divide Arg-tRNAArg into functionally separate routes, including as arginylation, translation, and the balance of long and short RARS isoforms. Our findings showed that the quantity of RARS enzymes or active translation are not direct determinants of intracellular arginylation activity. However, we discovered that the extended RARS' displacement from the MSC results in an increase in intracellular arginylation. ATE1 redistributes into the cytosolic fraction in cells when long RARS are absent, resembling a RARS redistribution of a similar nature. Our findings provide the first thorough examination of the connection between translation, arginyl-tRNAArg production, and arginylation, and they show that ATE1 is connected to non-canonical RARS roles in promoting the transfer of MSC into the cytosol.

Conflict of Interest

None.

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