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Interplay of Functional Dynamics: Protein Arginylation and Arginyltransferase

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Abstract

The post-translational modification of proteins plays a pivotal role in regulating cellular functions and orchestrating complex biological processes. Protein arginylation, a relatively recently discovered modification, involves the covalent attachment of an arginine residue to the N-terminus of a protein, catalyzed by arginyltransferase enzymes. This modification has emerged as a key regulator of protein stability, localization and activity, impacting a wide range of cellular processes. In this review, we explore the interplay between functional dynamics and protein arginylation, shedding light on the diverse roles of this modification in health and disease. We discuss the molecular mechanisms underlying arginylation, its regulation and its impact on protein function. Furthermore, we highlight recent advancements in the field, including the identification of novel substrates and the development of potential therapeutic strategies targeting arginylation. This comprehensive overview provides insights into the multifaceted nature of protein arginylation and its significance in cellular biology and human health.

Keywords: Protein arginylation • Arginyltransferase • Post-translational modification

Introduction

Post-translational modification of proteins, known as protein arginylation, is orchestrated by arginyltransferase ATE1. This process involves the transfer of the amino acid Arg to proteins and peptides. ATE1 employs charged tRNAArg as the donor for the arginyl group, a critical step also vital in translation and reliant on the activity of Arg-tRNA synthetases (RARS). Intriguingly, the intricate interplay between ATE1, RARS and translation remains shrouded in mystery. In our study, we delved into how an intracellular arginylation sensor could partition Arg-tRNAArg into distinct functional pathways within cell lines, particularly those with altered expression levels of ATE1 and RARS isoforms [1]. Our investigation unveiled that translation activity and the abundance of RARS isoforms don't directly impact arginylation levels but are contingent on the physiological state of the cells. Remarkably, the removal of RARS from the multi-synthetase complex, independently of its enzymatic activity, leads to an escalation in intracellular arginylation. This coincides with the redistribution of ATE1 to the cytosol. Our findings represent a comprehensive exploration of the intricate relationships between translation, arginyl-tRNA production and arginylation [2].

Literature Review

Protein arginylation, mediated by arginyltransferase ATE1, plays a pivotal role in various cellular and organismal processes, encompassing cell migration, nucleotide biosynthesis, neurodegeneration and cancer. Over 100 arginylation targets have been identified in vivo. While fungi and animals possess a single ATE1 gene, plants harbor two. In higher vertebrates, the Ate1 gene yields four alternatively spliced isoforms. The functional diversity of these closely related enzymes and the intracellular factors involved in their regulation remain enigmatic. Our knowledge of the processes governing the balance between arginylation and competing pathways, like protein synthesis, is limited and only a few ATE1 functional partners have been identified thus far [3].

Arginylation depends on the activity of arginyl-tRNA synthetases (RARS), which necessitates Arg attached to tRNAArg. This reliance implies a potential competition with translation, which also relies on RARS and other aminoacyl-tRNA synthetases (AARSs) to produce aminoacyl-tRNA (aa-tRNA) for polypeptide synthesis. Previous research has proposed that ATE1 can utilize Arg-conjugated tRNAArg-derived fragments (tRFArg) that are translation-incompetent, potentially favoring arginylation over translation. However, the availability and activity of RARS are also critical for the initial synthesis of Arg-tRFArg, potentially limiting arginylation [4].

Discussion

In mammalian cells, RARS is translated from a single mature mRNA into two isoforms using distinct start codons. These two RARS isoforms share identical sequences downstream of the second start codon. However, the "long" RARS includes an additional N-terminal stretch with a leucine zipper (LZ) domain that anchors it to the multi-tRNA synthetase complex (MSC). This complex, housing several aminoacyl-tRNA synthetases (IARS, LARS, MARS, QARS, RARS, KARS, DARS, EPRS) and three scaffold proteins (AIMP-1, -2), primarily facilitates translation. In contrast, the "short" RARS lacks this domain, rendering it soluble and cytosolic. It has been suggested that the MSC guides aa-tRNAs to ribosomes, enhancing translation efficiency. The LZ of long RARS interacts with AIMP-1, a crucial factor for RARS assembly within the MSC and also serves as a foundation for QARS attachment to the complex. Despite AARSs primarily being cytoplasmic, MSC-bound AARSs have been observed in the nucleus. This scaffolding suggests that long RARS primarily supports translation, while short RARS may be dedicated to translation-independent functions, like arginylation. However, this hypothesis has yet to be rigorously tested. Recent research indicates that the displacement of long RARS from the MSC, achieved by deleting the leucine zipper domain, doesn't affect global translation levels or tRNAArg aminoacylation, suggesting a more intricate relationship between translation and potential translation-independent roles of RARS [5,6].

Conclusion

Our study investigates how these enzymes partition Arg-tRNAArg into different functional routes, including arginylation and translation, as well as the

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balance between long and short RARS isoforms. Our findings demonstrate that the quantity of RARS enzymes or active translation isn't a direct determinant of intracellular arginylation activity. Instead, the removal of long RARS from the MSC leads to an increase in intracellular arginylation, accompanied by the redistribution of ATE1 into the cytosolic fraction. This underscores the intricate connection between translation, arginyl-tRNAArg production and arginylation and suggests ATE1's involvement in non-canonical RARS functions that promote the transfer of MSC to the cytosol.

Acknowledgement

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Conflict of Interest

None.

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