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Taking AIM at the Start of Translation

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The translation of mRNA during protein synthesis is among the most complex and conserved processes in the cell. The first step in translation is the attachment of the correct amino acid to its cognate tRNA, which is catalyzed by the ubiquitous aminoacyl-tRNA synthetase (aaRS) family of housekeeping enzymes. Although the catalytic activities of aaRSs are common among different species, there are distinct features that distinguish the higher eukaryotic versions from most of their prokaryotic counterparts. AaRSs are modular enzymes composed of conserved catalytic cores and additional appended domains acquired during evolution.[1,2] These domains are required for RNA recognition and proofreading activities and are also involved in protein–protein interactions and various other roles, thereby expanding aaRS functions beyond translation of mRNA. One of the most important roles of appended domains in higher eukaryotic and some archaeal aaRSs is to mediate the formation of intricate networks of protein–protein interactions between different components of the translation machinery and other components of the cell.[3] AaRSs have been shown to form a variety of complexes with each other and other components of the cell, one of the most complex and intriguing of which is the mammalian multi-synthetase complex (MSC). Among the 20 aaRSs, the mammalian MSC is composed of 9 aaRSs (ArgRS, AspRS, GlnRS, GluRS, IleRS, LeuRS, LysRS, MetRS, and ProRS) that associate with three auxiliary protein factors AIMP1 (p43), AIMP2 (p38), and AIMP3 (p18) [aaRS-interacting multifunctional protein (AIMP)].[4] Smaller aaRS-containing complexes have also been observed in lower eukaryotes and archaea.[3] Within the mammalian MSC, AIMP1 increases the catalytic activity of ArgRS, AIMP2 interacts with most of the MSC components and is considered an essential scaffolding protein in the complex, but the role of AIMP3 remained unknown.[5] A recent study of *Caenorhabditis elegans* showed that different MSC structures result from both additions and subtractions to aaRS cores and changes in AIMP content during evolution. It was observed that two clades of the bilaterian phylum reflect divergent evolution of the MSC, with the notable difference in arthropods being the absence of a fused Glu-ProRS, presence of ValRS instead of AspRS, presence of a p43 (AIMP1)-like domain fused to the C-terminus of MetRS, and absence of AIMP3.[6] These last two findings are of particular interest as they emphasize the importance of retaining MetRS in the MSC, which, in higher eukaryotes, occurs via direct interactions with AIMP3.[7] AIMP3 has significant sequence similarity to eukaryotic elongation factors, which raises questions as to how interactions between AIMP3 and MetRS in the MSC might impact translation.[8] In this issue, Kang *et al*. now show that AIMP3, rather than just being a scaffolding protein, plays a central role in translation by mediating the transfer of

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aminoacylated initiator tRNA from MetRS to the elongation initiation factor 2 (eIF2) complex.

Kang *et al*. reasoned that as AIMP3 both interacts strongly with MetRS in the MSC and has sequence similarity to elongation factors, it was likely to have a direct role in translation. Consistent with this prediction, they found that AIMP3 directly bound a form of tRNA, $\mathrm{Met-tRNA}_i^{\mathrm{Met}}$, that is reserved exclusively for translation initiation. A possible role in translation initiation was further supported by the fact that the corresponding tRNA used for translation elongation, $\mathrm{Met-tRNA}_e^{\mathrm{Met}}$, did not bind AIMP3. The specificity displayed by AIMP3 for methionine-charged initiator tRNAs is also a hallmark of eIF2γ, a subunit of eIF2 involved in tRNA binding during translation initiation complex formation.[9,10] Kang *et al*. then went on to show that AIMP3 recruits eIF2γ to MetRS, consistent with the overlapping tRNA binding activities of the three proteins. These interactions require both $\mathrm{Met-tRNA}_i^{\mathrm{Met}}$ and the active form of eIF2γ, the GTP binding domain of which interacts with MetRS and AIMP3. These findings together provide a model for the role of the MSC in initiation complex formation, the G domain of eIF2γ interacts with $\mathrm{AIMP3-Met-tRNA}_i^{\mathrm{Met}}\mathrm{-MetRS}$, followed by transfer of $\mathrm{Met-tRNA}_i^{\mathrm{Met}}$ to the groove formed between the G domain and domain II of eIF2γ. After the transfer of $\mathrm{Met-tRNA}_i^{\mathrm{Met}}$, domain III of eIF2γ can then interact with helix 44 of the 40S ribosome leading to formation of the 43S pre-initiation complex.[9] The authors provided preliminary support for this model using an AIMP3 knockdown, which caused a 40% reduction in global translation and changes to the co-localization of eIF2γ with ribosomes. While further studies are now required to further confirm the precise details of AIMP3 function, it is clear from the study of Kang *et al*. that it plays a pivotal role in maintaining the efficiency of translation initiation in higher eukaryotes.

The study by Kang *et al*. not only advances our understanding of AIMP3 function but also provides perhaps the most direct evidence to date that the higher eukaryotic MSC has a critical role in optimizing translation in addition to its known regulatory functions.[11,12] MSC formation has been implicated in a number of roles as a depot for releasable regulatory proteins, in which the aaRSs and auxiliary factors maintain ordinary activity but acquire new functions upon release from the complex.[11,13] The findings of Kang *et al*. and other recent studies from a number of laboratories are now starting to show that the roles of MSC components and aaRSs inside and outside translation may actually be quite intricately intertwined.[14,15] For example, under UV stress, phosphorylation by GCN2 reduces the activity of MetRS, thereby reducing translation initiation[16] and providing an additional level of control of AIMP3-mediated translation initiation. This, in turn, raises questions of how and under what circumstances AIMP3 itself is regulated. Whatever the answer is, the work of Kang *et al*. described in this issue adds significantly to our understanding of how aminoacyl-tRNA synthesis is linked to an increasing number of key cellular processes both inside translation and outside translation.

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