

Amino acid transporters: an integrated response of cells to nutritional stress

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Amino acid starvation induces a gene expression program that involves the phosphorylation of translation initiation factor eIF2 and the subsequent programmed expression of genes which mediate cell survival to stress. eIF2 phosphorylation which causes the decreased availability of ternary complexes (eIF2•GTP•Met-tRNA_i) and therefore a global decrease in protein synthesis, it also promotes synthesis of stress response proteins. The cationic amino acid transporter 1, which mediates the cellular transport of lysine and arginine increases during amino acid starvation via transcriptional and translational mechanisms. Both of these mechanisms depend on eIF2 phosphorylation. Transcriptional activation is part of the integrated stress response pathway that involves a feed back loop mechanism of the transcriptional activator ATF4 and the transcriptional repressor ATF3. Increased translation of the cat-1 mRNA involves an internal ribosome entry site (IRES) in the 5'-untranslated region of the cat-1 mRNA. The cat-1 IRES has an unusual feature; its activity increases during amino acid starvation via a mechanism that involves unfolding of the RNA and

refolding in a new RNA structure which recruits more efficiently the ribosome and therefore improves translation of the cat-1 mRNA. This conformational change of the cat-1 mRNA leader is mediated by the translation of an upstream open reading frame within the leader and is stabilized by the hnRNA binding proteins HnRNP L and PTB. We are testing the hypothesis that the newly transcribed cat-1 mRNA during amino acid starvation forms nuclear and cytoplasmic complexes which are important in IRES-mediated translation during stress. eIF2 phosphorylation is essential for formation of these complexes. We conclude that the coordinated transcriptional and translational control of cat-1 gene expression during amino acid starvation is part of the cell-survival gene expression program to nutritional stress.

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