

**P049** A novel mechanism for the control of translation initiation by amino acids, mediated by phosphorylation of eukaryotic initiation factor eIF2B

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Eukaryotic initiation factor (eIF) 2B plays a key role in controlling the initiation of mRNA translation. eIF2B is heteropentameric protein whose catalytic ( $\epsilon$ ) subunit promotes GDP/GTP exchange on eIF2.

Here we show that depriving human cells of amino acids rapidly results in the inhibition of eIF2B, independently of changes in eIF2 $\alpha$  phosphorylation. Although amino acid deprivation also inhibits signalling through the mammalian target of rapamycin complex 1 (mTORC1), a number of lines of evidence indicate that the inhibition of eIF2B activity by amino acid starvation is independent of mTORC1. Instead, amino acids repress the phosphorylation of a novel site in eIF2B $\epsilon$ .

Using a combination of methods, we have identified this site as Ser525, located adjacent to the known phosphoregulatory region in eIF2B $\epsilon$ . Mutation of Ser525 to Ala abolishes the regulation of eIF2B and protein synthesis by amino acids. This indicates that phosphorylation of this site is crucial for the control of eIF2B and protein synthesis by amino acids. These findings identify a new way in which amino acids regulate a key step in translation initiation and indicate that this involves a novel amino acid-sensitive signalling mechanism. This mechanism is independent of the eIF2 kinase, mGcn2, which is activated by uncharged tRNA. It may serve to allow translation initiation to be switched off without a requirement for accumulation of uncharged tRNAs, which could be detrimental to the fidelity of translation.