The GCN2 kinase is required for activating autophagy in response to indispensable amino acid deficiencies

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GCN2 can promote autophagy initiating events independently of mTORC1 inhibition


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INTRODUCTION
The imbalances in dietary amino acid (AA) supply, including deficits in one or more indispensable amino acids (IAA), are stressful conditions for the organism that needs to modulate a number of physiological functions in order to adapt to this situation. In particular, the release of free AA by degradation of functional proteins can rapidly become necessary, notably by macro-autophagy (hereafter “autophagy”). This process can be up-regulated within minutes inside cells in response to a number of stresses, by post-translational modifications of autophagy-related proteins already present in the cytosol. Until now, the activation of autophagy resulting from amino acid deficiencies has been considered exclusively as a consequence of mTORC1 inhibition. The protein kinase GCN2 is activated upon IAA scarcity in order to promote cell adaptation to a nutritional stress condition. Under IAA limitations, GCN2 is activated within minutes by uncharged transfer RNAs. By phosphorylating eIF2α on serine 51, GCN2 diminishes the overall protein synthesis rate, while simultaneously triggering a gene expression program through the translational upregulation of the transcription factor ATF4 (Figure). Our recent work has shown that the GCN2/p-eIF2α/ATF4 signaling pathway plays an essential role in the transduction of a number of autophagy-related genes for the maintenance of high levels of autophagy under IAA deficiencies (B’chir et al., 2013). In the present study we sought to determine whether GCN2 could play a role in regulating the early stages of autophagy activation.

REFERENCES


CONCLUSION
This study provides evidences that the early up-regulation of autophagy during IAA deficiencies can be promoted by GCN2 activation and eIF2α phosphorylation independently of ATF4 transcription factor. Furthermore, our data show that this GCN2-dependent mechanism can occur without concomitant inhibition of mTORC1 and involves the ULK1/ATG13 pre-initiation complex. Further studies are needed to understand how GCN2 activation/eIF2α phosphorylation and ULK1 are connected.