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PRESS RELEASE

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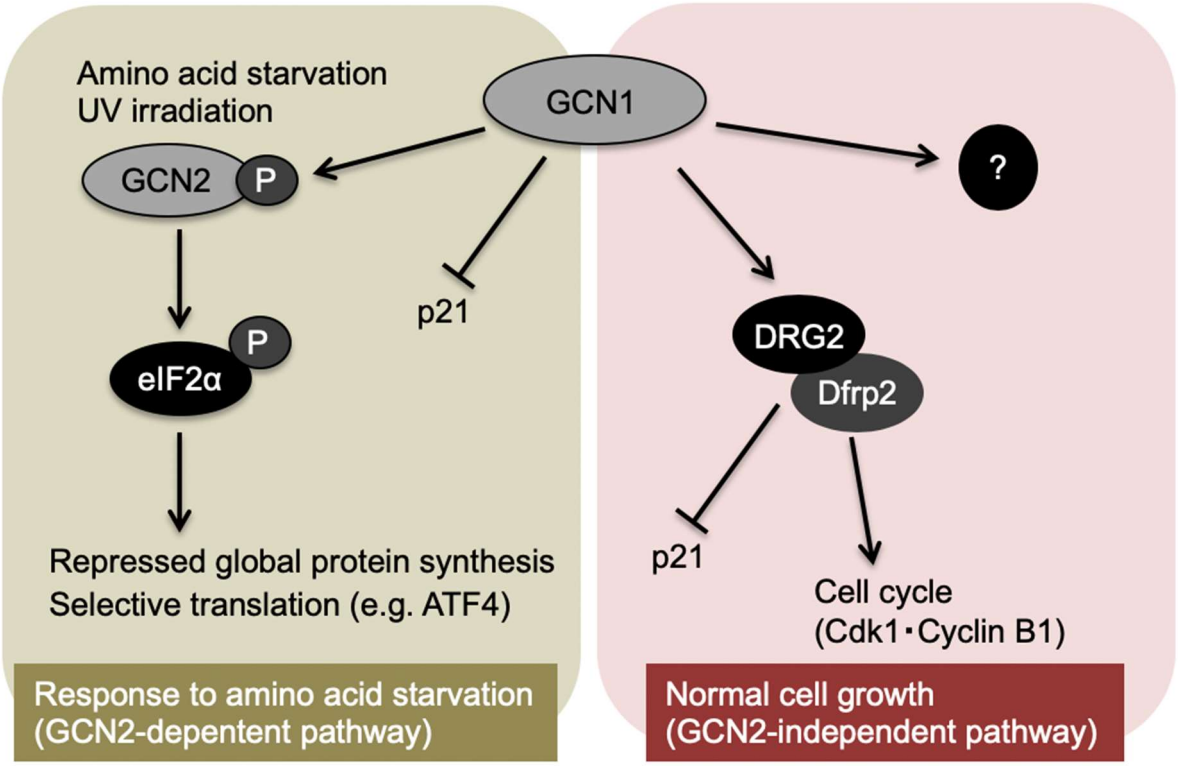
Amino acid starvation-responsive factor GCN1 regulates cell proliferation and embryonic development in mice

Researchers at Hirosaki University revealed that amino acid starvation-responsive factor GCN1 regulates cell proliferation and embryonic development in mice.

Protein translation is a highly energy demanding process. Therefore, it is important for the cells to repress overall protein translation and produce limited proteins which is

necessary for cell survival during various stresses. Upon exposure to stresses such as amino acid starvation (AAS), phosphorylation of translational initiation factor eIF2α represses general translation. At the same time, it increases the selective translation of cytoprotective proteins, such as ATF4, that transcriptionally activate a stress response to promote cell survival. Among four eIF2α kinases, GCN2 responds to AAS and phosphorylates eIF2α. In yeast, Gcn1 is required for Gcn2 activation by AAS. Upon AAS, uncharged tRNAs are increased and Gcn1 transfers the uncharged tRNA to Gcn2 at the ribosome. However, the roles of mammalian GCN1 remain to be established. In this study, the authors generated two types of mutant mouse lines: *Gcn1* knockout mice and *Gcn1*$^{\Delta RWDBD}$ mice which lack GCN2 binding domain. Both mutant mice showed growth retardation, which was not observed in the *Gcn2* KO mice. *Gcn1* KO mice died at the



intermediate stage of embryonic development because of severe growth retardation. *Gcn1*$^{\Delta RWDBD}$ embryos showed mild growth retardation and malformation, and died soon after birth, most likely due to respiratory failure. Collectively, it was revealed that GCN1 contributes to normal embryogenesis in a GCN2-independent manner. They further generated mice embryonic fibroblasts from GCN1 mutant embryos, and showed that GCN1 is necessary for response to AAS. Interestingly, GCN1 not only regulates the eIF2α-mediated stress response but also cell cycle and cell proliferation in a GCN2-independent manner. Taking these findings together, the researchers propose that GCN1 integrates cellular energetic status including amino acid availability to enhance cell viability.

As GCN1 KO and mutant mice showed severe phenotypes, it can be used as model mice of malformation, hypotrophy at embryonic stage and neonatal respiratory distress syndrome.

This achievement will be disclosed on 23 March, 2020 in PLOS Genetics.

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Article

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Title: Ribosome binding protein GCN1 regulates the cell cycle and cell proliferation and is essential for the embryonic development of mice

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