the chaperone roles in nascent polypeptide folding and in formation/propagation of self-perpetuating amyloid aggregates.

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Transcription factor TnrA inhibits the biosynthetic activity of glutamine synthetase in *Bacillus subtilis*

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The *Bacillus subtilis* glutamine synthetase (GS) plays a dual role in a cell metabolism by functioning as catalyst and regulator. GS catalyses the ATP-dependent synthesis of glutamine from glutamate and ammonium. Under nitrogen-rich conditions, GS becomes feedback-inhibited by high intracellular glutamine levels and then binds transcription factors GlnR and TnrA, which control the genes of nitrogen assimilation. While GS-bound TnrA is no more able to interact with DNA, GlnR-DNA binding was shown to be stimulated by GS complex formation.

The interaction of transcription factor TnrA with GS results in partial inhibition of GS activity *in vivo* and *in vitro*, while the GlnR protein does not affect enzymatic activity of GS. Furthermore, TnrA enhances the effect of feedback inhibitors, in particular, of glutamine. Addition of glutamine to wild-type and AmtB-deficient cells decreased the *in-situ* activity of GS by 60 – 70%, which is almost the same level of inhibition of GS by TnrA determined *in vitro*. These data can be explained by re-localizaiton of TnrA from GlnK to GS upon nitrogen-excess treatment and subsequent GS inhibition. Since TnrA has also the potential to interact with non-feedback inhibited GS, the interaction of TnrA with GS under nitrogen-limited growth would counteract the activity of GS. An important function of binding of TnrA to GlnK during nitrogen-limited growth could thus be prevention of unfavourable TnrA-GS interactions that could impair the activity of GS.

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The eIF2alphaS51 phosphorylation pathway acts downstream of Akt and mTOR to determine cell fate in response to stress and chemotherapeutic drugs

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mRNA translation is important for cell proliferation and tumor development and represents a valid target of pharmaceutical intervention in cancer. A key step in mRNA translation involves the regulation of initiation by the eukaryotic initiation factor eIF2. Eukaryotic cells respond to various forms of stress by inducing the phosphorylation of the alpha subunit of eIF2 at serine 51 (herein referred to as eIF2alphaP), a modification that leads to a general inhibition of protein synthesis. Increased eIF2alphaP is mediated by a family of kinases consisting of PKR, PERK, GCN2 and HRI, each of which becomes activated by distinct stimuli. eIF2alphaP can act either as a promoter of cell survival but also as an inducer of cell death in response to various forms of stress. Previous work by our group demonstrated that eIF2alphaP is induced in cells subjected to genetic as well as pharmacological inhibition of the phosphoinositide 3-kinase (PI3K)-Akt pathway [Sci. Signal. 4, ra62 (2011)]. We discovered that PI3K-Akt pathway disruption leads to the activation of PERK and consequently to increased eIF2alphaP. At the molecular level, we found that Akt negatively regulates PERK by phosphorylation at threonine (T)799. We showed that Akt inhibition decreases PERK phosphorylation at T799, a process that promotes PERK activation in response to stress. To better understand the molecular events that link Akt inactivation to increased eIF2alphaP, we investigated the role of the mammalian target of rapamycin (mTOR) in the regulation of PERK-eIF2alphaP arm. We found that mTOR inhibition with either rapamycin or the new generation of catalytic inhibitors increases PERK activity and eIF2alphaP. Moreover, genetic inactivation of mTOR, Raptor or Rictor by shRNAs in mouse and human cells led to the conclusion that mTOR complex 2 is responsible for inhibition of the PERK-eIF2alphaP arm and that rapamycin increases eIF2alphaP independent of mTOR. The biological significance of our findings is highlighted by the observation that cells deficient in tuberous sclerosis complex (TSC) contain elevated levels of the PERK-eIF2alphaP arm and are more susceptible to stress than cells with intact TSC. TSC-deficient cells contain low levels of mTORC2 and Akt activity, which account for PERK activation and increased eIF2alphaP. Our work shows that eIF2alphaP is a mechanism of translational control by the PI3K-Akt-mTOR pathway, which is distinct from cap-dependent translation mediated by the eIF4F complex. Disruption of PI3K-Akt-mTOR signaling not only causes inhibition of cap-dependent translation by the inactivation of eIF4F but also results in general protein synthesis inhibition by increased eIF2alphaP. Most importantly, increased eIF2alphaP provides a cytoprotective environment which has to be eliminated in order to increase the efficacy of anti-tumor drugs targeting the PI3K-Akt-mTOR pathway.

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Yap1 mediates tolerance to cobalt toxicity in the yeast *Saccharomyces cerevisiae*

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Cobalt has a rare occurrence in nature, but yet may accumulate in cells to toxic levels. As a consequence, living organisms have developed sophisticated mechanisms to counteract cobalt toxicity. Here, we report that yeast cells devoid of Yap1 exhibit increased sensitivity to cobalt stress. Using genetic and biochemical approaches we have shown that cobalt excess induces oxidative stress in yeast cells and that Yap1 is required to mitigate the oxidative damages. However, when challenged with high concentrations of cobalt, *yap1* mutant cells accumulate lower levels of this metal, suggesting that Yap1 is regulating cobalt cellular uptake. Accordingly, transcriptome analysis of *yap1* mutant revealed novel targets of Yap1 involved in low-affinity metal uptake, such as the genes of the high affinity phosphate transporter, *PHO84*, and of the low affinity iron transporter, *FET4*. Overall our results emphasize the important role of Yap1 in mediating cobalt-induced oxidative damages and reveal new routes for cell protection provided by this regulator.

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Genetic systems of toxin-antitoxin as modules responsible for stress

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Toxin-antitoxin systems (TAS) are present in the genomes of the overwhelming majority of bacteria and archaea. These systems

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