In this issue of *Molecular Cell*, De Virgilio and colleagues (Talarek et al., 2010) identify the Igo1/2 proteins as factors that protect mRNAs from degradation during quiescence.

Cells exposed to adverse growth conditions need to adapt to survive these environmental challenges. Eukaryotic cells respond to such conditions by switching into a reversible quiescent state, also called G0, which prolongs lifespan and increases cell survival. The key physiological responses induced during G0 include an overall reduction of metabolism, the activation of autophagy, and the transcriptional induction of genes that are necessary for survival. In the model eukaryote *S. cerevisiae*, G0 can be triggered experimentally by nutrient deprivation or by exposure to the drug rapamycin. The switch into G0 is activated by a signal transduction cascade that is controlled by the master regulator kinase Rim15 (Reinders et al., 1998). In rapidly growing cells, Rim15 is kept in an inactive state in the cytoplasm by the target of rapamycin complex 1 (TORC1) and protein kinase A (PKA) kinases (Figure 1); however, following glucose limitation or exposure to rapamycin, these kinases are inactivated, triggering the activation of Rim15 and the initiation of the quiescence response (Pedruzzi et al., 2003). Part of Rim15 function in G0 is to activate transcription of genes required during quiescence (Figure 1); though this transcriptional program has been well documented, the posttranscriptional mechanisms allowing the efficient expression of the induced genes have remained a puzzle. In particular, G0 is characterized by lower overall translation rates and by a dissociation of mRNAs from polysomes, followed by storage of these mRNAs as mRNPs in cytoplasmic P bodies (Brenquès et al., 2005). Later during quiescence, these P bodies can evolve into stress granules (SG), also called EGP bodies (Buchan et al., 2008; Hoyle et al., 2007), which are enriched in translation initiation factors (Hoyle et al., 2007). Thus, one of the key questions of gene regulation during quiescence is to understand how mRNAs induced during G0 by transcriptional activation by Rim15 escape translational repression and storage into P bodies and how they can return to translation.

In this issue of *Molecular Cell*, De Virgilio and colleagues provide a piece to this puzzle (Talarek et al., 2010). Talarek et al. identify the conserved Igo1 and Igo2 proteins (Initiation of G0; referred to as Igo1/2) as phosphorylation targets of the master regulator kinase Rim15 during quiescence (Figure 1). Igo1/2 are required for the proper initiation of G0 and for efficient expression and translation of mRNAs induced during quiescence. Interestingly, following exposure to rapamycin or during glucose limitation, Igo1/2 were found to interact with activators of the 5’-3’ mRNA degradation pathway, such as Dhh1. Dhh1 is enriched in P bodies and activates the decapping of mRNAs, thus enhancing their degradation. The authors show that Igo1/2 interact with Dhh1 and other degradation factors to prevent the association of G0 mRNAs with the 5’-3’ degradation machinery in P bodies, allowing them to escape degradation and/or translational repression.

The data provided by Talarek et al. converge to propose a model in which Igo1/2 might associate with mRNPs synthesized at the onset of G0 and escort them through P bodies (Figure 1). The authors show that Igo1/2 colocalize with a reporter mRNA expressed in G0 and associate with P bodies. Later in G0, Igo1/2 colocalize with stress granules/EGP bodies, which are known to assemble on pre-existing P bodies during quiescence (Buchan et al., 2008). Ultimately, Igo1/2 might accompany G0 mRNAs to the stress granules/EGP bodies, possibly to associate with translation initiation factors (including the polyA-binding protein, PAB), which would allow the return of G0 mRNAs to translation (Figure 1). Though the data provide evidence for a function for Igo1/2 in protecting G0 mRNAs from degradation, it is unclear whether the association between Igo1/2 and 5’-3’ degradation activators occurs in the context of an mRNP. The association of Igo1/2 with Dhh1 is not sensitive to RNase treatment, but a direct interaction between Igo1/2 and Dhh1 simultaneously with mRNPs targeted to P bodies would provide a physical explanation as to how G0 mRNAs are protected from degradation (Figure 1). As attractive as it is, this model needs to be refined by experimental data; despite the colocalization and genetic data, it is unclear whether Igo1/2 directly binds directly to G0 mRNAs and whether these proteins have any direct RNA-binding activities. In addition, further work will be required to understand the exact molecular event triggered by phosphorylation of Igo1/2 and why phosphorylation by Rim15 is required to activate Igo1/2.

A fascinating aspect of the report by Talarek et al. is that the stabilization of G0 mRNAs is entirely dependent on the promoter used for their expression. Indeed, expressing a *LacZ* reporter mRNA under the control of the *HSP26* promoter that is activated during quiescence is sufficient to confer stability to the *LacZ* mRNA. This result suggests that Igo1/2 might define the fate of G0 mRNAs very early during their biogenesis, possibly in a cotranscriptional manner (Figure 1). Igo1/2 cotranscriptional...
binding would allow the formation of an mRNP structure that would provide immunity from the RNA degradation pathway at a very early stage. As such, assessing the presence of Igo1/2 proteins in the vicinity of the chromatin of G₀-induced genes should clarify the stage of the mRNA biogenesis pathway at which they might associate with the mRNPs. Even if Igo1/2 are not present at the chromatin, the observed promoter-dependent effect could be explained by the cotranscriptional loading of an mRNP factor that might later associate with phosphorylated Igo1/2 and would confer immunity to degradation to G₀ mRNAs.

Finally, one very intriguing aspect of the study is the fact that orthologs of the Igo1/2 proteins are conserved in higher eukaryotes and that these orthologs (ENSA and ARPP-19) are capable of partially fulfilling the functions of Igo1/2 in protecting mRNAs from degradation. Although the signals responsible for triggering quiescence are quite distinct in yeast and mammalian cells, this result suggests that the intrinsic signal transduction pathways and the mechanisms of signal output are ultimately conserved across eukaryotes. However, the fact that ENSA and ARPP-19 can replace Igo1/2 in yeast does not necessarily imply similar physiological functions in human cells; the next challenge will be to understand whether these human orthologs indeed also function to prevent mRNA degradation during G₀ in human cells and to regulate their trafficking and translation.

REFERENCES


