SYSTEMS BIOLOGY

The dynamics of the cycle

As biological processes rarely stand still, it makes more sense, where possible, to study them dynamically, rather than by taking static snapshots. So that's exactly what de Lichtenberg *et al.* have done in their approach to analysing the dynamics of protein complexes during the yeast cell cycle.

Information on the peak expression point within the cell cycle of 600 periodically expressed genes, which was obtained using DNA-microarray time series, was combined with information about the physical interactions of the corresponding proteins (using pulldowns, two-hybrid screens, and so on). This resulted in a time-dependent interaction network placing 300 proteins in a temporal cell-cycle context, more than 10% of which were previously functionally uncharacterized.

A total of 60 protein complexes (or modules) were found to vary with the cell cycle. Virtually all of the complexes contained both periodically expressed (dynamic) and constitutively expressed (static) components. The static part accounted for ~50% of the direct interactions of the dynamic proteins throughout the entire cell cycle, and so transcriptional regulation affects all complexes both directly and indirectly.

During the bacterial cell cycle, entire protein complexes are made through 'just-in-time' synthesis, in which all of the genes that encode the components are turned on just before their protein products are needed. In yeast, however, only some of the components of each complex seem to be transcriptionally regulated, and thereby expressed just before their components are needed to function in the cell. The authors refer to this new design principle for complex formation as 'just-in-time' assembly (rather than synthesis). Using this tactic, cells would only need to tightly regulate the synthesis of a few dynamic components, rather than all components, to control the timing of complex assembly and function.

The approach of de Lichtenberg *et al.* could reproduce the dynamics of several well-characterized complexes, including the associations of Cdc28, the cyclin-dependent kinase, with its transcriptionally regulated cyclins and its inhibitor, even capturing transient phosphorylation and ubiquitylation events. The authors also found that the dynamically expressed proteins were much more likely to be phosphorylated by Cdc28 than the static ones, and contained more PEST (Pro, Glu, Ser, Thr) degradation signals. These findings support the dynamic role of the transcriptionally regulated proteins, as they are also mainly those that are regulated post-translationally. So the system seems to be set up to provide new, unmodified targets of Cdc28 in each cycle, the phosphorylation of which could either fine-tune protein function or control the subsequent degradation of these dynamic proteins.

As well as the task of extending this integrative approach to other biological systems, a future challenge will be to increase the resolution of temporal networks by gathering information about the lifetime of the complexes and the subcellular compartment in which they form.

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References and links

ORIGINAL RESEARCH PAPER de Lichtenberg, U. *et al.* Dynamic complex formation during the yeast cell cycle. *Science* **307**, 724–727 (2005)