



A study in yeast provides the first explicit evidence for a possibly widespread mode of evolution in transcriptional regulatory networks — the insertion of new layers of control between existing regulatory relationships.

In the yeasts *Saccharomyces cerevisiae*, *Candida albicans* and *Kluyveromyces lactis*, mating requires a set of haploid-specific genes (HSGs) that are regulated by the transcription factor a1–α2 (a heterodimer composed of two homeodomain proteins). Booth and colleagues showed that in *S. cerevisiae* and *C. albicans*,

a1–α2 binds upstream of HSGs to directly repress them. However, in *K. lactis*, a1–α2 does not bind at HSGs but regulates them indirectly through the transcriptional activator, Rme1, which is required for mating in this species. Rme1 is present in the other species but does not regulate HSGs and is not required for mating.

The authors propose a model in which the ancestor of all three species used direct regulation of HSGs by a1–α2. Subsequently, HSGs in the *K. lactis* lineage lost their binding sites for a1–α2 and gained sites for Rme1. Because Rme1 itself is negatively

regulated by a1–α2, the overall regulatory output is maintained. Unlike *S. cerevisiae* and *C. albicans*, *K. lactis* requires starvation to trigger mating. Booth and colleagues showed that Rme1 is upregulated by starvation to induce mating. So, the intercalation of a new layer of control into a transcriptional network — in this case, regulation by Rme1 — can maintain the overall logic of the regulation but allow additional inputs to be incorporated.

‘Intercalary’ network evolution has been proposed previously, but this study provides the first direct evidence, as well as showing how it can provide novelty. The relatively simple steps involved suggest that similar changes could explain the evolution of a range of other transcriptional networks.

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**ORIGINAL RESEARCH PAPER** Booth, L. N., Tuch, B. B. & Johnson, A. D. Intercalation of a new tier of transcription regulation into an ancient circuit. *Nature* **468**, 959–963 (2010)