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Puzzling out transcriptional networks on a genomic scale

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Abstract

In silico searches of promoter sequence motifs, combined with analysis of microarray data, have revealed potential synergistic interactions within the yeast transcriptional regulatory network

Significance and context

Some transcription factors display greater-than-additive effects when they interact with each other and the transcriptional machinery at a promoter - a phenomenon known as transcriptional synergy. To achieve precise gene control and to integrate signals using a limited repertoire of effectors, the cell has developed modular promoters/enhancers containing multiple binding sites for different factors, and modular transcription factors with both DNA-binding domains and domains for interacting with other proteins or ligands. Transcriptional synergy, in parallel with this combinatorial strategy, increases both the specificity and efficiency of transcription. In addition, the eukaryotic transcriptional machinery seems to be designed to respond synergistically to multiple activators. Synergistic effects have been widely analyzed in the context of both promoters and enhancers and involve the cooperative assembly of higher-order nucleoprotein complexes. Despite the importance of this phenomenon, its study has been limited to a series of well known systems. Now, Pilpel *et al*. have attempted to uncover synergistic interactions on a genomic scale in yeast, using an elegant approach that can be extended to higher eukaryotes. They have screened microarray expression data and sequence data for statistically significant combinations of promoter motifs responsible for particular patterns of gene expression during the cell cycle, sporulation and various stress-response conditions. The results of their search are displayed as motif synergy maps, giving a global view of the connections between regulators of transcriptional networks.

Key results

Pilpel *et al.* first established a database of known and putative regulatory motifs (329 motifs, including 37 known) and identified (using ScanACE12) the yeast promoters containing each motif. To assess the impact of each motif, or motif combination, on gene expression, they estimated the overall similarity of the expression profiles of all the genes containing that motif, in different physiological conditions (the expression coherence score). A pair of motifs was operationally considered as 'synergistic' if the expression coherence score of genes containing both motifs in their promoters was

significantly greater than that of genes containing either motif alone. Note that this is not formally equivalent to the concept of transcriptional synergy.

The authors identified several experimentally established transcriptional motif associations as well as many new 'synergistic' combinations. This analysis was, however, based only on co-occurrence of combinations in the same upstream region. To investigate further, the authors analyzed synergistic motif pairs for preferences in their relative locations within promoters (that is, whether one motif of the pair tends to be located closer to the ATG than the other). Analysis of the 115 identified synergistic pairs showed a significant orientation bias when compared with a random control set of motif pairs (18%, compared to 6% in the control sample). This confirms the notion that motif orientation is relevant to achieving synergy.

To unravel higher-order interactions between transcription regulators that participate in different cellular processes, Pilpel *et al*. generated a motif synergy map displaying the functional associations between motifs. The map shows an important degree of connectivity, reflecting the numerous synergistic interactions formed by a few motifs. It also suggests that a small number of transcription factors associating in various combinations may be sufficient to generate a panoply of expression patterns.

The authors point out that the availability of a motif synergy map may be useful for annotating the regulatory role of new motifs that co-cluster with known motifs (the 'guilt by association approach') and for predicting expression profiles based on promoter-motif composition. Such predictions will also be instrumental for dissecting the complex architecture of transcriptional networks in more complex eukaryotes.

Reporter's comments

To be functional, a transcription complex requires precise spatial arrangement of its components. Thus, the results presented here will obtain further support if an analysis of the spacing and phasing (and not only the orientation or position with respect to the ATG) of synergistic motif pairs is carried out. Transcriptional synergy might explain the phenotypic pleiotropy of mutations in transcription factors (as they cooperate in different pathways) and probably underlies haploinsufficiency (the situation in which an abnormal phenotype results from inactivation of one allele at a diploid locus). Thus, it is predictable that this kind of research will attract a lot of attention, especially in humans, for whom haploinsufficiency of an increasing number of transcription factors is being documented.

Table of links

Nature Genetics

References

1. Pilpel Y, Sudarsanam P, Church GM: Identifying regulatory networks by combinatorial analysis of promoter elements. Nat Genet. 2001, 29: 153-159. 1061-4036

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