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Ensemble regulation of large gene systems

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We report a novel, ensemble mechanism of transcriptional regulation where a large ensemble of transcription factors and histone remodeling enzymes quantitatively co-regulates a similarly large number of genes across all human chromosomes. We discovered this many-to-many type of combinatorial regulation by a rigorous meta-analysis of ENCODE, transcriptomics, phosphoproteomics, and knockout experiments. A specific ensemble of hundreds of jointly binding pairs of ~50 regulators integrates a wide spectrum of environmental and cellular signals from the mTORC1, JAK/STAT, and PI3K networks. This ensemble accurately co-regulates the transcription of ~170 genes that code for ribosomal proteins and hence protein synthesis, across ~28,000 samples of diverse normal, stressed, and cancer cells. The ensemble includes specific and unusually large pre-initiation complexes and determines a single direction for intensive transcription. We implicate new regulators in transcriptional amplification (i.e., steep induction of a large number of genes), which is present in embryonic stem cells as well. Rapid responses to modified conditions are facilitated by interactions among regulators that selectively activate or repress multiple functions of KAT2A, KDM2B, and SIX5. Genome-wide enrichment patterns of regulator binding sites indicate that similar ensemble mechanisms may govern other gene systems and fundamental biological processes.

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