**Figure Legend**

**Figure 1**

Schematic of the EN-CODEC companion resource. Columns list cell types and rows list assays. Pink box: “top-tier” cancer-associated resources in ENCODE. Yellow box: cell types with several assays in the main ENCODE Encyclopedia. Green box: our cell type specific analyses on top-tier cell lines. Blue box: our merged analyses on many cell types. The content of our resources (annotations, networks, background mutation rate) are shown in the dotted black box.

**Figure 2**

Background mutation rate (BMR) modeling and burden analysis. (A) Improvement of BMR estimation by accumulation of principal components of multiple genomic features (B) regression coefficients of remaining features in breast cancer after incorporating MCF-7 replication timing; (C) significantly burdened genes using coding regions, noncoding elements  (TSS), and extended genes, alongside germline mutational status in liver cancer; (E) expression of BCL6, which is only identified as recurrently mutated using extended genes, is correlated with patient survival.

**Figure 3**

Integration of ENCODE networks with expression profiles from cancer patients. (A) Heatmap of regulation potentials of TFs/RBPs to drive tumor-to-normal expression changes; red indicates up-regulation and blue means down regulation; (B) Elevated MYC regulation activity is associated with reduced disease specific survival (DSS) in breast cancer (top); MYC knockdown in MCF-7 leads to significantly larger expression reduction in MYC target genes (solid line); (C)  (i) MYC expression is more positively correlated with its target genes as compared to other TFs; (ii) MYC frequently form FFLs with NRF1, and these are mostly coherent; (iii) in the MYC-NRF1 FFLs, or-gate logic predominates. (D) Elevated SUB1 regulation activity is associated with increased overall survival (OS) in lung cancer (top); SUB1 knockdown in HepG2 leads to reduced target gene expressions.

**Figure 4**

Network hierarchy analyses. TFs are organized into layers such that TFs that tend to regulate other TFs are placed on top, and TFs that tend to be regulated by other TFs are placed on bottom. (A) The generalized network: TFs in top layers are enriched with cancer associated genes and demonstrate larger regulation potentials to drive tumor-to-normal gene expression changes. (B) Cell type specific network using K562 and GM12878: top layer TFs more significantly drives tumor-normal differential expression; also, bottom layer TFs are more often associated with burdened binding sites.

**Figure 5**

Network rewiring analysis. Green and red designate edge gain and loss respectively. (A) Rewiring index in a model for CML by direct edge counts using both proximal and distal networks (top) and by gene community analysis (bottom). (B) Examples of network rewiring for specific TFs in multiple cancer types; (C) conceptual schema for rewiring towards or away from a stem cell-like state; (D) genomic features associated with gained or lost edges.

**Figure 6**

(A) Schematic for stepwise prioritization scheme; first we prioritize large-scale regulators, then elements and single nucleotides. (B) Small scale validation results from luciferase assays using mutations prioritized in (A); (C) an example for multiscale integrative analysis on Sample 5. The figure shows multiple scales of functional genomics data including large-scale Hi-C linkages, zooming into an individual element, with histone marks and DNase hypersensitivity tracts and a variety of TF binding events, and then to the nucleotide level, where a motif of FOSL2 is disrupted.