PNAS Plus Significance Statements

Regulatory interplay of Cockayne syndrome B ATPase and stress-response gene *ATF3* following genotoxic stress

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Genotoxic attack results in temporary arrest of RNA synthesis. Mutations in the DNA repair factor Cockayne syndrome B gene product (CSB) that are responsible for the Cockayne syndrome phenotype lead to clinical features such as developmental and neurodegenerative defects and photosensitivity. In UV-irradiated CSB-deficient CS1AN cells, certain genes remain permanently repressed by the activating transcription factor 3, the product of a stress-response gene, which cannot be removed from promoter by the transcription machinery. We suggest (pp. E2261–E2270) that transcriptional defects observed in UV-irradiated CSB-deficient cells result from the permanent transcriptional repression of certain genes as well as from defects in DNA repair.

Target inference from collections of genomic intervals

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Recent innovations facilitate collecting genome-wide data from organisms, tissues, or individual cells. Analysis of the data commonly produce long lists of genomic intervals whose meaning is context-dependent. For example, an interval may signify a genomic region of cancer-related DNA copy number variation. We propose (pp. E2271–E2278) a method of explaining such data in terms of a much smaller number of fundamental recurrent intervals called "cores." Cores are useful, first, as a basis for studying subpopulation structure in a given primary tumor or metastasis; and, second, in delineating patterns of copy number aberrations in a given cancer type.

piggyBac transposase tools for genome engineering

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DNA transposons that translocate by excision from a donor site and insertion into a target site are often used for genome engineering by insertional mutagenesis and transgenesis. The *piggyBac* element is especially useful because it can excise precisely from an insertion site, restoring the site to its pretransposon state. Precise excision is particularly useful when transient transgenesis is needed, for example, in the transient introduction of transcription factors for induced pluripotent stem cell production. We have used (pp. E2279–E2287) mutagenesis to generate an Excision$^+$ Integration$^-$ transposase that allows *piggyBac* excision without potentially harmful reintegration. These mutations likely lie in a target DNA-binding domain.

Targeting of the MNK–eIF4E axis in blast crisis chronic myeloid leukemia inhibits leukemia stem cell function

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Cancer stem cells (CSCs) frequently acquire the ability to self-renew and persist in their hosts by coopting normal stem cell programs. Blast crisis (BC) chronic myeloid leukemia is a prototypic example, as the acquired activation of β-catenin signaling that enables BC CSC function is also important in normal hematopoietic stem cell maintenance. In identifying eIF4E phosphorylation by the MNK kinases as a necessary step in β-catenin activation in BC CSCs, but not normal hematopoietic stem cells, we define (pp. E2298–E2307) a therapeutic target in BC. Our studies suggest that clinical trials with MNK kinase inhibitors are warranted in BC chronic myeloid leukemia.

Chloride transport-driven alveolar fluid secretion is a major contributor to cardiogenic lung edema

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This study (pp. E2308–E2316) describes a novel mechanism for the formation of cardiogenic lung edema, a potentially fatal complication of left heart disease that was previously attributed to passive fluid filtration across an intact alveolo-capillary barrier. Instead, we demonstrate that a major part of cardiogenic edema results from active epithelial secretion of Cl^- and secondary fluid flux into the alveolar space. Transepithelial Cl^- secretion is triggered by inhibition of epithelial Na^+ uptake and mediated via cystic fibrosis transmembrane conductance regulator (CFTR) and Na^+-K^+-$2Cl^-$ cotransporter 1 (NKCC1), providing a mechanistic explanation for extrarenal effects of furosemide in lung edema.

Integrated platform for genome-wide screening and construction of high-density genetic interaction maps in mammalian cells

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While genomes are being sequenced at an accelerating pace, the elucidation of the function of human genes and their interactions remains a formidable challenge. Genetic interaction maps, which report on how genes work together, provide a powerful tool for systematically defining gene function and pathways. Here (pp. E2317–E2326) we present the complete quantitative framework underlying our recently developed approach for systematic mapping of genetic interactions in mammalian cells and demonstrate its broad potential. Maps obtained in different cell types and treatment conditions dissect context-dependent pathways. Our approach can provide a rational basis for defining combination therapies by targeting genes with strong genetic interactions.