The DNA Damage-Control Network: a New Class of Cancer Genes Discovered in Bacteria

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Cancer genes can be divided into two broad functional classes: the "gatekeepers", which change cellular properties to more cancer-like; and the genomic "caretakers"—DNA repair genes that suppress cancer by suppressing genomic instability, thus reducing mutations in gatekeeper genes. Most DNA damage that caretaker pathways ameliorate arises endogenously in cells. We report networks that identify a third functional class: the "DNA damage-control genes" using *Escherichia coli* with translation to human. We reasoned that genes that affect endogenous DNA-damage levels would be cancer genes because their perturbation could increase DNA-damage levels above repair capacity, causing repair deficiency *without* mutations in caretaker genes, and that these would be highly conserved metabolic and other genes.

Damage-control network discovered: Using high-throughput screens for *E. coli* that fluoresce when they experience DNA damage, we screened an overexpression library of all *E. coli* genes, to model gene amplifications that drive many cancers. We identified 238 DNA-damage-promoting genes. Only 8% are traditional "caretakers". The rest are a new class of DNA-damage-affecting genes.

Human damage-control genes in cancer: We identified 282 human homologs. These are highly significantly overrepresented in cancer-driver genome databases. Only 5% are traditional caretakers, implying a new cancer-gene functional class. We overproduced and have validated 25 as genuine human damage-promoting genes in human cells. Thus, these are genuine human DNA damage-control genes. These represent genes that would otherwise be mis-diagnosed as gatekeepers or cancer-role unknown. These data indicate cancer-promoting roles of many identified and some new cancer genes.

Network deconvolution: We developed tools to deconvolute functions in large protein networks, and parse how damage-control proteins promote damage. Using a 93-gene mutation-network as test-case, we successfully assigned function to >50% with broad function-based screens (*Science* 2012, now 65%, submitted). The human homologs of a DNA-damaging group in this test network are also overrepresented among cancer drivers. We are creating toolkits of synthetic proteins to trap and label specific DNA damages (*eLife* 2013; *Nat Comm* 2013) and their causes (submitted). We report the sorting of the bacterial damage-control network into bins of mechanisms of action with these tools. We also developed tools for forward genomics in *E. coli*—allowing rapid deconvolution of causative mutations from screens after whole-genome sequencing (submitted).

This project discovered a new functional class of cancer genes and created platforms for deep translation across phyolgeny from simple models to human disease.