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Commentary

Genome-Wide RNAi for DNA-Damage Response and Radiation Defense

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DESCRIPTION

Human cells are severely damaged by ionizing radiation, and DNA Double-Strand Breaks (DSBs) are thought to be the primary cytotoxic lesions triggered. Tumorigenesis is influenced by improper DSB processing, and numerous inherited diseases with a propensity for cancer are caused by mutations in DSB response genes. Here, we carried out a thorough search for genes that shield animal cells from ionizing radiation. In a genome-wide Ribonucleic Acid (RNA) interference screen for increased ionizing radiation sensitivity in germ cells, 45°C. Elegans genes in total were discovered. These genes include novel genes, such as human illness genes not previously connected to deficient Deoxyribonucleic Acid (DNA) damage responses, as well as orthologs of well-known human cancer propensity genes. Seven genes were crucial for apoptosis following exposure to radiation, and eleven genes were also affected by knockdown when radiation-induced cell-cycle arrest was present. On the basis of enhanced sensitivity to the DNA-damaging cancer medicines cisplatin and camptothecin, the gene set was further grouped. The fact that almost all genes are conserved across animal phylogeny and that their knockdown in human cells causes radiation sensitivity directly demonstrates their significance for humans. This group of genes is crucial for future cancer profiling and therapy development.

The cell cycle is momentarily stopped to allow for DNA repair by the DNA damage checkpoint, the first pathway known to be triggered in response to DNA damage. The checkpoint pathway uses the evolutionarily conserved Ataxia Telangiectasia Mutated (ATM) and ATR (ATM- and Rad3-related) kinase cascades to convey signals from DNA damage sites to the cell cycle machinery. In Drosophila cells, we performed a genome-wide RNA interference (RNAi) screen to find previously undiscovered genes and pathways necessary for the G2-M checkpoint brought on by DNA Double-Strand Breaks (DSBs). In addition to revealing the coordinated actions of specific classes of proteins, such as those involved in DNA repair, DNA replication, cell cycle control, chromatin regulation, and RNA processing, our large-scale analysis offered a systems-level understanding of the G2-M checkpoint. Also, we discovered previously unknown functions for the DNA damage response genes mus101 and mus312 through the screen and *in vivo* investigation.

Crucial for DSB repair, as well as the DNA replication preinitiation complex, also participate in the G2-M checkpoint. Our findings shed light on the various pathways that connect DNA damage to the pathway for checkpoint signaling. It is now known that DNA damage causes changes in microRNA (miRNA) expression. A miRNA microarray analysis will describe the miRNA profiles of various cell types and determine whether they share a core miRNA signature when responding to DNA damage. By either triggering the transcription of miRNA genes or by directly engaging with the processing and maturation machinery of miRNAs, DNA damage modifies the expression of miRNAs. More research is clearly needed to determine whether DNA damage impacts how miRNAs are degraded or modified, which in turn affects how miRNA expression is regulated.

We offer an experimental and computational method to automatically phenotype cell populations through high-throughput imaging and multipara metric computational analysis, creating a phenotypic map of a genome-wide set of RNAi-mediated perturbations. Around 10% of the targeted transcripts showed phenotypic alterations after being reduced by RNA interference (RNAi). By using a computational technique known as distance metric learning, which can learn a measure of (dis)similarity from a group of examples and extend this to unseen associations, the similarity or dissimilarity of phenotypes was measured from multipara metric descriptors.

To generate theories regarding the roles of the genes, the obtained measures of phenotypic similarity for each RNAi perturbation were displayed in a map. Unexpected associations may be found because the method is unbiased. In this study, we looked into four previously understudied genes and discussed how they function in the DNA Damage Response and Repair (DDR).

Many cellular functions, such as cytoskeleton reorganization, signaling, cell division, and cell survival, are broadly reflected by cell morphology. The method gives us the ability to identify

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components in a wide range of processes, much as forward genetic screens. Although it might miss modulators that could be found with targeted but more sensitive assays, we think that this strategy assures coverage of a wide range of symptoms and for the examination of numerous functions of a single gene. Nonetheless, it makes it easier to analyses different aspects of a single gene's function and identify unexpected functional connections.