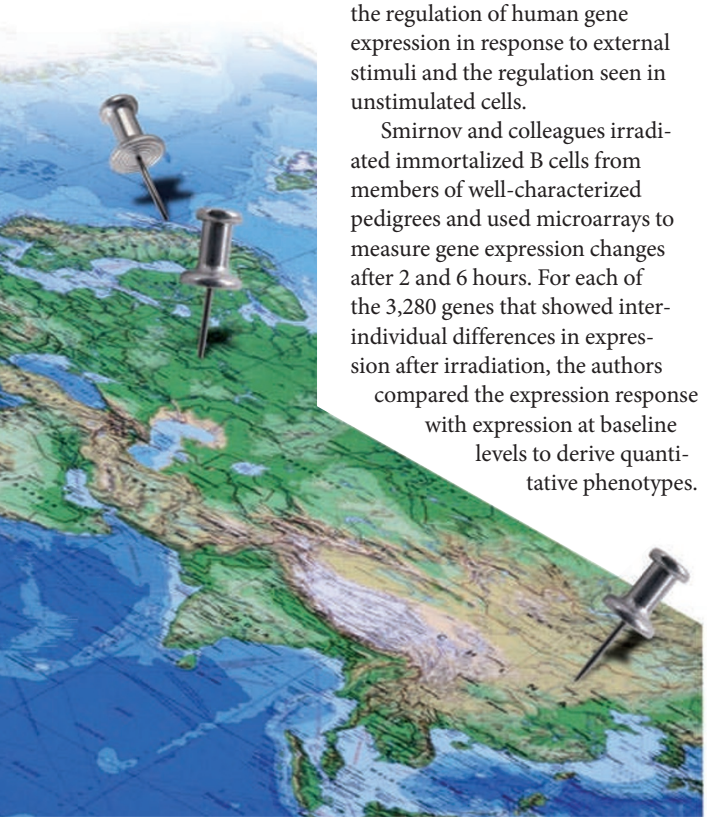
GENETICS OF GENE EXPRESSION

Putting radiation response on the map



Mapping the genetic variation that underlies differences in gene expression between individuals provides new insights into mechanisms of gene regulation and the genetic basis of phenotypic variation. A new study on human cells explores the genetic basis of response to a medically important exposure: ionizing radiation. The findings highlight fundamental differences between the regulation of human gene expression in response to external stimuli and the regulation seen in unstimulated cells.

Smirnov and colleagues irradiated immortalized B cells from members of well-characterized pedigrees and used microarrays to measure gene expression changes after 2 and 6 hours. For each of the 3,280 genes that showed inter-individual differences in expression after irradiation, the authors compared the expression response with expression at baseline levels to derive quantitative phenotypes. These phenotypes were then used in linkage studies that correlated differences in expression response to SNPs located across the genome. Significant linkage was seen for more than 1,250 of these genes, including some already known to function in the response to radiation.

The variants that underlie these linkage signals suggest a strikingly different mode of gene regulation in response to radiation compared with baseline regulation. Whereas *cis*-regulation dominates in unstimulated cells, the vast majority of SNPs that showed linkage to radiation-induced expression suggest *trans*-regulation (that is, they lie more than 5 Mb from the gene they regulate). This is similar to responses to external stimuli that have been studied in *Caenorhabditis elegans* and yeast. The authors also identified several regulatory 'hot spots' — genomic regions of 5 Mb that show evidence of regulating multiple target genes.

Family-based association mapping was used to confirm and refine the findings. For example, the authors confirmed that one radiation-responsive gene, *BAX*, was *trans*-regulated and they showed that SNPs in a known regulator of *BAX*, *TP53BP2*, were responsible for the linkage. For *trans*-linkage peaks that did not contain a regulatory candidate, the genes that lie under the peak were prioritized for association testing using a text-mining approach to search for evidence of a regulatory relationship with the target. This approach identified potential *trans* regulators for 13 radiation-responsive genes. Validation that the authors had identified genuine *cis* and *trans* regulatory relationships came, respectively, from evidence of allele-specific differences in the expression response and RNAi-based knockdown experiments to confirm the effects of candidate *trans* regulators on their targets. Interestingly, as well as transcription factors, the *trans* regulators that were identified include less obvious candidates, such as the cell surface receptor *CD44*.

These findings provide new insights into specific gene-regulatory relationships that underlie the response to radiation in human cells, and lay the ground for applying a similar approach to charting the regulatory landscape for other important stimuli. They also identify genetic variants that contribute to differences in response between individuals, which could be used to tailor radiation-based treatments according to genotype.

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ORIGINAL RESEARCH PAPER
Smirnov, D. A. *et al.* Genetic analysis of radiation-induced changes in human gene expression. *Nature* 6 Apr 2009 (doi: 10.1038/nature07940)
FURTHER READING Rockman, M. V. & Kruglyak, L. Genetics of global gene expression. *Nature Rev. Genet.* **7**, 862–872 (2006)