Using RNA interference to identify genes that protect from cancer

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Cancer is caused by genetic changes[1]. Oncogenes harbor activating mutations that cause or promote cancer, whereas tumor suppressor genes[2] protect from cancer. In this model, genetic changes in one copy of an oncogene, but both copies of a tumor suppressor gene are required to initiate cancer. This simple model is complicated by the fact that more than one genetic change is usually required to initiate cancer, and that other so called epigenetic changes (such as promoter hypermethylation) are also important.

Myelodysplastic syndromes are malignant disorders of the bone marrow that show insufficient production of blood cells and harbor the risk of progressing to acute myeloid leukemia. The 5q syndrome is a distinct subtype that is characterized by loss of genetic material at chromosome 5q31, a characteristic morphology of the bone marrow, and a fairly benign clinical course. We would expect to find a tumor suppressor gene in the deleted region on chromosome 5, but no genetic changes on the other allele of chromosome 5 could be detected. The traditional strategies to identify the genetic changes responsible for the 5q syndrome therefore didn't work.

Research by Benjamin Ebert et al. presented at the American Society of Hematology meeting in December and now published in Nature[3] claims to have finally identified the genetic change responsible for 5q syndrome. They used RNA interference to in turn knock out each of the 40 genes in the common deleted region on chromosome 5q31. They observed the phenotype of human hematopoetic progenitor cells transfected with short hairpin RNAs. The shRNA targeting the gene RPS14 recapitulated the phenotype of patients with 5q syndrome.

To confirm the role of RPS14 in 5q syndrome, RPS14 was overexpressed in hematopoetic cells from patients with 5q syndrome and indeed reverted the erythroid differentiation effect. Reduced expression or inactivating mutations of the one remaining RPS14 gene in 5q syndrome patients was ruled out by sequencing and gene expression profiling.

Further evidence for the importance of RPS14 in 5q syndrome comes from studies

of related genes. Expression of RPS14 is required for proper function of the 40s ribosomal subunit. Germline mutations of two other ribosomal proteins, RPS19 and RPS24, have been identified in the congenital disorder Diamond-Blackfan anemia, and the disease in these children has similar features.

As a medical student, I was fortunate enough to listen to Alfred Knudson give a talk about is two-hit hypothesis of tumor suppressor genes[2], and I was fascinated by cancer genetics ever since. Genetics continues to be a driving force in our understanding of cancer. The next big step in the 5q syndrome story will be a better understanding of why the drug lenalidomide works so well in this disease, and how this relates to RPS14 function. More information about the Ebert paper can be found in this Nature News and Views article.

fn1. Croce C. Oncogenes and Cancer

fn2. Knudson AG. Mutation and Cancer: Statistical Study of Retinoblastoma

fn3. Ebert BL et al. Identification of RPS14 as a 5qsyndrome gene by RNA interference screen