HYPOTHESIS

The null oncogene hypothesis and protection from cancer

M P Davenport, R L Ward, N J Hawkins

Tumour progression involves the inactivation of tumour suppressor genes and the activation of proto-oncogenes. Inactivation of both copies of a tumour suppressor gene is required for carcinogenesis, while germline deletion or inactivation of one copy results in an increase in the risk of cancer and is responsible for many of the known hereditary cancer syndromes. In contrast, activation of only one copy of a proto-oncogene is required for carcinogenesis. Germline deletion or inactivation of one copy of a proto-oncogene halves the risk of activation at this locus. We propose that studies of high risk cancer patients will show such “null oncogene” mutations.

Most hereditary cancer syndromes, such as familial adenomatous polyposis (FAP) and the Li-Fraumeni syndrome, involve the germline inactivation of “tumour suppressor genes” and are dominantly inherited.1 Tumour suppressor genes normally function as “stop” signals for cell division, but are inactivated during carcinogenesis, resulting in unregulated cell division. However, the presence of one functional copy is sufficient to maintain function, and thus both copies of the gene need to be inactivated for carcinogenesis. (Knudson’s “two hit” hypothesis).2 If the spontaneous mutation rate is M, the probability of one mutation occurring at a given tumour suppressor gene locus is 2M (that is, two alleles, sum of M for each allele). The probability of the second allele being affected is M (there being only one remaining normal copy). Thus the probability of both copies of a tumour suppressor gene being inactivated independently (in sporadic cancer) is the product of these; 2M × M = 2M². Since most familial cancers involve the constitutive inactivation of one copy of a tumour suppressor gene, only the second “hit” (with probability M) is required to inactivate the remaining functional copy (fig 1).

Null oncogenes and animal models

Animal models clearly provide an opportunity to explore the role of null oncogenes. Interestingly, some models of this phenomenon may already exist. A murine model has been developed involving a heterozygous “knockout” mouse in which one copy of the Grb2 gene has been inactivated.3 Grb2 (growth factor receptor bound protein-2) is an adaptor protein implicated in several human malignancies, including breast carcinoma.5 When these heterozygous Grb2 knockout mice were bred with transgenic mice genetically predisposed to the development of mammary tumours, the time taken to develop these tumours almost doubled.6 One explanation for this event is that it is the result of a reduced probability of an activating mutation, although the Grb2 gene in the tumour was not sequenced. However, the effects of reduced gene function may also have been of importance, since it was observed that the growth of the normal breast tissue in the heterozygous Grb2 knockout mice was significantly retarded.6

This illustrates a potential secondary effect of a null oncogene. If the presence of only one functional copy of a proto-oncogene quantitatively decreases the function of the gene in normal cellular replication (a smaller “Go” signal), this may act independently to reduce the risk of neoplastic progression. For example, a reduction in cell numbers or cell turnover in an organ may reduce the number of cellular “targets” in which mutations can arise. Similarly, decreased cell turnover may reduce the proliferation of cells carrying mutations in other genes, thereby decreasing the possibility of these cells acquiring further mutations.7 Reduced basal levels of expression of proto-oncogenes may also
inhibit the carcinogenic effects of mutations in other genes. Proto-oncogene protein products are components of complex signalling pathways leading to cell proliferation, and other members of these pathways are reliant on normal levels of expression of the proto-oncogene to transduce their signals. Where a particular proto-oncogene is a rate limiting step in an important signalling pathway, reduced levels of expression owing to the null oncogene effect will act as a “bottle neck” to negate the effects of mutational activation of other genes in the pathway.

The relative importance of the decreased risk of mutational activation and the decreased gene function of a proto-oncogene may vary depending on the gene and tumour involved. In many cases, gene function may be unimpaired by the presence of only one functional copy of the gene. However, where normal gene function is reduced, this may act synergistically with the reduced probability of mutational activation of the proto-oncogene to reduce the risk of cancer further. Future proto-oncogene “knockout” studies in mice predisposed to cancer should aim to sequence the proto-oncogene within the tumour and to measure the rate of cell proliferation. This will allow a more detailed analysis of the effects of a null oncogene.

Null oncogenes in human populations

To date, there has been no systematic search for germline null mutations of oncogenes. In fact, since the presence of cancer is the usual criterion for the study of oncogenes, there is an inbuilt bias against the detection of protective mutations. Analysis of the null oncogene effect in human populations will first require the identification of a sufficient number of carriers of the genes.

Both gain of function and loss of function mutations of the RET proto-oncogene have been found. Germ line loss of function of one copy of the RET proto-oncogene is identifiable because of its association with Hirschsprung disease (congenital megacolon). Germ line mutations leading to gain of function of the RET proto-oncogene are associated with multiple endocrine neoplasia syndrome type 2 (MEN 2). Somatic mutations in the RET proto-oncogene are also frequent in sporadic medullary thyroid carcinomas. The null oncogene hypothesis predicts that the germline inactivation of the RET proto-oncogene in Hirschsprung disease patients should lead to lower rates of thyroid and endocrine neoplasms in these patients. Studies of the rates of endocrine neoplasia in Hirschsprung disease patients are complicated by a small subgroup of patients who have point mutations in either codons 609, 618, or 620, and have both Hirschsprung disease and MEN 2. However, these point mutations represent only a small minority of the mutations found in Hirschsprung disease, many of which include large deletions or frameshifts which result in decreased RET expression without constitutive dimerisation. The hypothesis predicts that patients with a null mutation in the RET proto-oncogene should have lower rates of sporadic thyroid carcinoma and perhaps other endocrine neoplasms than the general population (fig 2).

### Figure 1

A simplified model of the development of cancer. Carcinogenesis requires both inactivating mutations (\(\times\)) in tumour suppressor genes and activating mutations (\(\checkmark\)) in proto-oncogenes. The probability of a mutation inactivating a tumour suppressor gene or activating a proto-oncogene is \(M\). In sporadic cancer, the risk of inactivating both copies of a tumour suppressor gene and activating at least one copy of a proto-oncogene can be calculated as \(4M^3\) (A). Most hereditary cancers involve the constitutive inactivation (black) of a tumour suppressor gene, increasing the risk of cancer to \(2M^2\) (B). By contrast, the constitutive inactivation of a proto-oncogene produces the “null oncogene effect” and reduces the risk of both sporadic and familial cancer by half (C).

A  Sporadic cancer:

- Tumour suppressor gene: \((2M^2)\)
- Proto-oncogene: \(2M\)
- Cancer: \(4M^3\)

B  Familial cancer:

- Tumour suppressor gene: \(M\)
- Proto-oncogene: \(2M\)
- Cancer: \(2M^2\)

C  Familial cancer and “null oncogene effect”:

- Tumour suppressor gene: \(M\)
- Proto-oncogene: \(M\)
- Cancer: \(M^2\)
Null oncogene mutations are unlikely to be very common, both because they have not been observed during studies of oncogenes to date and because homozygosity for null oncogene mutations may be lethal. The search for other null mutations in human proto-oncogenes should focus on long term survivors from populations at high risk of cancer. For example, activating point mutations of the K-RAF proto-oncogene occur in up to 50% of colon cancers. However, the null oncogene hypothesis predicts that mutations which result in a complete loss of function of RET should lead to Hirschsprung disease and a reduced rate of thyroid carcinoma. Identification of patients carrying null oncogene mutations will enable direct analysis of the effects of these mutations on the risk of cancer in humans.

CONCLUSIONS  

Theoretical predictions of the effects of germline null oncogene mutations suggest that functional haploidy at oncogene loci may result in reduced rates of cancer. This prediction is supported by the results of experiments in transgenic mice. Germline mutations of proto-oncogenes are one obvious cause of oncogene inactivation, and the discovery of null oncogene mutations in Hirschsprung disease suggests the possibility that these mutations may be present in the human population. It is also important to consider that epigenetic modification of genes may lead to inactivation of one copy of an oncogene. This is interesting to consider in the context of genomic imprinting, where monoallelic expression of both copies of a gene occurs. This may explain why patients with the FAP phenotype have a reduced risk of cancer compared to those with the MEN 2 phenotype.

Figure 2 Predicting a decreased risk of cancer in patients with Hirschsprung disease. Germline RET mutations that result in a constitutive dimerisation of receptor (gain of function) may lead to MEN 2A [A]. Mutations that lead to decreased expression of the receptor but constitutive dimerisation of the remaining receptor result in Hirschsprung disease and MEN 2A [B]. However, the null oncogene hypothesis predicts that mutations which result in a complete loss of function of RET should lead to Hirschsprung disease and a reduced rate of thyroid carcinoma [C].16 17

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