

1998 Runme Shaw Memorial Lecture: Somatic Evolution of Cancer

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Abstract

The interpretation of cancer as a somatic evolutionary process involving genetic mutation followed by selection, traces its origins to the early years this century. The dramatic developments in molecular genetics have substantiated these early ideas. Through the application of positional cloning and genomic analysis, many mutations in particular genes, both dominant oncogenes and tumour suppressor genes have now been found in a wide variety of tumours. Other genetic events such as non-disjunction leading to haploid expression of a gene and so reduced gene dosage, or epigenetic changes following, for example, changes in methylation patterns leading to reduced or increased gene expression, may also play critical roles in the progression of a cancer.

The analysis of mutations at different stages of colorectal cancer provides a good model for following the initiation and progression of a cancer. Mutations in the APC gene, which explain familial adenomatous polyposis, occur in a high proportion of sporadic colorectal carcinomas and appear to be the earliest known changes. Patterns of mutation in the gene suggest dominant negative or gain of function effects, and also reveal important low penetrance subpolymorphic missense mutations that nevertheless may have a very significant impact on the genetic contribution to colorectal cancer susceptibility. Mutations are also found in related genes in the APC pathway, such as β -catenin and E-cadherin. Mutations in mismatch repair genes (hMLH1 and hMSH2) have also been shown to occur, as well as reduced expression due to methylation changes, in 10% to 20% of sporadic colorectal carcinomas. In addition, mutations in the well known oncogenes p53 and ras are commonly found.

The growth of a cancer is a balance between the rate of cell division and the rate of cell death or apoptosis. Thus, genetic changes which reduce the probability of apoptosis, such as p53 and probably hMLH1, are as important a feature of the evolution of a cancer as those which enhance the independence (APC) and rate of cell division (growth factors). Simple models for the evolution of a cancer that take into account these two processes, show that cancers evolve initially by a series of finite increases in cell population size, following which there may be long periods of cell turnover during which there is an opportunity for further mutation and selection. This explains the long lag periods between the initiation and subsequent progression of most cancers.

Our rapidly developing understanding of cancers at the fundamental genetic level provides new opportunities for developing targeted treatments, as well as novel approaches to prevention and early detection.

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