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Special Lecture

Cancer as a Complex Developmental Disorder—Nineteenth Cornelius P. Rhoads Memorial Award Lecture[1]

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Abstract

The processes of differentiation and tumorigenesis have been long thought to be connected. The recent identification of *Patched*, a gene essential for *Drosophila* embryonic development, as a tumor suppressor has focused attention on the concept that tumorigenesis involves abnormalities of development. In fact, a large number of genes in the signalling pathway of the *Patched* gene are either tumor suppressors or oncogenes. This supports the concept that growth control is a critical requirement of differentiation, and that aberrant cellular development can contribute to malignancy. Whereas the identification of genes that result in dominantly inherited cancer syndromes has played a vital role in understanding cancer, the vast majority of "sporadic" cancers have properties of a complex genetic disease. Approaches to identify common alleles in cancer-associated genes promise to increase our understanding of the disease and aid the rational design of preventative and therapeutic strategies.

In the 25 years since the publication of analyses of RB[3] that led to the tumor suppressor concept (1), over 20 tumor suppressor genes have been cloned. Unlike the oncogenes, most tumor suppressor genes are not related to genes of known function or to each other. Therefore, the mechanism of action of most of these genes has been elusive and has impaired efforts to link tumor suppressor genes together in a pathway that connects events at the cell surface to the regulation of cell division in the nucleus.

Tumor Suppressor Genes and Embryonic Development

The NBCCS is an autosomally inherited disorder in which patients develop multiple basal cell carcinomas, typically appearing at an early age (2). Some NBCCS patients also develop medulloblastomas as well as jaw cysts, both of which display loss of heterozygosity for markers near the NBCCS locus on 9q22.3 (3, 4). In addition, these individuals are subject to a wide variety of development abnormalities including abnormal bone development and generalized overgrowth.

The human orthologue of the *ptc* gene was identified as the locus responsible for NBCCS, and *PTCH* is mutated in the germ-line of patients with the syndrome (5–8). The *PTCH* gene is also mutated in nearly all sporadic basal cell carcinomas, consistent with the model Knudson proposed for retinoblastoma (9). The *ptc* gene was first identified in a search for genes essential for embryonic development in flies, and it falls into a category of genes involved in the formation of the boundaries between the segments of the developing *Drosophila* embryo (10). This process is controlled by the interdependent secretion of two morphogens, WG and HH; by cells on either side of the segment boundary. Thus, HH protein induces the expression of WG, and this feedback loop functions for a critical period of development. This same pair of proteins is later used to provide directionality to the development of adult structures such as wings and legs (13–15).

HH binds to a complex formed by PTCH and the SMO protein, a 7-transmembrane, G-protein-coupled receptor (16, 17). After HH binding, SMO is activated, initiating a signalling cascade that includes the tyrosine kinase fused, costal2, and the *cubitus interruptus* gene product (a zinc finger protein; Ref. 18). The end result is the transcription of the *ptc*, *wg*, and *dpp* genes. The formation of new PTC protein serves to suppress SMO and shut off the signalling cascade. Thus, in the absence of PTC, there is constitutive signalling of SMO, independent of HH.

HH and WG Genes in Growth Control and Development

Most of the genes in the HH and WG pathways have been shown to be conserved in mammals and play equally critical roles in development (19–22). In addition, a remarkable number of these genes are either tumor suppressor genes or oncogenes (Fig. 1). For instance, homologues of *cubitus interruptus* and *wg* (*GLI1* and *WNT*, respectively) are oncogenes in mammalian cells (15, 23–25), whereas *ptc* and homologues of the WG and DPP signalling pathways (APC and MAD) are tumor suppressors (5, 6, 26, 27). Constitutive expression of HH in the skin leads to abnormal growth (28), and some basal cell carcinomas that lack PTCH alterations have activating mutations in SMO (29).

The *Wnt1* oncogene is frequently found at the integration site for mouse mammary tumor virus (24). The WNTs are expressed in cell-specific patterns in early development and play critical roles in the formation of several differentiated cell types (15). Mammalian homologues of the *frizzled* gene family are involved in the WNT signalling process (30), and vertebrate orthologues of WNT pathway members include glycogen synthase kinase 3B and β-catenin (31). The *APC* gene, a tumor suppressor, interacts with β-catenin (32–34), and mutations in APC eliminate its ability to down-regulate β-catenin (Fig. 1). Thus, pathways of gene products that are essential for cellular differentiation also contain proteins that provide both positive and negative signals for growth control (35).

TGF-β-related Genes

The DPP protein is also secreted by HH-responsive cells, and DPP is related to (TGF-β). TGF-β can act as a negative regulator of cell growth in many cell types (36, 37). The DPP receptor is a dimeric complex that signals via the *mad* gene product (38). Mammalian TGF-β family members include BMP-2 and BMP-4, which play crucial roles in the development of the limbs and gut. *DPC4*, a *mad*-related gene, is frequently deleted in pancreatic tumors and is

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[3] The abbreviations used are: RB, retinoblastoma; NBCCS, nevoid basal cell carcinoma syndrome; WNT, *wg*-related gene; TGF, transforming growth factor; *ptc, Drosophila Patched*; PTCH, *human Patched*; WG, product of the *wingless* gene; HH, hedgehog; SMO, smoothened; PTC, patched; BMP, bone morphogenetic protein; CDK, cyclin-dependent kinase; SNP, single nucleotide polymorphism; CGAP, Cancer Genome Anatomy Project; DPP, decapentaplegic; APC, adenomatous polyposis coli; MAD, mothers against DPP; pRB, retinoblastoma protein.

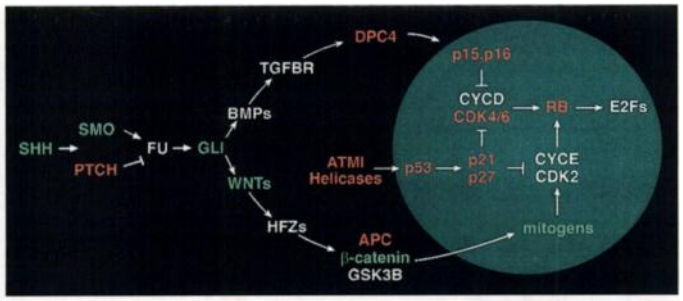

Fig. 1. Segment polarity gene pathways include tumor suppressors and oncogenes. The mammalian orthologues that act in HH signalling are shown, with tumor suppressors in *red* and growth activators/oncogenes in *green*. WNTs signal through mammalian DFZ2 homologues (*HFZs*) and cause the release of armadillo/β-catenin from its complex with APC and GSK3B. The β-catenin protein can stimulate cell division, perhaps working as other mitogens through the activation of cyclin E/CDK2. TGF-β and BMPs signal through cell surface receptors (*TGFBR*), DPC4, and related proteins. TGF-β has been shown to inhibit cell division though the inhibition of p27. The p27, p53, and p16 proteins have all been shown to function in the repression of phosphorylation of *RB*, the RB gene (see text, adapted from Refs. 43 and 47).

believed to act downstream of the TGF-β family of receptors (25). Finally, TGF-β signals can regulate the RB protein in the nucleus through the regulation of $p15^{INK4B}$ (39). Therefore, conserved signalling pathways initiated by the HH protein in *Drosophila* contain a number of the genes that are involved in tumor formation and/or growth control in mammalian cells. Both the WG/WNT and DPP/TGF-β/BMP pathways converge on the nucleus and regulate both cell division and differentiation.

Nuclear Tumor Suppressor Genes

Pathways linking the action of several nuclear tumor suppressor genes have been described previously (40). Several connections involve the activation of pRB by phosphorylation. Phosphorylated pRB forms complexes with members of the E2F transcription factor, resulting in the activation of genes required for cells to pass the restriction point in the G_1 phase of the cell cycle (41). The pRB protein is regulated by at least two cyclin/CDK complexes (42, 43). The p15 and p16 proteins repress the cyclin D-CDK4/6 complex, helping to explain why the loss of p15/p16 is a common event in tumors. The CDK inhibitor p21 can block the activity of both CDK2 and CDK4/6. DNA damage due to chemical agents or radiation leads to the accumulation of p53 protein. P53 induces the expression of p21 and prevents the cell from entering S phase with a damaged genome. Cells that cannot repair their DNA can be induced to undergo apoptosis.

Thus, many of the genes identified as tumor suppressors from human cancer pedigrees can be placed into cellular pathways that are essential for the growth control of cells. This knowledge suggests additional candidate genes that may be mutated in tumors and provides a number of cellular targets for cancer chemotherapy. If these pathways are indeed common to most tumor cells, then some of these compounds could have broad activity.

Cancer as a Complex Disease

Whereas identification of the genes that cause Mendelian cancer syndromes has led to the discovery of many of the loci mutated in sporadic tumors, there are likely to be numerous genes that contribute to cancer susceptibility. This suggests that cancer should be approached with the same methods used to study other complex diseases, such as diabetes and schizophrenia. One type of susceptibility locus would have a normal allele that would not confer any risk for cancer and another allele that would raise an individual's risk above the background, so that only some individuals with the susceptibility allele get cancer (Fig. 2*A*). This allele could require an environmental influence to have its effect, so that only individuals with both the environmental exposure and the genetic risk would be affected (Fig. 2*B*). Two examples of alleles of tumor suppressor genes that fit these models have been described. Laken *et al.* (44) identified an alteration in the *APC* gene that increases the length of a polyadenylate track in the gene and proposed that individuals with those alleles have a higher risk of colon cancer (44). Storey *et al.* (45) characterized a variant in the *P53* gene that may influence susceptibility to papilloma virus-associated cervical cancer. In some cases, it is also likely that multiple genes cause identical or indistinguishable phenotypes (Fig. 2*C*).

Several different approaches are used to identify the genes involved in complex diseases. These include the analysis of sibling pairs or twins, both of which are linkage-based approaches. Alternatively, association studies are used such as case control or cohort analyses. Analysis of sibling trios, in which the alleles inherited by affected individuals from their heterozygous parents are compared to nontransmitted alleles, shows a reduction in artifacts due to population stratification that can confound association analyses.

An approach that we have successfully used to identify the genes involved in complex diseases is direct gene analysis. In this approach, a candidate gene in which there is biological evidence to suggest involvement in a specific phenotype is scanned for mutations. These alterations are then compared to control individuals from the same population or cohort. The advantage of this approach is that each gene is selected to have a high probability of playing a role in the pheno-

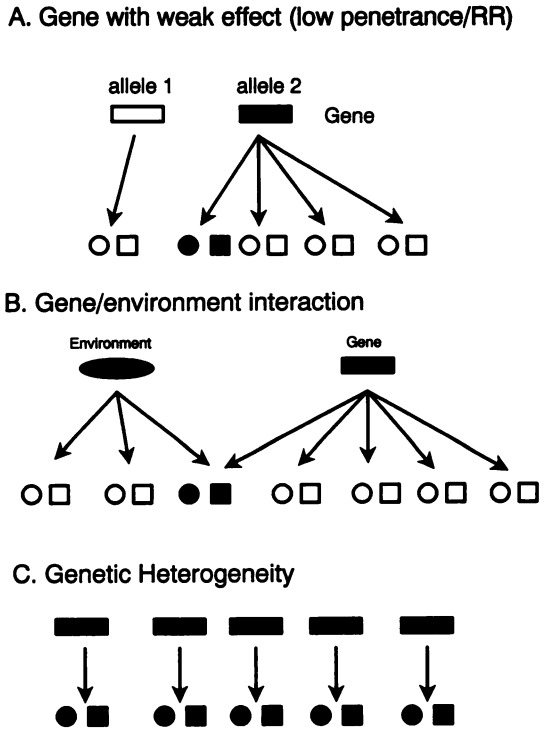

Fig. 2. Models for complex diseases. A complex disease can be caused by a combination of multiple genes, genetic and environmental factors, and genes with weak effects. In *A*, a gene is depicted with two alleles; one that confers no risk of disease (□), and a second that confers a raised risk for disease (■). Thus, some of the individuals that inherit allele 2 will develop the trait (cancer, for example). Such an allele is said to exhibit incomplete penetrance, because inheritance of the allele does not always confer disease and to have a low relative risk (*RR*). A gene's effect could depend on an environmental exposure (*B*) such that those that inherit the susceptibility locus also require interaction with a virus, radiation, chemical, and so forth. Thus, the genetic background modifies the risk of disease for exposed individuals (risk could be raised or lowered). Several different genes (*C*) could give rise to phenotypes that are hard to distinguish. In this scenario, studies of families are complicated when many families are combined in an attempt to map a gene by linkage analysis.

type. If as few as 1% of the subjects have an alteration in this candidate gene, then it is likely to be discovered in a reasonably sized sample. Direct gene analysis does not require the collection of family members, and for common diseases, an adequate sample can be obtained from any large hospital or medical center. Examples of the successful use of direct gene analysis include the identification of a deletion in the chemokine receptor 5 gene involved in HIV resistance (46) and the involvement of the *ABCR* gene in macular degeneration (47).

SNPs

The type of variation that is most often responsible for disease is a SNP. SNPs are particularly useful for genetic analysis because they are frequent (as many as 3 million in the human genome), and they can be genotyped by automated methodology, such as arrays or DNA chips (48). SNPs are potentially useful for population-based (linkage disequilibrium) methodologies. For these reasons, there are several efforts underway to systematically identify SNPs throughout the genome.

Because linkage disequilibrium normally does not extend over large distances, SNPs directly in genes are expected to be the most useful. The most valuable SNPs will be those in the coding region, particularly those that alter the amino acid sequence of the protein. For this reason, the National Cancer Institute has undertaken an effort to identify SNPs in cancer-related genes, which will be a component of the CGAP. This project will be a collaborative effort between our laboratory and the Laboratory of Population, headed by Ken Beutow, in conjunction with Carol Dahl and Bob Strausberg at CGAP and David Lipman at the National Center for Biotechnology Information. SNPs identified by the project, the Genetic Annotation Initiative, will be made publicly available for research in cancer and other diseases.

Cancer-associated genes will include oncogenes; tumor suppressor genes; genes involved in the regulation of the cell cycle, development, DNA repair, drug metabolism, and immune response; and genes involved in angiogenesis and other correlates of metastasis. In addition, genes that are aberrantly expressed in tumors and those that are exclusively expressed in important target organs will also be included in the analysis. The goal will be to reveal common variants in those loci that might influence the development, progression, or treatment of malignancies.

As a pilot project, our group has begun to explore the feasibility of directly scanning the coding region of genes for polymorphism. Because many of the genes of interest do not yet have their genomic structure determined, it is not practical to analyze the exons of the genes for variation. We have used RNA from immortalized B cell lines to amplify a single 250-400-bp segment from each of 300 cancer-related genes. Approximately 70% of the genes yielded a fragment of the expected size, indicating that those genes were expressed at detectable levels in B cell lines. These products are then used to detect variants that are then sequenced. To efficiently identify polymorphisms, we are using denaturing high-performance liquid chromatography (49). In this method, DNA is bound to a column by hydrophobic interactions at an elevated temperature (50–65°C), and under an increasing gradient of acetonitrile, DNA will elute from the column. Heteroduplex molecules elute before homoduplexes, allowing the detection of heterozygous samples. Samples displaying an apparent variation are then directly sequenced to identify the SNP. Using this approach, we have identified variation in genes such as ELK1, XPD, XPC, cyclins D2 and T2, and XRCC (data not shown).

SNPs will be confirmed by demonstrating the segregation of the alleles in families and by determining their frequency in different racial and ethnic groups. The production phase of the project will involve a diverse set of samples to capture alleles common to different racial groups. The analyses can be extended to RNA from cancer patients to detect rarer variants that are cancer associated and to tumor cell lines to detect somatic alterations.

Once complete, this project, in combination with other data from CGAP (50), will provide a much clearer picture of the role that genetic background contributes to either raising or lowering cancer risk. By also identifying those alterations that occur somatically in tumor cells as part of tumor formation or progression, those components in the environment that contribute to risk, and the variation of gene expression that accompanies tumorigenesis, there will be a much better understanding of the process. Only from this clearer vantage point can we be positioned to develop effective prevention, early detection, and treatment strategies for cancer.

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