1. THE ORIGIN OF CANCER

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INTRODUCTION

Cancer is a complex genetic disease. Work over the past fifty years confirms that the genetic alterations found associated with human cancers impair the function of pathways critical to controlling cell growth and differentiation. In aggregate, these genetic mutations allow a malignant cell to acquire a set of biologic attributes leading to autonomous proliferation and metastatic spread. Despite this paradigm, the precise nature and timing of each of the events that conspire to program the malignant cell remain incompletely understood.

Although familial cancer syndromes are responsible for only a minority of human cancers, the study of these kindreds has facilitated our understanding of cancer genetics. In many such syndromes, individuals inherit one defective, predisposing allele in the germline, and only later in life do they acquire a second loss of function mutation. As first described by Knudson, this "two hit" hypothesis helps explain such inherited cancer syndromes such as retinoblastoma and Wilms' tumors (1). Although the tumors in these patients express mutations in specific inherited genes, the finding that these tumors also harbor a myriad of other genetic changes indicates that further alteration by somatic mutation are required for tumor development (2).

However, the majority of human cancers lack a readily definable predisposing genetic defect and appear to be the result of a concert of acquired genetic alterations. Work from many laboratories, using both patient-derived material and experimental cancer models, have begun to define these malignant genetic mechanisms.

In spontaneously arising human cancers, we still cannot determine the exact number and nature of genetic alterations involved in the process of transformation from a normal cell to a malignant one. Since cancer encompasses more than 100 different types of malignant diseases with great heterogeneity of clinical characteristics, every tumor could hypothetically be completely unique. Thus, cancers, in general, could harbor an undecipherable number of genetic and epigenetic changes leading to their development.

Alternatively, pathogenesis of human cancers may be dependent on a distinct set of genetic and biochemical alterations that apply uniformly to most if not all human tumors. These changes may alter the functions of specific pathways involved in important biological functions and facilitate malignant transformation, endowing cells with specific changes in cell physiology, termed "acquired capabilities," ensuring their survival and continued success (3). In particular, cancer cells generate their own mitogenic signals, proliferate without limits, resist cell cycle arrest, evade apoptosis, induce angiogenesis, and eventually devise mechanisms for invasion and metastasis.

GENETIC REQUIREMENTS FOR CANCER

Epidemiologic analyses have shown that four to six rate-limiting events must occur before a tumor becomes clinically apparent (4,5). The changes that must occur are genetic and/or epigenetic in nature. Most of these events result from somatic mutations that occur infrequently or are induced by carcinogen exposure, and only in aggregate do they lead to the tumorigenic state.

The colorectal carcinoma model

In a seminal series of studies, Vogelstein and his colleagues described a stepwise genetic history of colorectal tumors (6). Since colorectal carcinoma develops intraluminally and tissue is readily available for examination, specific histopathological alterations that occur in cancer development are readily observed in different stages. By studying tissue derived from specific histopathologic stages, ranging from normal colonic epithelium to frank carcinoma, they catalogued genetic alterations specific for each stage, thereby developing a model that dissected an accumulation of separate genetic mutations that could in combination lead to malignancy (7,8).

A vast majority of early adenomatous polyps were found to exhibit an inactivated mutant form of the tumor suppressor gene, adenomatous polyposis coli *(APC)* (9). Alterations in this gene had been previously shown to be responsible for Familial Adenomatous Polyposis (FAP) (10,11). However, patients with germline mutations of *APC* have a greater risk for but do not necessarily develop colorectal cancer. In addition to the germline mutation, somatic mutation of the wild-type *APC* allele must also occur (9,12).

When they investigated intermediate size adenomas, they found that approximately half carry activating mutant *RAS* oncogenes (6,13). Interestingly, normal colonic epithelium harboring *RAS* mutations alone, do not lead to neoplasia (14), and these cells may eventually succumb to apoptosis (15), suggesting that other genetic alterations are necessary for *RAS* mutation to contribute to tumor formation. In a subset of larger