

Chapter 2

Cancer and Alcohol: An Overview of Tumorigenesis

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Abbreviations

AKT	Protein kinase B
APC	Adenomatous polyposis coli
BRAF	v-raf Murine sarcoma viral oncogene homolog B1
Bcl2	B-cell lymphoma 2
CRC	Colorectal cancer
Kras	v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
MAPK	Mitogen-activated protein kinase
PI3K	Phosphoinositide 3-kinase
P53	Tumor protein 53
Rb	Retinoblastoma protein
TGFβ	Transforming growth factor beta

Introduction

The word *cancer*, derived from the Greek term for crab (*carcinos*), was coined by the father of medicine, Hippocrates (460–370 BC), in describing the physical resemblance of malignant tumors that had spread throughout the human body. Today, we know cancer to be a collection of diseases characterized by uncontrolled growth and spread of abnormal cells (Kleinsmith 2006). Cancer is the second most common

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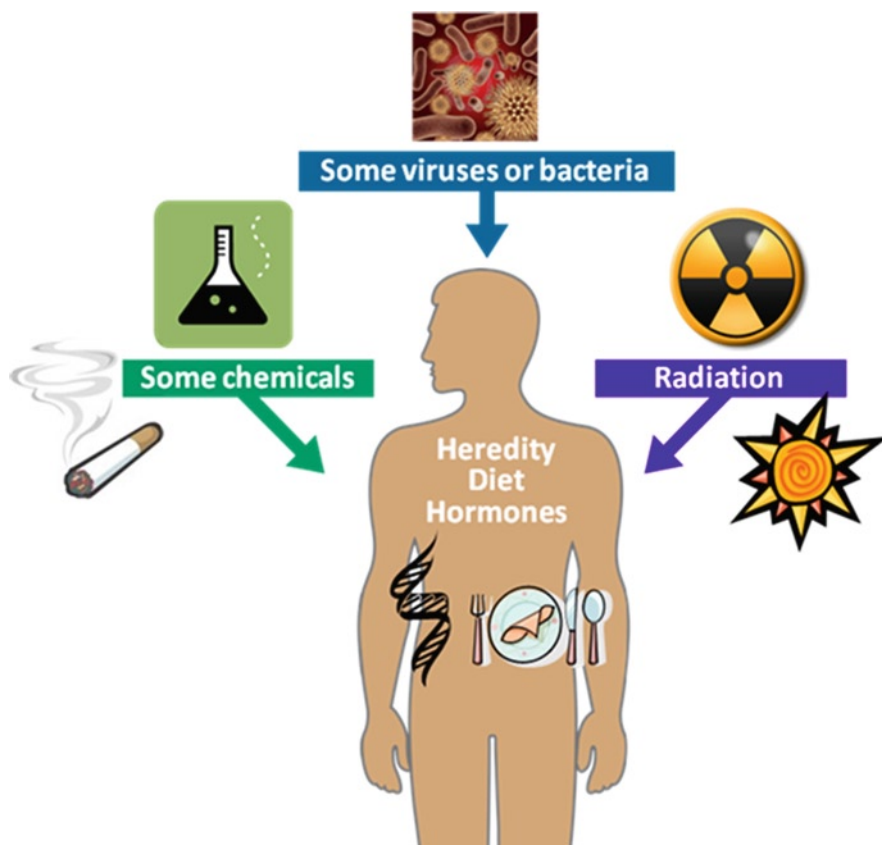


Fig. 2.1 Known causes of cancer. Modified with permission from the *Understanding Cancer Series*, National Cancer Institute (Kleinsmith et al. 2004)

cause of death, accounting for nearly one of every four deaths in the USA (American Cancer Society 2009). It encompasses more than 100 distinct diseases based on differences in their tissue of origin and the cell types involved.

The process by which a normal cell becomes malignant is referred to as *transformation*. Cellular transformation is an intricate, multistep process that typically occurs over a period of decades. Research over many years has identified several of the underlying causes of cancer (Fig. 2.1). Besides heredity, which can affect one's susceptibility to certain types of cancer, environmental and lifestyle risk factors, such as exposure to carcinogenic chemicals (e.g., those found in tobacco smoke and alcohol), radiation, infectious agents, and diet, all contribute, often in combination, to the development of cancer.

Multistep Process of Tumorigenesis

Cancer development is a multistep process by which normal cells acquire abnormal biological capabilities (Fig. 2.2) (Kleinsmith 2006). In simple terms, this neoplastic evolution begins from an initial genetic or epigenetic change in the cell. Fortunately, the cell has in place many mechanisms to repair damaged DNA, thus ensuring these are rare events. There are no outward manifestations at this stage. As the *initiated* cell proliferates, hyperplasia eventually leading to dysplasia may be histologically evident. Cancer progression describes a period after cancer has formed. During this phase, the accumulation of genetic and epigenetic abnormalities creates cells possessing increasingly aberrant traits (discussed in *Hallmarks of Cancer* section below). Such leverage provides a selective advantage to certain cells within the tumor. Repeated rounds of this clonal selection and genomic alteration generate a predominant population of cells whose cellular properties are now clearly aligned with what we recognize as *cancer*.

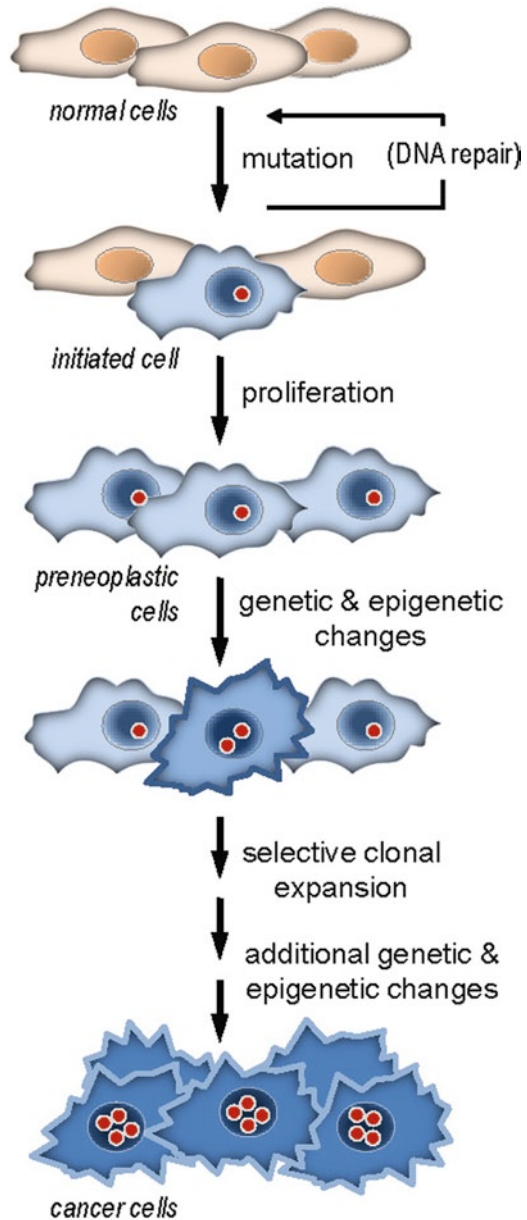
Cancer Genes and the Significance of Mutations

Although the main causes of cancer are quite diverse, they often lead to the common outcome of mutagenizing our genome. Currently, it is believed that mutations in at least 350 (1.6%) of the approximately 22,000 protein-coding genes in the human genome may contribute to cancer development (Futreal et al. 2004; Stratton et al. 2009). Updated lists of gene mutations causally implicated in cancer may be found at <http://cgap.nci.nih.gov/cgap.html> and <http://www.sanger.ac.uk/genetics/CGP/Census/>.

For a given human cancer, it is believed that at least four to six distinct somatic mutations are required for tumorigenesis (Hahn and Weinberg 2002). Cancer-relevant genes fall into three main classes: oncogenes, tumor-suppressor genes, and stability genes.

Oncogenes are altered genes whose protein products contribute to cancer development. They arise from normal genes (*proto-oncogenes*) which encode proteins that function as mitogenic growth factors and their corresponding receptors, cytoplasmic protein kinases, cell cycle or cell death regulators, and nuclear transcription factors. Proto-oncogenes may be converted to oncogenes by a number of mechanisms, including mutation, gene amplification, and chromosomal translocation. By these mechanisms, cancer cells produce excessive amounts or abnormal versions of these proteins, thus creating an advantageous condition for unrestrained growth. Since their discovery in the 1970s, several dozens of oncogenes have been identified in human cancer (see Chap. 6), many of which have become therapeutic targets for drug development.

Fig. 2.2 Multistep carcinogenesis



Tumor-suppressor genes are normal genes whose absence or inactivation by mutation or epigenetic silencing may also contribute to cancer. Occasionally referred to as *anti-oncogenes*, they encode proteins which normally constrain cell growth or promote cell death. Functional loss of such genes would, therefore, allow cancer cells to evade normal growth and survival controls. In contrast to oncogenes,

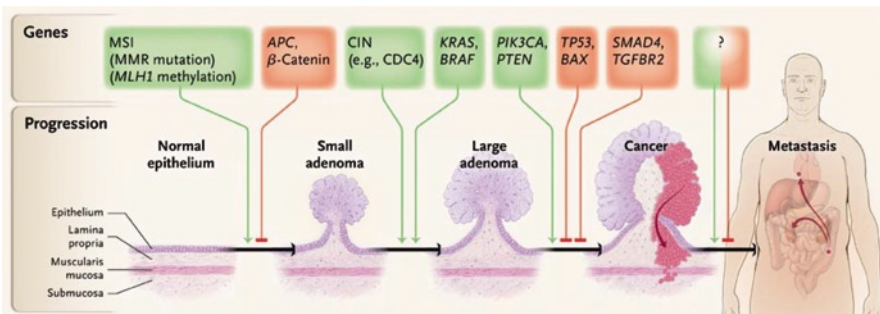


Fig. 2.3 Molecular basis of colorectal cancer. *Green* denotes oncogenic mediators that are activated while *red* represents tumor-suppressor factors that are turned off in colorectal cancer. Each successive genetic or epigenetic alteration is associated with increasingly abnormal cellular properties, all of which occur over a period of years. *Question mark (?)* denotes unknown genetic and epigenetic changes involved in metastasis. *MSI* microsatellite instability, *MMR* mismatch repair, *CIN* chromosomal instability. Adapted from *N Engl J Med*, Molecular origins of cancer: Molecular basis of colorectal cancer, Markowitz SD, Bertagnolli MM. Copyright © 2009 Massachusetts Medical Society. All rights reserved

tumor-suppressor genes generally follow the “two-hit hypothesis” first proposed by Knudson (1971) which implies that both alleles of a particular gene must be affected before an effect is manifested.

The third class of cancer genes, called *stability genes* (Vogelstein and Kinzler 2004), promotes carcinogenesis in a completely different manner when mutated. As compared to oncogenes and tumor suppressors which, when altered, drive the proliferative and survival aspects of carcinogenesis, stability genes are responsible for repairing errors made during DNA replication and those induced by carcinogen exposure. Stability genes also control chromosomal segregation and mitotic recombination processes. Inactivation of this class of cancer genes would facilitate genome-wide increases in mutation rates and chromosomal anomalies, thus indirectly contributing to cancer development.

Stepwise Model for Colorectal Cancer

The concept by which a series of mutations leads to malignancy is best illustrated by the disease of colorectal cancer (CRC). Data from a number of laboratories have contributed to a sequence of transformation from normal colonic epithelium to metastatic carcinoma driven by a stepwise accumulation of genetic and epigenetic alterations that may take decades to accrue (Fig. 2.3).

Characteristic molecular changes observed in patient-derived samples include the activation of the Wnt-signaling pathway and inactivation of the p53 and transforming growth factor beta (TGFβ) pathways by loss-of-function mutations in the tumor-suppressor genes *APC*, *P53* (or *TP53*), and *SMAD4*, respectively (Fig. 2.3; Baker

et al. 1989, 1990; Kinzler et al. 1991; Powell et al. 1992; Takagi et al. 1996; Howe et al. 1998; reviewed by Markowitz and Bertagnolli 2009). These changes are often accompanied by the oncogenic mutation of *KRAS* or *BRAF* which activates the mitogen-activated protein kinase (MAPK)-signaling pathway (Bos et al. 1987; Rajagopalan et al. 2002; reviewed by Markowitz and Bertagnolli 2009). Accumulation of these genetic and epigenetic changes correlates with increasing malignancy such that benign adenomas possess only a few of these genetic lesions, whereas aggressive tumors display most if not all of them (Fig. 2.3). It is also important to note that these molecular alterations may not always occur in the order depicted in Fig. 2.3. Taken together, our understanding of CRC serves as an excellent example of how a defined set of genetic and epigenetic alterations may confer a sequential, selective advantage to the cells in which they arise.

Acquired Capabilities of Cancer Cells

The Hallmarks of Cancer

Hanahan and Weinberg (2000) proposed a simplified model of cancer development consisting of six molecular, biochemical, and cellular traits which are shared by most, if not all, highly advanced human cancers. According to their theory, these traits or novel capabilities, referred to as the *hallmarks of cancer* (Fig. 2.4, top half), are acquired during tumorigenesis through both genetic and epigenetic (see Chap. 5) mechanisms. These are the following:

1. *Self-sufficiency in growth signals.* Normal cells require exogenous mitogenic signals prior to undergoing cell division. Cancer cells escape such a prerequisite by production of abnormal proteins that inappropriately trigger cell proliferation in the absence of environmental cues, a feat achieved primarily through the activity of oncogenes. Mechanistically, cancer cells may achieve growth factor autonomy by (a) ectopically secreting growth factors in a cell autonomous manner; (b) overexpressing growth factor receptors or possessing, by mutation, structurally altered forms which establish a hyperresponsive signaling environment; and (c) acquiring mutations in downstream intracellular components that facilitate ligand-independent signaling. Indeed, Hanahan and Weinberg (2000) have suggested that growth-signaling pathways are dysregulated in virtually all human cancers.
2. *Insensitivity to antigrowth signals.* If they are to continue to divide, cancer cells must evade a variety of inhibitory mechanisms that protect normal tissues from inappropriate growth. At the molecular level, many antiproliferative factors, such as the TGF β family of ligands, impinge upon late G₁ phase of the cell cycle at a transition known as the restriction point. These inhibitory effects often converge on the retinoblastoma protein, Rb, a tumor-suppressor protein whose hyperphosphorylation allows passage into the S phase of the cell cycle and whose functional disruption renders cells insensitive to cell cycle control.

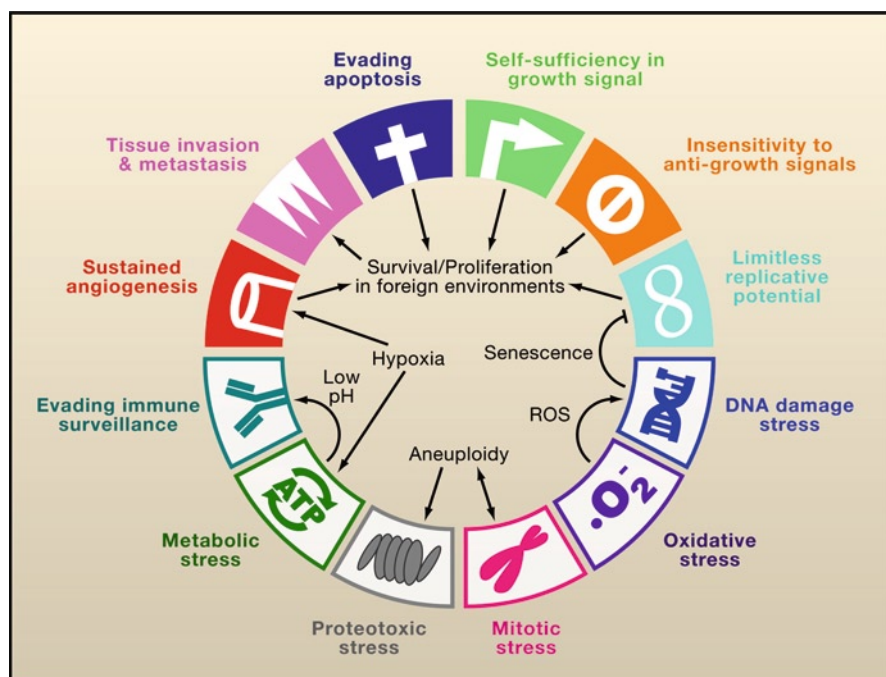


Fig. 2.4 The expanded hallmarks of cancer. In addition to the six hallmarks of cancer first proposed by Hanahan and Weinberg in 2000 (upper half, *white symbols*) and evasion of immune surveillance suggested by Kroemer and Pouyssegur (2008), Elledge and colleagues recently proposed a set of additional hallmarks that depict the stress phenotypes of cancer cells (lower half, *colored symbols*). Reprinted from *Cell*, 136, Luo J, Solimini NL, and Elledge SJ, *Principles of Cancer Therapy: Oncogene and Non-oncogene Addition*, p823–836, (2009), with permission from Elsevier

3. *Evading apoptosis*. In normal tissue, a balance exists between the production of new cells by cell division and the elimination of damaged or unwanted cells by a genetic mode of cellular suicide or *apoptosis*. The intrinsic apoptotic pathway functions in response to various intracellular stresses, including DNA damage to lead to the accumulation of the p53 tumor-suppressor protein, mitochondrial release of cytochrome c, activation of caspase proteases, and ultimate cell killing. In cancer, this program of cell death is functionally silenced. Moreover, other anti-apoptotic pathways, such as survival signals mediated by PI3K and AKT protein kinases, are also enhanced in a substantial number of human tumors. The ability to evade apoptosis appears to be a hallmark of nearly all types of cancers and likely contributes to their ability to accumulate mutations and progress toward malignancy.
4. *Limitless replicative potential*. Normal cells are limited in the number of times they may divide. When this limit is reached, cells enter senescence. This replicative potential is determined by structures at the ends of chromosomes called telomeres, which are progressively lost upon completion of each cell cycle.

To avoid such chromosomal attrition which would otherwise lead to apoptosis, cancer cells have acquired mechanisms to maintain and lengthen telomeric DNA, thereby achieving the ability to replicate indefinitely. The vast majority of malignancies accomplish this feat through transcriptional activation of *telomerase*, an enzyme which promotes telomere repair and is aberrantly activated in cancer cells.

5. *Sustained angiogenesis*. Formation of a blood vasculature to nourish cancer cells is an essential step in allowing a neoplasm to expand and metastasize. Cancer cells initially lack the capacity to initiate tumor angiogenesis, the process by which new blood vessels are formed from preexisting vessels, and thus remain physically confined to their site of origin. However, during early tumorigenesis, neoplastic cells shift the balance between pro- and anti-angiogenic factors in favor of establishing an independent blood supply, thereby fueling tumor growth.
6. *Tissue invasion and metastasis*. Metastasis is the most common cause of cancer deaths from solid tumors. In order for cancers to spread, cells must dissociate from the primary tumor mass, invade the surrounding tissues, enter and travel through the lymphatic or circulatory systems, and colonize new tissues elsewhere in the body. At a mechanistic level, both invasion and metastasis utilize similar physical strategies involving (a) loss of cell–cell adhesion; (b) activation of extracellular proteases; and (c) enhanced cell motility. Among the hallmarks of human cancer, the acquisition of invasiveness and metastatic ability by cancer cells are often the very last to emerge.

According to Hanahan and Weinberg (2000), each of these physiologic changes represents the successful breaching of an anticancer defense mechanism hardwired into normal human cells, the sum of which dictates malignant growth. Since their report was published, additional hallmarks, for which no further detail would be provided, have been proposed.

7. The ability to evade elimination by the immune system (Zitvogel et al. 2006; Kroemer and Pouyssegur 2008) and
8. The presence of an inflammatory microenvironment (Coussens and Werb 2002; Colotta et al. 2009; Mantovani 2009). The role of alcohol in enhancing inflammation and suppressing immune surveillance and its implications for cancer are discussed in detail in Chaps. 9 and 10, respectively.

A conceptual update by Elledge and colleagues (Luo et al. 2009) expanded upon the classic hallmarks to include the “stress phenotypes of tumorigenesis” (Fig. 2.4, lower half). These are

9. DNA damage and replication stress;
10. Proteotoxic stress;
11. Mitotic stress;
12. Metabolic stress; and
13. Oxidative stress.

Although these cancer phenotypes may not be responsible for initiating tumorigenesis, Elledge and colleagues suggest that they represent a common set of oncogenesis-associated cellular stresses that cancer cells must endure through stress-supported

pathways if they are to survive. Ultimately, cancer development is a complex interplay among these hallmarks, whether they involve traits that promote cell proliferation and survival or capabilities that mitigate cellular stresses. For example, most cancer cells rely on aerobic glycolysis, the conversion of glucose to lactate regardless of whether oxygen is present, as a means of generating ATP (Vander Heiden et al. 2009). Known as the Warburg effect, this reliance on glycolysis allows cancer cells to adapt to hypoxia and acidify their microenvironment, conditions which favor subsequent tumor invasion and suppression of immune surveillance (Fig. 2.4; Luo et al. 2009).

Molecular Bases of Cancer Hallmarks

The molecular underpinnings of these cancer hallmarks involve somatic mutations to key cancer genes that accumulate over the lifetime of the cancer patient (reviewed by Hahn and Weinberg 2002; Vogelstein and Kinzler 2004; Stratton et al. 2009). These *driver mutations* impart clonal growth advantages to cells and have been causally implicated in oncogenesis (reviewed by Stratton et al. 2009). Also present are *passenger mutations* that, due to the nature of the genetic change, fail to impart carcinogenic properties to a cell. These mutations propagate during clonal expansion, but are thought not to contribute to cancer development. A half-dozen driver mutations may be sufficient to convert normal cells to cancerous ones, though recent analyses suggest that number may be underestimated (Sjoberg et al. 2006; Beerenwinkel et al. 2007). The ability to distinguish driver from passenger mutations is a major goal of ongoing efforts cataloging somatic mutations of individual cancer genomes and provides insight into the mutational processes that drive human malignancies (Fig. 2.5; reviewed by Futreal et al. 2004; Stratton et al. 2009).

Although cancer genes are important, it is really the dysregulation of associated signaling pathways resulting from their mutation that promotes carcinogenesis. Genetic and epigenetic alterations to cancer genes lead to the derailment of homeostatic programs controlling growth, migration, and survival (see Chap. 6), and thus serve as the driving force behind the phenotypic traits of malignancy.

For example, gain-of-function mutation, copy number changes, and chromosomal rearrangements allow for the conversion of proto-oncogenes to oncogenes during cancer development (Fig. 2.5). As seen in activating mutations in members of the *RAS* family of GTPases, dysregulation and inappropriate activation of the MAPK pathway follow (see Chap. 6). Continuous mitogenic signaling independent of ligand binding represents an essential step of malignant transformation. Indeed, approximately 20–30% of all human cancers produce mutant *RAS* protein (Bos 1989; Medema and Bos 1993) making it the most frequently mutated oncogene in human cancers.

Loss of tumor suppressors via deletion, loss-of-function mutation, or epigenetic silencing also facilitates the acquisition of malignant phenotypes. For instance,

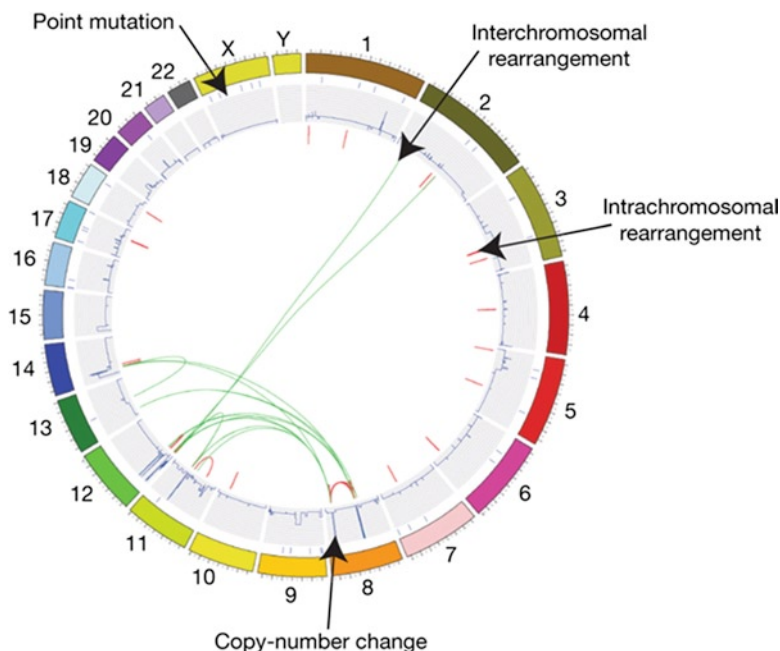


Fig. 2.5 A catalogue of somatic mutations present in a single cancer genome. Part of catalogue of somatic mutations in the small-cell lung cancer cell line NCI-H2171. Individual chromosomes are depicted on the outer circle followed by concentric tracks for point mutation, copy number, and rearrangement data relative to mapping position in the genome. *Arrows* indicate examples of the various types of somatic mutations present in this cancer genome. Reprinted by permission from Macmillan Publishers Ltd: *Nature*, Stratton et al., *The Cancer Genome*, © (2009)

somatic mutations involving the tumor-suppressor gene *p53* occur in greater than half of all tumor specimens examined, making it arguably the most commonly mutated gene in human malignancies (reviewed by Levine and Oren 2009). Loss of this tumor-suppressor protein eliminates a cell's ability to either arrest the cell cycle and repair damaged DNA following a genotoxic insult or initiate apoptosis if the DNA damage proves to be irreparable (see Chap. 6). While a detailed discussion of cancer genes and the signaling pathways they control during carcinogenesis is beyond the scope of this chapter, we refer the reader to several comprehensive reviews on the topic of the molecular circuitry of cancer cells (Hahn and Weinberg 2002; Vogelstein and Kinzler 2004; Yeang et al. 2008).

As more cancer genomes are sequenced, it is becoming clear that a large number of cancer genes function in a handful of signaling pathways (Copeland and Jenkins 2009; see Chap. 6), corroborating the hypotheses proposed by Hanahan and Weinberg nearly a decade ago. Understanding this tenant is critical for the development of target-based cancer therapeutics directed against the deregulated signaling pathways themselves rather than the individually mutated genes (Copeland and Jenkins 2009).

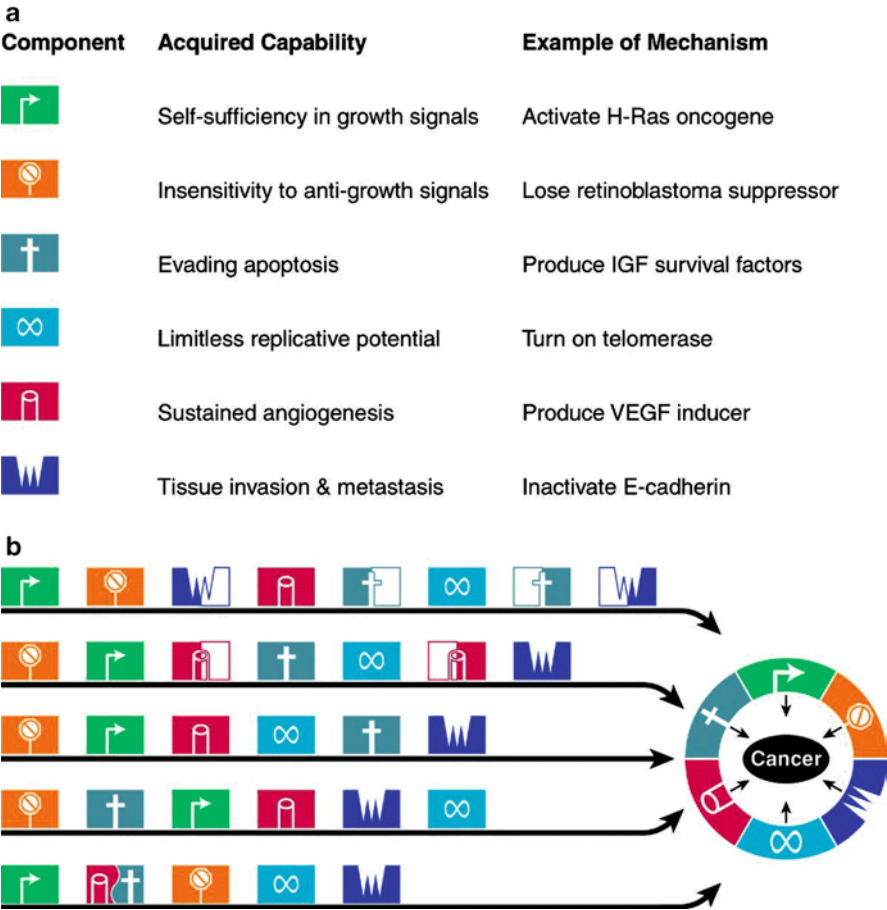


Fig. 2.6 Parallel pathways of tumorigenesis. Reprinted from *Cell*, 100 Hanahan D, and Weinberg RA, *The Hallmarks of Cancer*, p57–70, (2000), with permission from Elsevier

Conceptual Oncogenesis: Hallmarks Revised

While Hanahan and Weinberg propose that virtually all cancers acquire the same six originally proposed hallmarks (Fig. 2.6a), the timing and mechanisms governing such transformation may differ among malignancies (Fig. 2.6b). Mutations in certain oncogenes and tumor suppressors could vary sequentially, occurring early in some models of carcinogenesis while late in others. Consequently, the order in which hallmark capabilities appear during tumor progression may vary, both within and between cancer types (Fig. 2.6b).

In certain cancers, a specific genetic alteration may confer not only one, but also multiple traits simultaneously, thus lowering the number of distinct mutations required for completion of tumor progression (Fig. 2.6b). As an example, loss of the

tumor-suppressor *p53* may contribute to both the anti-apoptotic and pro-angiogenic properties of a cancer cell (as illustrated in the five-step scheme of Fig. 2.6b). Alternatively, a given hallmark may only be achieved through the functional cooperation of two or more genetic or epigenetic lesions, thereby increasing the total number of molecular events required for tumorigenesis. This concept is illustrated by the eight-step scheme (Fig. 2.6b) in which the novel capabilities of invading tissues and resisting apoptosis are each acquired in two distinct steps, involving separate genetic alterations.

Nonetheless, Hanahan and Weinberg (2000) propose “that independent of how the steps in these genetic pathways are arranged, the biological endpoints that are ultimately reached – the hallmark capabilities of cancer – will prove to be shared in common by all types of tumors.”

Cancer and Alcohol

The mechanisms by which alcohol consumption exerts its carcinogenic effect are not fully understood but appear to occur during all stages of tumorigenesis (Fig. 2.7; reviewed by Poschl and Seitz 2004; Boffetta and Hashibe 2006; Seitz and Stickel 2007). Both animal and in vitro studies have shown that the main metabolite of alcohol, acetaldehyde, is capable of causing DNA damage that may lead to cancer

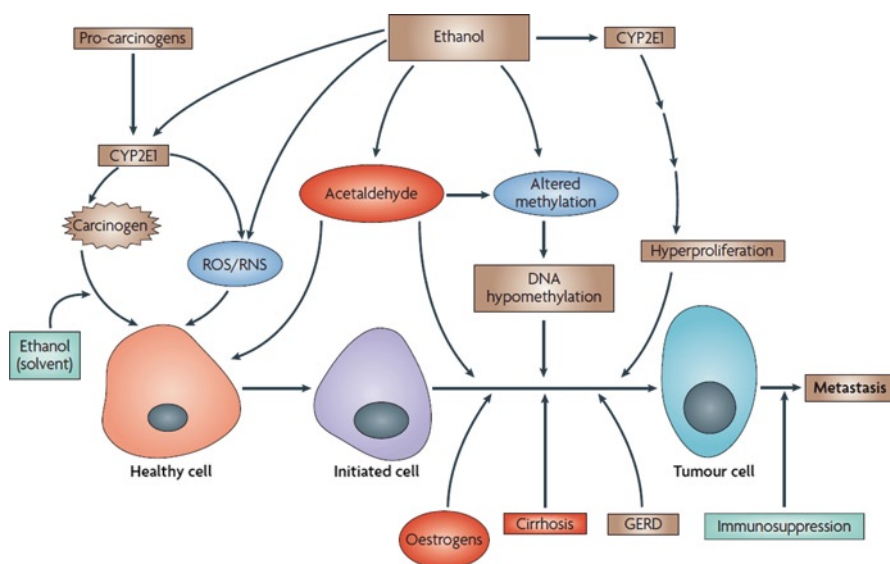


Fig. 2.7 Alcohol may promote carcinogenesis at many levels. Mechanisms with *strong evidence* are shown in red, with *moderate evidence* in blue and with *weak evidence* in green. Details contained within this text and cited reviews. Reprinted by permission from Macmillan Publishers Ltd: *Nat Rev Cancer*, Molecular mechanism of alcohol-mediated carcinogenesis, Seitz HK, Stickel F, © 2007

(see Chaps. 1 and 4). Alcohol metabolism or the presence of its metabolite acetaldehyde per se may *initiate* carcinogenesis by increasing the cytochrome P450 2E1 (CYP2E1)-mediated activation of various procarcinogens present in alcoholic beverages, tobacco smoke, and diets (see Chap. 4). Production of reactive oxygen species and successive lipid peroxidation may also contribute to the mutagenic effects of alcohol. During cancer *promotion* and/or *progression*, alcohol and acetaldehyde alter DNA methylation which may lead to epigenetic modifications to important cancer genes (see Chap. 5). Moreover, alcohol-associated damage to DNA and perturbations in both pro- and anti-oncogenic-signaling pathways have been observed following chronic alcohol use (see Chap. 6). Disruption in retinoic acid metabolism (see Chap. 7) and protein homeostasis (see Chap. 8) adds to the complexity of effects of alcohol on cancer development. And during cancer *progression*, alcohol consumption may contribute to inflammatory (see Chap. 9) and immunosuppressive (see Chap. 10) environments, thus allowing tumor cells to propagate and spread. Finally, the impact of alcohol on stem cells (see Chap. 11) and the role this interaction plays in alcohol-induced carcinogenesis warrants further investigation. These mechanisms and others by which alcohol contributes to oncogenesis are detailed in subsequent chapters.

Acknowledgments This chapter is based largely on information presented in *Principles of Cancer Biology* by Lewis Kleinsmith (2006) and from the seminal review *The Hallmarks of Cancer* by Douglas Hanahan and Robert Weinberg (2000).

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