CHAPTER 10.

Key characteristics of carcinogens

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Introduction

The agents documented and listed as *carcinogenic to humans* (Group 1) in Volume 100 of the *IARC Monographs* show several key characteristics that distinguish them as carcinogenic agents. Many appear to act via multiple mechanisms, causing various biological changes in the multistage process of carcinogenesis. Others appear to act by a single predominant mechanism.

The participants in the IARC Workshop on Tumour Site Concordance and Mechanisms of Carcinogenesis, after considering previously published options for classification of carcinogens and related matters (see Chapter 11, by Stewart, and Chapter 12, by DeMarini), extensively debated the mechanisms by which carcinogens produce cancer. The Workshop participants concluded that carcinogens commonly show one or more of 10 key characteristics (Table 10.1).

To achieve wide dissemination and assessment, these key characteristics have been described in an open access journal publication (Smith et al., 2016) that also delineates their application, and hence complements material presented in this chapter and, to a broader extent, this Scientific Publication. Here, these key characteristics are defined, and reference is made to subsequent chapters where these particular characteristic properties are extensively discussed.

The Workshop participants also discussed several modulating factors that, along with mechanistic differences, may explain the lack of concordance or coherence between tumour sites in humans and experimental animals. Neither the list given in Table 10.1 nor the set of modulating factors mentioned by the Workshop participants is meant to be exhaustive, but they were agreed upon as being established characteristics or modulating factors. It is hoped that they will assist future *IARC Monographs* Working Groups in evaluating additional potential human carcinogens.

Characteristic 1: Is electrophilic or can be metabolically activated to electrophiles

Electrophiles are electron-seeking molecules that commonly form addition products, generally referred

Table 10.1. Key characteristics of carcinogens

1. Is electrophilic or can be metabolically activated to electrophiles
2. Is genotoxic
3. Alters DNA repair or causes genomic instability
4. Induces epigenetic alterations
5. Induces oxidative stress
6. Induces chronic inflammation
7. Is immunosuppressive
8. Modulates receptor-mediated effects
9. Causes immortalization
10. Alters cell proliferation, cell death, or nutrient supply

to as adducts, with cellular macromolecules including DNA, RNA, lipids, and proteins. Some chemical carcinogens are direct-acting electrophiles, whereas others require biotransformation by enzymes in a process termed metabolic activation (Miller, 1970).

Examples of direct-acting electrophilic carcinogens are formaldehyde, sulfur mustard, and ethylene oxide (see Chapter 1, by Bond and Melnick). The classic examples of chemical agents that require metabolic activation to become carcinogenic are polycyclic aromatic hydrocarbons and benzene, which by themselves are relatively inert chemically. This lack of reactivity puzzled chemists working on experimental carcinogenesis for many years until the Millers discovered metabolic activation by the mixed-function oxidase system (Conney et al., 1957). It is now known that several human enzymes can biotransform relatively inert chemical compounds to potent toxic and carcinogenic metabolites or reactive intermediates. These enzymes include cytochrome P450 isozymes, flavin mono-oxygenase, prostaglandin synthase, and various peroxidases (O'Brien, 2000; Hecht, 2012). The ability to form adducts with DNA and protein is a common property of these electrophilic and metabolically activated human carcinogens.

Characteristic 2: Is genotoxic

The term "genotoxic" refers to an agent that induces DNA damage, but this damage may or may not necessarily be processed by the cell into a mutation (see Chapter 12, by DeMarini). Thus, if an agent is found to induce DNA damage, it can be called a genotoxicant or a genotoxin, and if it is shown that the agent also induces mutations in a mutagenicity assay, it can be classified as a mutagen. Most of the IARC Group 1 carcinogens are considered to be genotoxic, and many are mutagenic (Waters et al., 2010), although this may not be their primary mechanism of carcinogenesis.

DNA damage from genotoxicity may be in the form of DNA adducts or single- or double-strand breaks. Other types of DNA damage are oxidized or fragmented bases or the intercalation of a molecule between two bases. The DNA damage is by itself not a mutation and generally does not alter the linear sequence of nucleotides (or bases) in the DNA, whereas a mutation is defined as a change in the DNA sequence, which usually arises as the cell attempts to repair the DNA damage.

Characteristic 3: Alters DNA repair or causes genomic instability

Normal cells try to avoid deleterious mutations by replicating their genomes with high accuracy. However, the fidelity of DNA replication can vary widely depending on the DNA polymerase involved, and this introduces the possibility of error. Indeed, most spontaneous mutations are caused by polymerase error (Preston et al., 2010). The nature of the mistake, the flanking sequence, the presence of DNA damage, and the ability to correct errors all have an impact on the outcome of this process (Arana and Kunkel, 2010). As a consequence, defects in processes that determine DNA replication fidelity can confer strong mutator phenotypes that result in genomic instability. Thus, carcinogens may act not only by producing DNA damage directly but also by altering the processes that control normal DNA replication.

Similarly, the major DNA repair pathways – such as base excision repair, nucleotide excision repair, and double-strand break repair – involved in the removal of DNA adducts and other lesions may also be altered by environmental exposures. Furthermore, whereas especially excision repair pathways are predominantly error-free and thus protective, double-strand break repair is largely error-prone and may contribute to genomic instability.

Genomic instability is a well-recognized feature of many cancers (Bielas et al., 2006). Studies of cultured cells exposed to ionizing radiation have shown that instability is a relatively late-occurring event that appears several cell generations after irradiation and results in a reduced ability to replicate the genotype faithfully (see Chapter 18, by Hill and Ullrich). The events that indicate genomic instability include chromosomal aberrations, gene mutations, microsatellite instability, and apoptosis. The instability phenotype may play a major role in radiation-induced cancers and other forms of cancer by providing the cell and its progeny with a constantly elevated rate of any of the various genetic and epigenetic changes that may occur in multistage carcinogenesis (Aypar et al., 2011).

Characteristic 4: Induces epigenetic alterations

The term "epigenetic" refers to all stable changes in gene expression and chromatin organization that are independent of the DNA sequence itself and that can be mitotically inherited over cell divisions. Epigenetic phenomena, including genomic imprinting, X-chromosome inactivation, global reconfiguration of the DNA methylome, and changes in chromatin compaction states and histone modification patterns, occur during development and contribute to the lineage-specific epigenome that is maintained over the lifetime of an organism. Many of these same phenomena are altered during carcinogenesis (see Chapter 20, by Rice and Herceg).

A wide range of known and suspected carcinogens (including chemical, physical, and biological agents) have been shown to deregulate the epigenome, and it has been suggest-ed that their mode of action may involve disruption of epigenetic mechanisms. Because the evidence for a truly causal role of epigenetic changes in cancer produced by Group 1 agents was deemed to be limited in Volume 100, for many agents their impact on the epigenome was not considered to be a secondary mechanism of carcinogenesis. However, it should be noted that most carcinogens (even those considered for Volume 100 in 2008 and 2009) were evaluated by IARC Working Groups before new data on their epigenetic effects became available. Many recent studies have demonstrated the impact of several Group 1 agents included in Volume 100 on epigenetic mechanisms (Koturbash et al., 2011; Ravegnini et al., 2015; Chappell et al., 2016). This rapidly evolving area will generate new mechanistic data on carcinogens in the next few years.

Characteristic 5: Induces oxidative stress

Many human and animal carcinogens are capable of influencing redox processes and redox balance within target cells (see Chapter 15, by Bucher). An imbalance between formation of reactive oxygen and/or nitrogen species and their detoxification is commonly referred to as oxidative stress. Reactive oxygen species, which can arise from inflammation, may contribute to genomic instability and – along with other free radical species – play key roles in many of the processes identified as being necessary for the conversion of normal cells to cancer cells. Oxidative damage is considered a major factor in the generation of mutations in DNA, and more than 100 different oxidative DNA adducts have been identified (Klaunig et al., 2011).

Reactive oxygen species produce at least 24 base modifications, as well as DNA–protein cross-links and other lesions (Berquist and Wilson, 2012), all potentially leading to genomic instability. Oxidative damage to DNA can lead to point mutations, deletions, insertions, or chromosomal translocations, which may cause activation of oncogenes and inactivation of tumour suppressor genes, potentially leading to initiation of carcinogenesis (Klaunig et al., 2011; Berquist and Wilson, 2012). Thus, agents that generate and promote oxygen radical-induced cellular injury may be carcinogenic.

Characteristic 6: Induces chronic inflammation

Chronic inflammation from persistent infections, such as that caused by *Helicobacter pylori* as well as that produced by silica or asbestos fibres, has been associated with several forms of cancer (see Chapter 17, by Kane). Indeed, inflammation is an "enabling characteristic" of cancer (Hanahan and Weinberg, 2011), and it has been hypothesized to contribute to cancer initiation, promotion, and progression (Trinchieri, 2012).

Inflammation acts by both intrinsic and extrinsic pathways. Persistent infection and chronic inflammation disrupt local tissue homeostasis and alter cell signalling, leading to the recruitment and activation of inflammatory cells. These constitute extrinsic pathways linking inflammation to cancer (Multhoff and Radons, 2012). In contrast, intrinsic pathways driven by activation of proto-oncogenes in pre-neoplastic and neoplastic cells recruit host-derived inflammatory cells that accelerate tumour promotion and progression (Grivennikov et al., 2010). Strong links exist between inflammation and

the induction of oxidative stress and genomic instability; this makes it difficult to separate out the importance of each of these mechanisms.

Characteristic 7: Is immunosuppressive

Immunosuppression is a reduction in the capacity of the immune system to respond effectively to foreign antigens, including antigens on tumour cells. Persistent immunosuppression presents a risk of cancer, especially excess risk of lymphoma when it is accompanied by continuing exposure to foreign antigens such as after organ transplantation, or when it occurs in individuals who are latently infected with an oncogenic virus (Gutierrez-Dalmau and Campistol, 2007; Münz and Moormann, 2008; Shelton et al., 2016).

Immunosuppression differs from other mechanisms of carcinogenesis in that agents that cause immunosuppression may not directly transform normal cells into potential tumour cells. Potentially neoplastic cells that arise naturally, or that have been transformed by other carcinogens acting by a mechanism such as genotoxicity or by the various mechanisms of action associated with oncogenic viruses, escape immune surveillance in immunosuppressed individuals. As a result, survival of these cells and their replication to form tumours is greatly facilitated by immunosuppression.

Several Group 1 agents included in Volume 100 act entirely or largely by immunosuppression, often in concert with other Group 1 agents, especially oncogenic infectious agents. The Group 1 agents that act by immunosuppression include human immunodeficiency virus type 1 (HIV-1) and the immunosuppressive drugs ciclosporin and azathioprine (IARC, 2012a, c).

Characteristic 8: Modulates receptor-mediated effects

Hormonally active agents that are associated with carcinogenic effects typically act as ligands via nuclear receptors, and in some cases via receptors located on the cell surface. There are many other agents that may be carcinogenic by acting on receptor proteins, even though some of these also have genotoxic effects, for example polycyclic aromatic hydrocarbons such as benzo[*a*]pyrene. Receptor activation falls into two broad categories: (i) activation of intracellular receptors that translocate into the nucleus and act on DNA as transcription factors, and (ii) activation of cell surface receptors and some intracellular receptors that activate signal transduction pathways, resulting in biological responses (see Chapter 14, by Bosland).

The predominant effect of receptor activation is on gene transcription. Although some exogenous ligands act as agonists by competing for binding with an endogenous ligand, others may bind but lack intrinsic activating activity for the receptor they bind to and have an antagonistic effect. There are also receptors for which no endogenous ligand has been identified, such as the aryl hydrocarbon receptor. One other important type of potential effect of exogenous agents on receptor-mediated mechanisms involves modulation of the amount of endogenous ligand available for binding and activating its receptor, by affecting biosynthesis, bioavailability, bioactivation, and/or degradation of the ligand (Rushmore and Kong, 2002).

Characteristic 9: Causes immortalization

Volume 100 of the *IARC Monographs* identifies several human DNA and RNA viruses that are *carcinogenic to humans* (Group 1); these include various types of human papillomavirus (HPV), Epstein–Barr virus (EBV), Kaposi sarcoma-associated herpesvirus (KSHV), hepatitis B virus (HBV), hepatitis C virus (HCV), and HIV-1. These viruses have evolved multiple molecular mechanisms to disrupt specific cellular pathways to facilitate aberrant replication.

Although oncogenic viruses belong to different families, their strategies in human cancer development show many similarities and involve viral-encoded oncoproteins targeting the key cellular proteins that regulate cell growth. Recent studies have shown that virus and host interactions also occur at the epigenetic level (Allday, 2013). The result of these viral effects is to immortalize the cells of the target tissue such that they are not subject to the Hayflick limit, the point at which cells can no longer divide due to DNA damage or shortened telomeres.

For example, the HPV type 16 (HPV16) *E6* and *E7* oncogenes are selectively retained and expressed in cervical carcinomas, and expression of *E6* and *E7* is sufficient to immortalize human cervical epithelial cells (Yugawa and Kiyono, 2009). E6 and E7 proteins do not possess intrinsic enzymatic activities but instead function through several direct and indirect interactions with cellular proteins, some of which are well-known cellular tumour suppressors, including p53 and Rb.

Characteristic 10: Alters cell proliferation, cell death, or nutrient supply

There are at least three scenarios related to cancer and cancer mechanisms in which alterations in cellular replication and/or cell-cycle control have been described. The first

invokes the predisposition for unrepaired DNA damage to lead to cancer-initiating mutations in replicating cells. The second has attempted to identify sustained replication as a key mechanistic event, and the third describes the ability of a transformed cell to escape normal growth control and to continue replication. A component common to all three scenarios is the evasion of apoptosis or other terminal programming, including autophagy, in at least a proportion of the cell population (Ryter et al., 2014).

Sustained cellular proliferation has been argued to be a factor in increased cancer susceptibility. As summarized in the United States Environmental Protection Agency guidance assessing risk of cancer from early-life exposures (EPA, 2005), more frequent cell division during development can result in enhanced fixation of mutations because of the reduced time available for repair of DNA lesions, while clonal expansion of a mutated cell produces a larger population of mutant cells. For mature organisms, sustained proliferation has also been postulated to increase risk of cancer, based on the same rationale.

The mechanism by which necrosis may enable cancer induction is also part of the description of the hallmarks of cancer. In contrast to apoptosis and autophagy, necrotic cell death releases pro-inflammatory signals into the surrounding tissue microenvironment, resulting in recruitment of inflammatory cells of the immune system that can participate in tumour promotion through their influence on cancer cell proliferation and invasiveness.

In addition to cell death caused by direct toxicity of an agent, cells within a tumour may die as a result of impaired nutrient supply. The exponentially increasing number of neoplastic cells may quickly outstrip the supply capabilities of the existing tissue vasculature. Neo-angiogenesis, in which new blood vessels grow into a tumour, is key to providing this supply of nutrients. Thus, agents that promote or inhibit angiogenesis, such as arsenic, will promote or delay tumour growth (Yang et al., 2014).

Multiple mechanisms of action of human carcinogens

The number of mechanisms by which chemicals are known to contribute to carcinogenesis can be extensive if one includes all biochemical or molecular end-points, but the mechanisms can be grouped into a limited number of categories (genotoxicity, immunosuppression, etc.). Guyton et al. described 15 types of key events associated with carcinogenesis, which collectively represent the majority of known carcinogenic modes of action (Guyton et al., 2009).

The IARC Workshop participants initially identified 24 mechanistic end-points, with several subcategories in each. This was considered too many categories, and it was determined that several of them could be merged. The Workshop participants then concluded that carcinogens commonly show one or more of the 10 key characteristics described above (see Table 10.1). These represent the majority of known carcinogenic mechanisms of action.

It is increasingly evident that multiple biological alterations or sets of different perturbations are necessary to convert a normal cell into a transformed cell, and ultimately a tumour (Hanahan and Weinberg, 2011). Carcinogens appear to have an impact on this complex process in multiple ways and can act through multiple mechanisms of action to induce cancer and other adverse health outcomes. As an illustration of this point, the evidence has been evaluated for which key characteristics contribute to the carcinogenicity of benzene, an IARC Group 1 carcinogen, in humans and in experimental animals. The results are shown in Table 10.2, where the level of evidence for a particular characteristic is classified on a scale with 2 = strong evidence, 1 = moderate evidence, and 0 = weak evidence. For benzene, there is strong evidence in my view that metabolic activation, genotoxicity, and immunosuppression are established mechanisms of carcinogenicity in both animals and humans (McHale et al., 2012). There is weak or no evidence that inflammation and immortalization play a role in the carcinogenicity of benzene. However, moderate evidence exists for the other five key characteristics or mechanisms in humans. This suggests that there is strong or moderate evidence that eight of the key characteristics of carcinogens contribute to the carcinogenicity of benzene and that they are consistently observed, for the most part, both in humans and in experimental animals (Table 10.2).

Factors modulating human carcinogenesis

Lack of concordance or coherence between tumour sites in humans and experimental animals may be explained by several modulating factors that, along with mechanistic effects, cause discordance between the findings. For example, physiological differences exist between animals and humans, including the fact that rodents are nose-only breathers,

Table 10.2. Key characteristics of the carcinogen benzene[a]

Characteristic	Level of evidence[b]		
	IARC (2012b)	Humans	Animals
1. Is electrophilic or can be metabolically activated to electrophiles	2	2	2
2. Is genotoxic	2	2	2
3. Alters DNA repair or causes genomic instability	1	1	1
4. Induces epigenetic alterations	1	1	0
5. Induces oxidative stress	1	1	1
6. Induces chronic inflammation	0	0	0
7. Is immunosuppressive	2	2	2
8. Modulates receptor-mediated effects	1	1	1
9. Causes immortalization	0	0	0
10. Alters cell proliferation, cell death, or nutrient supply	1	1	1

[a] This table shows the overall weight of evidence as stated in Volume 100F of the *IARC Monographs* (IARC, 2012b), and the levels of evidence from studies in humans and animals, respectively.
[b] 2 = strong evidence, 1 = moderate evidence, 0 = weak evidence.

whereas humans breathe through both the nose and mouth. Rodents do not retain their urine as humans and dogs do, perhaps explaining the lack of carcinogenicity of aromatic amines to rodents (see Chapter 2, by Beland and Marques).

Experimental animals may also exhibit differences in the pharmacokinetics or toxicokinetics of a chemical: they may absorb, distribute, metabolize, and excrete a compound in ways that are different to those seen in humans. There are many examples of this kind. For instance, mice hydrolyse 6-propylthiopurine to mercaptopurine, which has a potent carcinogenic effect, whereas humans oxidize the drug at two positions in the molecule without hydrolysis, and the end products are not carcinogenic. With regard to infectious agents, it is clear that a human infectious agent, for example a human tumour virus that is not infectious to other animal species, will not produce carcinogenic effects in these species (see Chapter 9, by Lambert and Banks).

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