J Exp Clin Med 2013;5(6):203–209

Contents lists available at ScienceDirect

Journal of Experimental and Clinical Medicine

journal homepage: http://www.jecm-online.com

REVIEW ARTICLE

Chemical-induced Carcinogenesis

Takuji Tanaka [1,2,3*], Masahito Shimizu [4], Takahiro Kochi [4], Hisataka Moriwaki [4]

[1] Clin-ToxPath (C-Top) Consulting, Ichihashi, Gifu City, Japan
[2] Tohkai Cytopathology Institute, Cancer Research and Prevention, Minami-Uzura, Gifu, Japan
[3] Department of Tumor Pathology, Gifu University Graduate School of Medicine, Yanagido, Gifu, Japan
[4] Department of Medicine, Gifu University Graduate School of Medicine, Yanagido, Gifu, Japan

ARTICLE INFO

Article history:
Received: Sep 16, 2013
Revised: Oct 9, 2013
Accepted: Oct 16, 2013

KEY WORDS:
carcinogenesis mechanisms;
carcinogenic chemicals;
chemical carcinogenesis

Historically, evidence of chemical carcinogenesis has played a significant role in verifying conclusions draw from epidemiological studies. Chemical agents that were suspected to have a certain role in human chronic diseases, such as cancers, have been tested in animals to establish firmly a causative risk or link to risk. The three best examples are: (1) tobacco smoke and lung cancer; (2) asbestos and mesothelioma; and (3) aflatoxin and hepatic cancer. New chemical compounds are synthesized every day, and a number of natural or synthetic compounds are incorporated in foods either as a result of their processing or to preserve or enhance them. Chemical carcinogenesis studies using model animals have greatly contributed to understanding the mechanisms underlying the development and prevention of carcinogenesis. The carcinogenesis process is generally considered to include three steps: initiation, promotion, and progression. Each step is characterized by morphological and biochemical alterations resulting from genetic and epigenetic changes, including mutations in proto-oncogenes and tumor suppressor genes that control proliferation, cell death, and cellular repair. Long-term *in vivo* assays using laboratory animals enable the identification of carcinogenic compounds and their modes of action. Based on these findings, we should be able to establish effective strategies to treat and prevent malignancies resulting from exposure to potentially carcinogenic chemicals.

1. Introduction

Neoplasms can be classified as benign or malignant depending on their biological characteristics. The malignant cells show a variety of biological features (Figure 1). They proliferate autonomously, invade adjacent tissues, and frequently metastasize to distant tissues that are not related to the primary site.[1] The most important biological characteristic of a malignant neoplasm is its ability to metastasize. By contrast, benign neoplasms grow more slowly, but can compress their adjacent normal tissue.[2] Therefore, the histopathological observation/diagnosis of neoplasms (benign or malignant; and epithelial or nonepithelial origin) is important for understanding the pathogenesis and pathobiology of the neoplasms.[3–5] The histological and cytological changes that occur during tumorigenesis are illustrated in Figure 2. Malignant epithelial cells multiply clonally, escape from apoptosis, and accumulate genetic and/or epigenetic alterations.[6] When malignant neoplasms originate from nonepithelial cells, they are called sarcomas. The escape of malignant cells from apoptosis results in uncontrolled growth of neoplastic cells, and this is a critical point that determines the malignant potential of the cells,[7] and thus apoptosis induction is considered to be one of the mechanisms that can be targeted for cancer chemoprevention.[8]

The term “carcinogenic” is defined as the capacity of a chemical compound to induce the development of cancer in certain tissues under certain conditions.[9,10] A compound is considered to be “carcinogenic” when its administration to laboratory animals produces a statistically significant increase in the incidence of several histological types of neoplasms compared with the control group not exposed to the compound.

The carcinogenic factors that are responsible for cancer development are classified as either exogenous or endogenous.[10] The exogenous factors include agents associated with food preservation and preparation, socio-economic status, lifestyle, ionizing and nonionizing radiation, natural and synthetic chemical compounds, and xenobiotics including *Helicobacter pylori*, Epstein–Barr virus, human T-lymphtropic virus, human papillomavirus, hepatitis B virus, hepatitis C virus, and certain parasites.[11,12] Alcohol consumption, tobacco smoking, and the intake of certain foods contaminated by mycotoxins are also responsible for causing certain types of neoplasms.[12]

Endogenous carcinogenic factors include conditions and agents that cause immune system disruption and subsequent

* Corresponding author. Takuji Tanaka, Clin-ToxPath (C-Top) Consulting, 1-7-9 Ichihashi, Gifu City 500-8381, Japan.
E-mail: T. Tanaka <takutt@toukaisaibou.co.jp>

1878-3317/$ – see front matter
http://dx.doi.org/10.1016/j.jecm.2013.10.009

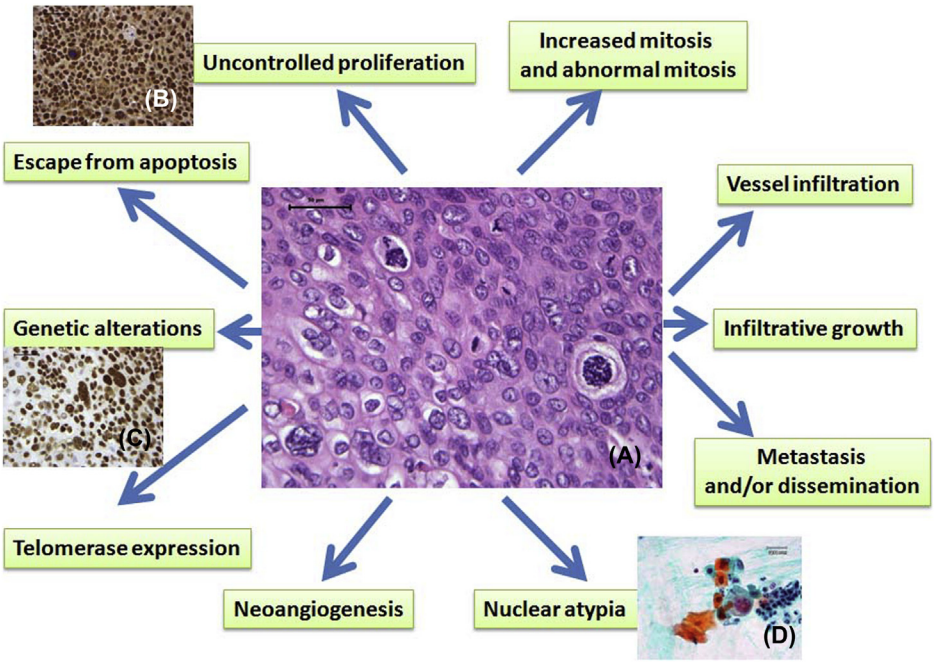

Figure 1 Biological characteristics of malignant cells. (A) Histology of human skin squamous cell carcinoma; (B) PCNA immunohistochemistry; (C) p53 immunohistochemistry, and (D) scraped cytology of human skin cancer. (A) hematoxylin and eosin stain and (D) Papanicolaou stain. Bars are 50 μm (A–C) and 20 μm (D). PCNA = proliferating cell nuclear antigen.

inflammation, such as ulcerative colitis.[2,12–16] Epidemiological studies suggest that the risk of developing cancer varies between different population groups, and these differences are associated with both genetic differences and lifestyle-related factors and habits. Indeed, the migration of certain populations to new regions with different lifestyles can result in the development of new types of cancer not previously prevalent in that group.[17] For example, exposure to Western lifestyles had a substantial impact on breast cancer risk in Asian migrants to the USA during their lifetime.[18] A study conducted by Maskarinec and Noh[19] showed that the migrant effect was strongest for colon and stomach cancers; prostate and breast cancers were affected to a lesser degree; and lung cancer risk differed little between Japanese in Japan and Hawaii. Migration led to lower risk of stomach, esophageal, pancreatic, liver, and cervical cancers, but to higher rates for all other cancers.[19]

Neoplastic development is based on the existence of genetic mutations. In most cases, the effects of such mutations are assumed to vary between tissues and among species. During cell division, spontaneous genetic errors occur with an estimated frequency of around 10^{-5}–10^{-6} nucleotides per cycle of cell division. Although numerous repair systems exist within the cells to correct these errors, if the damage persists and reaches a gene responsible for neoplastic development, then cancer can develop. Indeed, studies

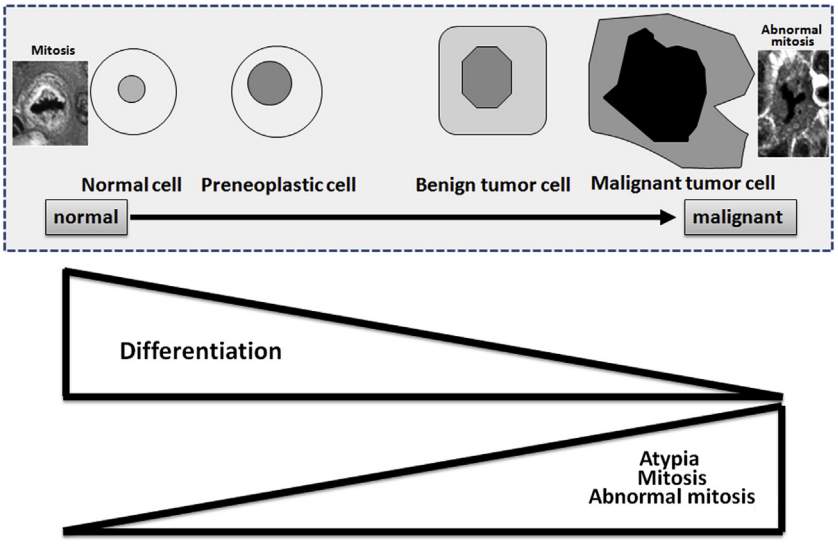

Figure 2 Differentiation and atypia of normal, preneoplastic, and neoplastic cells. Cellular differentiation is decreased during carcinogenesis. Nuclear atypia and number of mitoses including abnormal mitoses are increased during carcinogenesis. An abnormal mitosis in this figure is tripolar mitosis.

to date have consistently shown that human cancer is a genetic disease.[20]

This short review, starting with the historical studies of chemical carcinogenesis, aims to summarize several aspects of chemical carcinogenesis that have been extensively studied to establish causative associations between environmental exposures and increased cancer risk.

2. The history of chemical carcinogenesis

The first experimental work on chemical carcinogenesis was carried out in 1915 by Dr Katsusaburo Yamagiwa (a pathologist) and his assistant Koichi Ichikawa.[21] They painted rabbit ears with coal tar and observed the development of skin squamous cell papillomas and carcinomas. Subsequently, other researchers extensively studied carcinogenesis of other tissues, such as the lungs, bladder, liver, kidneys, and pancreas using laboratory animals, and showed that the experimental use of animals and carcinogens was helpful for studying human cancers, and could provide insight into the causes of cancers.

Drs Beremblum and Shubik used polycyclic aromatic hydrocarbons and croton oil to investigate skin carcinogenesis in mice, and demonstrated that cancer develops through several stages.[22] When applied as a single application to the skin at a low dose, 9,10-dimethyl-1,2-benzanthracene (DMBA) caused only a few or no skin tumors. However, multiple skin tumors developed when croton oil was applied repeatedly after this low-dose DMBA treatment. When croton oil was applied repeatedly prior to the DMBA treatment, no skin tumors developed. Based on these observations, they suggested that carcinogenesis was a complex process that included "initiation" and "promotion" stages. During the next decade, based on the studies by Rous and Beard[23] and Greene,[24] Foulds[25] introduced the term "progression" after investigating experimentally induced breast adenocarcinoma in female mice. Prior to when carcinogens were known to bind to DNA, the cancers produced by chemical carcinogens were believed to be due to their interaction with proteins in specific tissues.[26] By the end of the 1960s, increasing evidence pointed to a correlation between the DNA binding capacity of a carcinogen and its biological potency.[27]

3. Understanding chemical carcinogenesis

3.1. The multiple steps of carcinogenesis

Human cancer development is characterized by the five "Ms", namely multifactorial etiology, multistep, multiyear, multigenetic alterations, and multipath disease. Chemical carcinogenesis also involves multistage and multistep processes. Although the process includes multiple molecular and cellular events that lead to the transformation of normal cells into malignant neoplastic cells, evidence has defined at least three steps in the chemical carcinogenesis process.[3,10] These steps are "initiation",[2] "promotion",[22] and "progression"[25] (Figure 3). The first step, "initiation", is the stage where a normal cell undergoes unrepaired DNA damage and DNA synthesis to produce a mutated (initiated) cell. The production of an initiated cell can occur through interactions with physical carcinogens, i.e., UV light irradiation, as well as chemical carcinogens that possess DNA damaging or mutagenic properties. Additionally, during cell proliferation, mutations may be acquired through misrepair of damaged DNA, resulting in spontaneously initiated (mutated) cells. Following the formation of an initiated cell, chemicals and/or endogenous physiological substances can cause the selective clonal growth of the initiated cell through the process of tumor promotion. Tumor promotion involves the expansion of the initiated cell(s) to a focal lesion. The tumor promotion process is not a direct DNA-reactive or damaging process, but involves modulation of the gene expression, which results in an increase in cell number through cell division and/or decrease in apoptotic cell death.[28] Following continual cell proliferation, additional mutations might be acquired in the preneoplastic cells, resulting in the induction of a neoplasm. The term "conversion" during progression stage implies that benign tumors gain malignant phenotypes. The third step, "progression", involves additional damage to the genome and, unlike the "promotion" step, is irreversible. The multistep

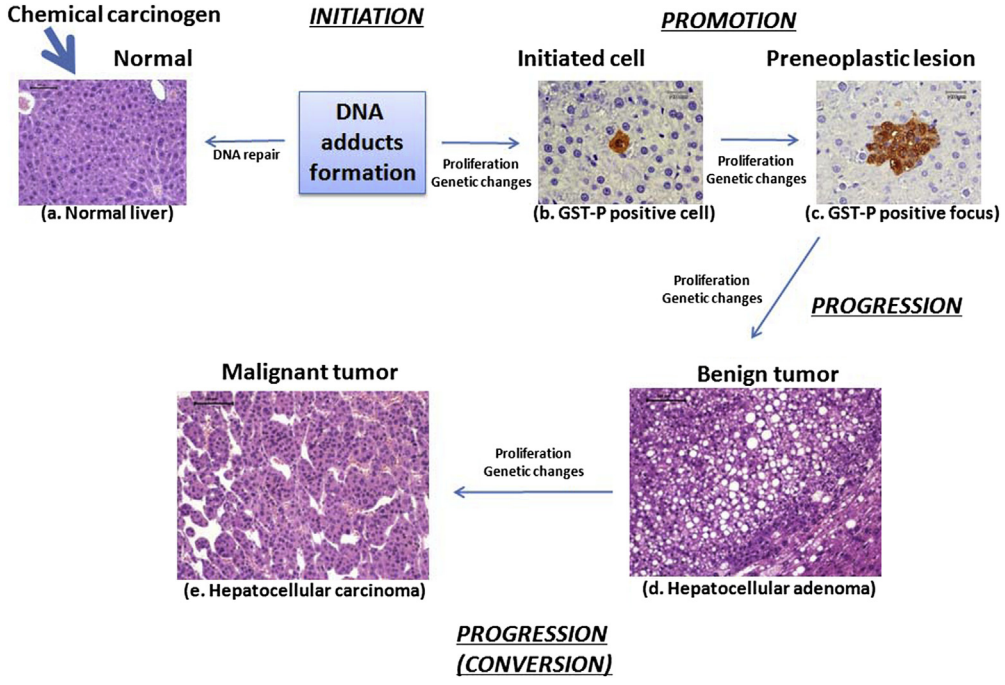

Figure 3 Multistep chemical carcinogenesis.

process has been well defined in rodent systems, and evidence has shown that similar processes occur in humans.

In humans, the clinical detection of a tumor that has developed may not occur for 20–50 years after an individual is exposed to a carcinogen.[29] The multistep process of carcinogenesis has been studied extensively in colon cancer, with the progression from hyperplastic crypts, to adenoma to cancer, and then finally metastasis, all being well characterized.[2]

3.1.1. Initiation

DNA damage can be repaired by enzymatic mechanisms.[30] However, initiated cells that are proliferating have less time to repair damaged DNA and remove covalent bonds with their DNA (DNA adducts).[31] When the initiated cells survive without repair for weeks, months, or years, they can grow in an autonomous and clonal fashion.[32] During the initiation process, cell division remains symmetrical by creating two new initiated cells. Mitogenic stimulation (which leads to an increase in the number of new cells and apoptosis inhibition) by intrinsic and/or extrinsic factors results in the clonal expansion of initiated cells, which then survive. An increase in DNA damage is especially important in stem cells, because damaged stem cells can survive for a long time in the tissues, and may remain hidden.[9]

3.1.2. Promotion

The most important activity of tumor promoters is mitogenic stimulation.[11] In order to exert the tumor-promoting effects that depend on the concentration, the tumor promoter's stimulation must continue for a long duration (weeks, months, or years) in the target tissues.[33] Promotional effects are reversible. When the tumor promoter disappears, regression of the tumor occurs, possibly through apoptosis mechanisms. Some tumor promoters are tissue-specific, but others act simultaneously on several different tissues.[34]

A long-term and/or high-dose exposure, a tumor promoter can sometimes induce preneoplasms and neoplasms even without initiation stimuli.[11] Examples of agents that can cause such lesions are phenobarbital, benzene, asbestos, and arsenic.[6] This is explained by two possibilities: the genotoxicity of these compounds may not be detected, leading to a lack of repair, or the initiated cells may spontaneously develop in response to the insult. In the latter case, an increase in the frequency of cell division can enhance the DNA replication errors as well as mutations. Not all cells exposed to a tumor promoter undergo to the promotion step, and only cells that are stimulated to divide and escape from apoptosis go on to the next step, "progression".[6]

3.1.3. Progression

The sequence of lesions identified by histopathological examinations between the initiation and promotion steps are designated as preneoplasms and/or benign neoplasms.[2,4,5] Their transformation into malignant lesions (with metastasis) is the last step, called "conversion", of the carcinogenesis process.[9,35] During the progression step, a neoplastic or malignant phenotype is obtained through genetic and epigenetic mechanisms.[1,2] In this step, the proliferation is independent of the presence or absence of progression-related stimuli.[36] Progression is characterized by irreversibility, genetic instability, growth factor production, invasion, metastasis, and alterations in the biochemistry, metabolism, and morphology of affected cells.[11,37] Neoangiogenesis is essential to the neoplastic progression.

3.1.4. Metabolism of chemical carcinogens

The metabolism of carcinogens has been discussed mainly in terms of the enzymes involved in the activation[38] and detoxification[39] of these chemicals. Miller[40] and Ames et al[41] developed the concepts of bioactivation, detoxification, and genotoxicity of carcinogens. Chemical carcinogens are absorbed after their oral, inhaled, cutaneous, or injection-based exposure, and are distributed in a variety of tissues.[42] The substances absorbed orally pass through the liver, and only then are they distributed to the other tissues. The carcinogens that first enter the lungs following inhalation are distributed by the bloodstream prior to reaching the liver.[43] The carcinogens that act directly on DNA are classified as direct-acting carcinogens. However, most chemicals require enzymatic conversion to act as carcinogens, and thus it is often the metabolites of compounds that cause the neoplastic changes (Figure 4). These carcinogens are classified as indirect-acting carcinogens or procarcinogens.[44] Metabolic activation, mostly in the liver, is controlled by Phase I reactions, whereas Phase II reactions generally protect the tissues through the transformation of activated compounds into inert products that are easily eliminated from the body.[35,45]

Metabolic activation occurs predominantly in the liver at the plain endoplasmic reticulum where the cytochrome P450s are abundant, and to a lesser degree in other tissues, including the bladder, skin, gastrointestinal tract, esophagus, kidneys, and lungs. During Phase I reactions, the cytochrome P450 monooxygenases introduce a reactive polar group into the carcinogen, making it lipophilic, and then convert it into a powerful electrophilic product that is capable of causing DNA adduct formation.[46] Phase II reactions are catalyzed by hepatic and extra-hepatic, cytoplasmic and cytochromic enzymes, acting separately or cooperatively.[47] Conjugation reactions enable these enzymes to decompose the polar group in glucose, amino acids, glutathione, and sulfate, which are less toxic metabolites that are more soluble in water and more easily excreted via the urine and bile.[48]

The metabolic activation of carcinogens is equally important for both humans and animals, although there are qualitative and quantitative differences between them, leading to incorrect interpretations when animal models are used in the research and analysis of the carcinogenic properties of chemical compounds.[49] There are several exogenous and endogenous factors that influence the susceptibility to carcinogenesis.[50]

3.1.5. Epigenetic mechanisms involved in chemical carcinogenesis

The most well understood epigenetic mechanisms involve DNA methylation and histone acetylation, methylation, and phosphorylation. The demethylation of promoter regions at the CpG sequences can lead to an overexpression of proto-oncogenes, and silencing of gene expression can occur as a result of hypermethylation, sometimes leading to chromosome condensation.[35] There appears to be a relationship between DNA methylation and histone modifications; patterns of histone deacetylation and histone methylation are associated with DNA methylation and gene silencing. Interestingly, these epigenetic changes in chromatin can also alter the sensitivity of DNA sequences to mutation, thus rendering genes more or less susceptible to a toxic insult.[37]

4. Molecular targets of chemical carcinogens

When oncogenes are transfected into immortalized mouse cell lines, they are able to induce neoplastic transformation. However, there are other genes that can influence neoplastic transformation.[30] For example, there are several genes that intervene in carcinogenesis.[30,51] Alterations in proto-oncogenes, tumor suppressor genes, and cell cycle regulatory genes are especially important during carcinogenesis.[7,35,52] Although there are several genetic diseases where mutations in one gene can cause disease, neoplastic development requires the presence of errors in the cellular defense mechanisms, which are controlled by checkpoints

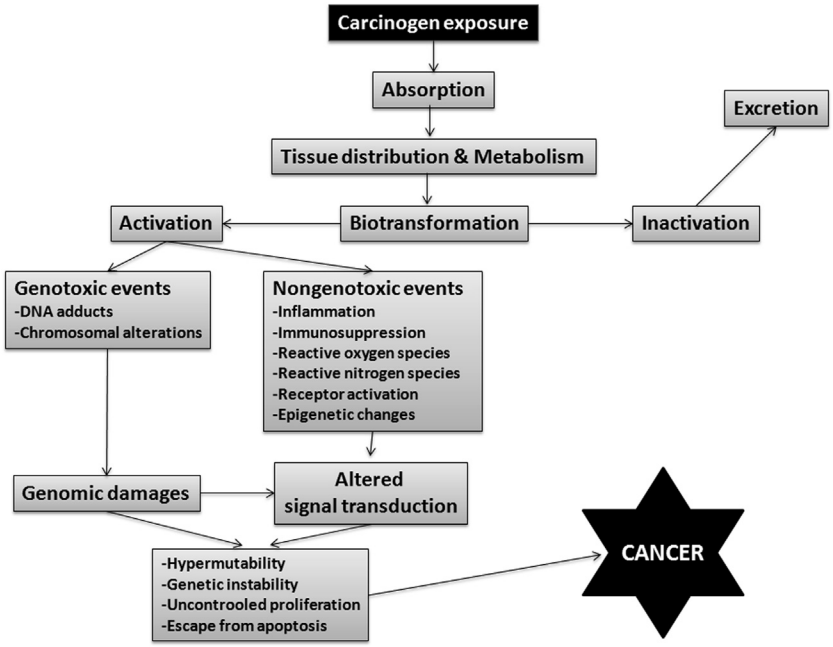

Figure 4 Metabolism and biological effects of genotoxic and nongenotoxic carcinogens on carcinogenesis.

that may prevent the entry of cells with DNA damage into the cell cycle prior to when DNA repair occurs and the cell divides.[53] The capacity of cancer cells to evade the cellular defense mechanism strongly contributes to carcinogenesis.

Alterations in the *ras* gene have been identified in several chemical-induced neoplasms in rodents. Mutations of the *ras* gene exist in about 20% of human neoplasms in the colon, breast, lung, and bladder.[54] An analysis of the *ras* gene isolated from the DNA of neoplasms revealed that changes in the sequence of nucleotides correspond to the places where carcinogens interact with DNA. Of note, each chemical compound appears to create its own unique fingerprint on the DNA.

The tumor suppressor genes, such as those encoding *p53*, *p21*, and *pRb*, play crucial roles in cellular protection, because they encourage the blockade of the cell cycle at the G1 phase.[55] The loss of the pRb protein function provokes an increase in the cell proliferation rate and an absence of terminal differentiation. *p53* can interrupt the cell cycle at G1 and allow cells to repair DNA damage.[37]

The most prominent and best-studied tumor suppressor is *p53*. When DNA is damaged, *p53* can induce either cell cycle arrest or apoptosis in order to maintain the stability of the cell's genome.[56] The loss of *p53* during carcinogenesis can predispose preneoplastic cells to accumulate additional mutations by blocking the normal apoptotic response to genetic damage.[35] The loss of *p53* function also activates proto-oncogenes and inactivates other tumor suppressor genes, and therefore has an integral role in chemical carcinogenesis.[27] The biological activity of p53 protein is largely related to its ability to bind transcriptional regulatory elements in the DNA. The search for critical genes regulated by *p53* led to the discovery of the gene encoding *p21*, which inhibits cyclin-dependent kinases, thus providing a functional link between *p53* and the cell cycle.[30]

The mismatch repair pathway is also influenced by the *p53* family. *p53* and *p73* induce the expression of p53R2, a gene that is homologous to the R2 regulatory subunit of ribonucleotide reductase.[57] p53R2 functions in a nonspecific manner to increase the pool of free dNTPs when the need for repair arises. Although p53R2 and R2 are similar, they differ in their N-terminal amino acid sequence and regulation. p53R2 is induced by p53 and p73, whereas R2 synthesis occurs during S phase. The p53R2 and R1 complex functions as an active ribonucleotide reductase.[58] p53 also upregulates two very important proteins in the mismatch repair pathway: human MutS homologue 2 (hMSH2) and proliferating cell nuclear antigen (PCNA).[59] Mutations of hMSH2 result in hereditary nonpolyposis colorectal cancer, a colorectal cancer syndrome. hMSH2 functions in mismatch recognition and binds mismatched bases.[60] PCNA, a cofactor for DNA polymerase δ is another p53 target gene that interacts with hMSH2 to facilitate hMSH2 transfer to mismatched bases.[61]

The genes involved in carcinogenesis are classified as caretakers and gatekeepers.[51,62] This classification is based on their involvement in maintaining the genomic integrity and DNA repair, respectively.[62] The caretakers are responsible for maintenance of the genome stability. Mutations in the caretaker genes, which are considered to be typical tumor suppressors, compromise the genome stability, and more specifically, increase the probability of mutation in the gatekeepers, which include both tumor suppressor genes and oncogenes.[63] Gatekeeper genes regulate neoplastic development by inhibiting the cell growth.[51] By contrast, the inactivity of caretaker genes does not support the induction of neoplasia, instead favoring genetic instability, which results in an increase in mutations across all genes, including the gatekeeper(s). Neoplasms with an inactive gatekeeper gene can progress quickly as a consequence of its effect on genes that directly control cell death.[51]

5. Proteomics in chemical carcinogenesis

Chemical carcinogenesis studies and, in consequence, biomarker discovery research, have usually placed their focus on the initiation part of the initiation/promotion model of carcinogenesis, which becomes apparent when looking at the impressive number of biomarker studies targeting genotoxic effects. However, exposure to some chemicals has been shown to result in carcinogenesis without involving the initiation step. The mechanism of nongenotoxic carcinogenesis is still incompletely understood, and an active debate continues regarding the relative contribution of procarcinogenic endogenous mechanisms, including the

generation of free radicals and the perturbation of epigenetic mechanisms by chemical carcinogens. The next critical step in carcinogenesis is the point when these altered cells start clonal expansion. It is important to identify and validate biomarkers indicating the start of clonal expansion. For this purpose, a proteomic analysis focusing on the effects of chemical carcinogens would be useful. Two-dimensional electrophoresis with subsequent matrix-assisted laser desorption and ionization time-of-flight mass spectrometry for protein separation and identification can be applied in these proteomic studies.[64]

Alterations of highly abundant proteins have been identified, which, irrespective of the wide differences in study design and technologies used, can be grossly assigned into three functional classes: (1) proteins related to the cellular stress response; (2) inflammation; and (3) stimulation of the immune system.[65] Of note, the observed protein alterations are not causal factors in the development of chemically induced cancer, but rather reflect common reactions to cellular perturbations. In order to gain deeper insights into the process of chemical carcinogenesis, the previously applied "shotgun" analyses have to be abandoned in favor of targeted proteomic approaches focusing on the accurate identification and quantification of selected proteins. Advanced analytical techniques, such as selective reaction monitoring and multiple reaction monitoring, may have the potential to contribute to the elucidation of chemical carcinogenesis.

6. MicroRNA

A number of recent studies have reported the involvement of microRNAs (miRNAs) in the regulation of cancer initiation, development, and metastasis.[66] In malignant cells, miRNAs are often dysregulated, with their expression patterns being correlated with clinically relevant tumor characteristics.[67] Several studies on the relationship between miRNAs and carcinogen exposure have also been reported.[68] These studies indicated that alterations in genes encoding miRNA genes play an important role in chemical carcinogenesis. A number of genotoxic carcinogens that dysregulate miRNA expression have been identified. The currently available information suggests that miRNA expression is associated with tumor initiation.[68,69] The expression of many miRNAs is readily changed in cells and target tissues after acute or chronic exposure to genotoxic carcinogens. Many of the differentially expressed miRNAs are involved in regulating genes that are important for carcinogen metabolism, DNA repair, apoptosis, and other cancer-related functions.

The progression phase of carcinogenesis is less well understood. During this phase, there is further growth and expansion of the tumor cells over that of normal cells. The genetic material of the tumor is thus more fragile and prone to additional mutations. These mutations occur in genes that regulate the growth and cell functions, such as oncogenes, tumor suppressor genes, and DNA mismatch-repair genes. These changes contribute to tumor malignancy. Because miRNAs can function as oncogenes or as tumor suppressor genes, miRNAs have been found to have a role in the progression of chemical-induced tumorigenesis.[68] Alterations in the miRNA expression in tumors induced by chemical carcinogens play an important role in tumor development.[68]

Therefore, the current evidence shows that miRNAs play important roles in every stage of chemical carcinogenesis, including initiation, promotion, and progression. Changes in the miRNA(s) occur prior to tumor formation, and are not merely a consequence of a transformed state. The expression of a large number of miRNAs is readily changed in the target tissues after acute or chronic exposure to carcinogens, but these changes are not observed in nontarget tissues or following exposure to noncarcinogenic chemicals. Many of the miRNAs deregulated by carcinogens are involved in regulating genes that are important for chemical carcinogenesis.

7. Conclusion and future perspectives

Chemical carcinogenesis has multiple stages and multifactorial processes, which are associated with genetic alterations. The acquisition of the capacity to survive and grow independently from other cells represents a crucial event in the process of cancer development. Most of the morphological, biochemical, and genetic changes should be considered to be a reflection of the adaptation of neoplastic cells to survive. The prediction of chemical carcinogenicity is of great importance for human risk assessment.

The research on chemical carcinogenesis has a rich history of scientific accomplishment that includes the fields of cancer biology, cancer risk assessment, public health policy, and an understanding of lifestyle- and occupation-related causes of cancer, as well as cancer chemoprevention. The gene−environment interactions and interindividual variations in the molecular epidemiology of human cancer risk are beginning to be understood based on studies of chemical carcinogenesis, cellular and molecular biology, and epidemiology. Based on these investigations of chemical carcinogenesis, many biomarkers of cancer risk and detection have been developed. These include carcinogen-DNA adducts, somatic mutations, and the mutation spectrum linking carcinogen exposure and DNA adduction with mutation.

Chemical carcinogens and viral interactions may have synergistic effects on cancer development: dietary AFB_1 and HBV infection results in the occurrence of hepatocellular cancer. Chemical carcinogenesis using rodent models has also played, and continuous to play, an important role in the field of cancer chemoprevention and in our understanding of the mechanisms of inflammation-associated cancer and the contribution of miRNAs to cancer. However, additional studies of chemical carcinogenesis related to stem cells and the epigenetic alterations that occur during chemical carcinogenesis are warranted to provide a better understanding of carcinogenesis and to gain an insight into better strategies to prevent, detect, and treat cancer.

Acknowledgments

Funding was provided from the Ministry of Health and Welfare (a Grant-in-Aid for the 2nd and 3rd Terms Comprehensive 10-Year Strategy for Cancer Control) and the Ministry of Education, Science, Sports, and Culture (Grants-in-Aid, Nos. 13671986 and 23501324) of Japan.

References

1. Shacter E, Weitzman SA. Chronic inflammation and cancer. *Oncology (Williston Park)* 2002;**16**:217−26. 29; discussion 230−2.
2. Tanaka T. Colorectal carcinogenesis: review of human and experimental animal studies. *J Carcinog* 2009;**8**:5.
3. Tanaka T. Chemoprevention of human cancer: biology and therapy. *Crit Rev Oncol Hematol* 1997;**25**:139−74.
4. Tanaka T, Ishigamori R. Understanding carcinogenesis for fighting oral cancer. *J Oncol* 2011;**2011**:603740.
5. Tanaka T, Miyazawa K, Tsukamoto T, Kuno T, Suzuki K. Pathobiology and chemoprevention of bladder cancer. *J Oncol* 2011;**2011**:528353.
6. Trosko JE. Commentary: is the concept of "tumor promotion" a useful paradigm? *Mol Carcinog* 2001;**30**:131−7.
7. Nguyen-Ba G, Vasseur P. Epigenetic events during the process of cell transformation induced by carcinogens (review). *Oncol Rep* 1999;**6**:925−32.
8. Tanaka T. Role of apoptosis in the chemoprevention of cancer. *J Exp Clin Med* 2013;**5**:89−91.
9. Williams GM. Mechanisms of chemical carcinogenesis and application to human cancer risk assessment. *Toxicology* 2001;**166**:3−10.

10. Tanaka T. Effect of diet on human carcinogenesis. *Crit Rev Oncol Hematol* 1997;**25**:73–95.
11. Pitot HC, Dragan YP. Facts and theories concerning the mechanisms of carcinogenesis. *FASEB J* 1991;**5**:2280–6.
12. Weisburger JH. Carcinogenicity and mutagenicity testing, then and now. *Mutat Res* 1999;**437**:105–12.
13. Tanaka T. Introduction for inflammation and cancer. *Semin Immunopathol* 2013;**35**:121–2.
14. Tanaka T, Ishikawa H. Mast cells and inflammation-associated colorectal carcinogenesis. *Semin Immunopathol* 2013;**35**:245–54.
15. Ohshima H, Bartsch H. Chronic infections and inflammatory processes as cancer risk factors: possible role of nitric oxide in carcinogenesis. *Mutat Res* 1994;**305**:253–64.
16. Ohshima H, Tatemichi M, Sawa T. Chemical basis of inflammation-induced carcinogenesis. *Arch Biochem Biophys* 2003;**417**:3–11.
17. Shimizu H, Mack TM, Ross RK, Henderson BE. Cancer of the gastrointestinal tract among Japanese and white immigrants in Los Angeles County. *J Natl Cancer Inst* 1987;**78**:223–8.
18. Ziegler RG, Hoover RN, Pike MC, Hildesheim A, Nomura AM, West DW, Wu-Williams AH, et al. Migration patterns and breast cancer risk in Asian-American women. *J Natl Cancer Inst* 1993;**85**:1819–27.
19. Maskarinec G, Noh JJ. The effect of migration on cancer incidence among Japanese in Hawaii. *Ethn Dis* 2004;**14**:431–9.
20. Vogelstein B, Papadopoulos N, Velculescu VE, Zhou S, Diaz Jr LA, Kinzler KW. Cancer genome landscapes. *Science* 2013;**339**:1546–58.
21. Yamagiwa K, Ichikawa K. Experimental study of the pathogenesis of carcinoma. *CA Cancer J Clin* 1977;**27**:174–81.
22. Berenblum I, Shubik P. The role of croton oil applications, associated with a single painting of a carcinogen, in tumour induction of the mouse's skin. *Br J Cancer* 1947;**1**:379–82.
23. Rous P, Beard JW. The progression to carcinoma of virus-induced rabbit papillomas (shope). *J Exp Med* 1935;**62**:523–48.
24. Greene HS. Familial mammary tumors in the rabbit: iv. the evolution of autonomy in the course of tumor development as indicated by transplantation experiments. *J Exp Med* 1940;**71**:305–24.
25. Foulds L. The experimental study of tumor progression: a review. *Cancer Res* 1954;**14**:327–39.
26. Miller EC, Miller JA. *In vivo* combinations between carcinogens and tissue constituents and their possible role in carcinogenesis. *Cancer Res* 1952;**12**:547–56.
27. Luch A. Nature and nurture—lessons from chemical carcinogenesis. *Nat Rev Cancer* 2005;**5**:113–25.
28. Klaunig JE, Wang Z, Pu X, Zhou S. Oxidative stress and oxidative damage in chemical carcinogenesis. *Toxicol Appl Pharmacol* 2011;**254**:86–99.
29. Loeb LA, Harris CC. Advances in chemical carcinogenesis: a historical review and prospective. *Cancer Res* 2008;**68**:6863–72.
30. Bertram JS. The molecular biology of cancer. *Mol Aspects Med* 2000;**21**:167–223.
31. Heidelberger C. Chemical carcinogenesis. *Cancer* 1977;**40**:430–3.
32. Scott RE, Wille Jr JJ, Wier ML. Mechanisms for the initiation and promotion of carcinogenesis: a review and a new concept. *Mayo Clin Proc* 1984;**59**:107–17.
33. Butterworth BE, Popp JA, Conolly RB, Goldsworthy TL. Chemically induced cell proliferation in carcinogenesis. *IARC Sci Publ* 1992;**116**:279–305.
34. Yuspa SH, Poirier MC. Chemical carcinogenesis: from animal models to molecular models in one decade. *Adv Cancer Res* 1988;**50**:25–70.
35. Klaunig JE, Kamendulis LM, Xu Y. Epigenetic mechanisms of chemical carcinogenesis. *Hum Exp Toxicol* 2000;**19**:543–55.
36. Lutz WK. A true threshold dose in chemical carcinogenesis cannot be defined for a population, irrespective of the mode of action. *Hum Exp Toxicol* 2000;**19**:566–8. discussion 571–2.
37. Dixon K, Kopras E. Genetic alterations and DNA repair in human carcinogenesis. *Semin Cancer Biol* 2004;**14**:441–8.
38. Guengerich FP. Roles of cytochrome P–450 enzymes in chemical carcinogenesis and cancer chemotherapy. *Cancer Res* 1988;**48**:2946–54.
39. Jakoby WB. *Enzymatic basis of detoxification*. New York: Academic Press, Inc.; 1980.
40. Miller JA. Carcinogenesis by chemicals: an overview—G. H. A. Clowes memorial lecture. *Cancer Res* 1970;**30**:559–76.
41. Ames BN, Durston WE, Yamasaki E, Lee FD. Carcinogens are mutagens: a simple test system combining liver homogenates for activation and bacteria for detection. *Proc Natl Acad Sci U S A* 1973;**70**:2281–5.
42. Conolly RB, Reitz RH, Clewell 3rd HJ, Andersen ME. Pharmacokinetics, biochemical mechanism and mutation accumulation: a comprehensive model of chemical carcinogenesis. *Toxicol Lett* 1988;**43**:189–200.
43. van Leeuwen IM, Zonneveld C. From exposure to effect: a comparison of modeling approaches to chemical carcinogenesis. *Mutat Res* 2001;**489**:17–45.
44. Sarasin A, Meunier-Rotival M. How chemicals may induce cancer. *Biomedicine* 1976;**24**:306–16.
45. Hayes JD, Pulford DJ. The glutathione S-transferase supergene family: regulation of GST and the contribution of the isoenzymes to cancer chemoprotection and drug resistance. *Crit Rev Biochem Mol Biol* 1995;**30**:445–600.
46. Straub KM, Burlingame AL. Carcinogen binding to DNA. *Biomed Mass Spectrom* 1981;**8**:431–5.
47. Gonzalez FJ. The use of gene knockout mice to unravel the mechanisms of toxicity and chemical carcinogenesis. *Toxicol Lett* 2001;**120**:199–208.
48. Oesch F, Herrero ME, Hengstler JG, Lohmann M, Arand M. Metabolic detoxification: implications for thresholds. *Toxicol Pathol* 2000;**28**:382–7.
49. Guengerich FP. Metabolism of chemical carcinogens. *Carcinogenesis* 2000;**21**:345–51.
50. Bartsch H, Hietanen E. The role of individual susceptibility in cancer burden related to environmental exposure. *Environ Health Perspect* 1996;**104**(Suppl. 3):569–77.
51. Kinzler KW, Vogelstein B. Cancer-susceptibility genes. Gatekeepers and caretakers. *Nature* 1997;**386**:761,763.
52. Suzuki R, Miyamoto S, Yasui Y, Sugie S, Tanaka T. Global gene expression analysis of the mouse colonic mucosa treated with azoxymethane and dextran sodium sulfate. *BMC Cancer* 2007;**7**:84.
53. Khan QA, Dipple A. Diverse chemical carcinogens fail to induce G(1) arrest in MCF–7 cells. *Carcinogenesis* 2000;**21**:1611–8.
54. Pritchard JB, French JE, Davis BJ, Haseman JK. The role of transgenic mouse models in carcinogen identification. *Environ Health Perspect* 2003;**111**:444–54.
55. Khan QA, Vousden KH, Dipple A. Lack of p53-mediated G1 arrest in response to an environmental carcinogen. *Oncology* 1999;**57**:258–64.
56. Hanawalt PC, Ford JM, Lloyd DR. Functional characterization of global genomic DNA repair and its implications for cancer. *Mutat Res* 2003;**544**:107–14.
57. Nakano K, Bálint E, Ashcroft M, Vousden KH. A ribonucleotide reductase gene is a transcriptional target of p53 and p73. *Oncogene* 2000;**19**:4283–9.
58. Guittet O, Håkansson P, Voevodskaya N, Fridd S, Gräslund A, Arakawa H, Nakamura Y, et al. Mammalian p53R2 protein forms an active ribonucleotide reductase *in vitro* with the R1 protein, which is expressed both in resting cells in response to DNA damage and in proliferating cells. *J Biol Chem* 2001;**276**:40647–51.
59. Scherer SJ, Maier SM, Seifert M, Hanselmann RG, Zang KD, Muller-Hermelink HK, Angel P, et al. p53 and c–Jun functionally synergize in the regulation of the DNA repair gene hMSH2 in response to UV. *J Biol Chem* 2000;**275**:37469–73.
60. Lamers MH, Perrakis A, Enzlin JH, Winterwerp HH, de Wind N, Sixma TK. The crystal structure of DNA mismatch repair protein MutS binding to a G x T mismatch. *Nature* 2000;**407**:711–7.
61. Flores-Rozas H, Clark D, Kolodner RD. Proliferating cell nuclear antigen and Msh2p-Msh6p interact to form an active mispair recognition complex. *Nat Genet* 2000;**26**:375–8.
62. Lai C, Shields PG. The role of interindividual variation in human carcinogenesis. *J Nutr* 1999;**129**:552S–5S.
63. Vogelstein B, Kinzler KW. Cancer genes and the pathways they control. *Nat Med* 2004;**10**:789–99.
64. Schmitz-Spanke S, Rettenmeier AW. Protein expression profiling in chemical carcinogenesis: a proteomic-based approach. *Proteomics* 2011;**11**:644–56.
65. Yasui Y, Tanaka T. Protein expression analysis of inflammation-related colon carcinogenesis. *J Carcinog* 2009;**8**:10.
66. Ventura A, Jacks T. MicroRNAs and cancer: short RNAs go a long way. *Cell* 2009;**136**:586–91.
67. Deng G, Sui G. Noncoding RNA in oncogenesis: A new era of identifying key players. *Int J Mol Sci* 2013;**14**:18319–49.
68. Chen T. The role of MicroRNA in chemical carcinogenesis. *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev* 2010;**28**:89–124.
69. Pogribny IP. MicroRNA dysregulation during chemical carcinogenesis. *Epigenomics* 2009;**1**:281–90.