Carcinogenesis vol.20 no.4 pp.519–527, 1999

REVIEW

Environmental factors as regulators and effectors of multistep carcinogenesis

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This review highlights current knowledge of environmental factors in carcinogenesis and their cellular targets. The hypothesis that environmental factors influence carcinogenesis is widely supported by both epidemiological and experimental studies. The fact that only a small fraction of cancers can be attributed to germline mutations in cancer-related genes further buttresses the importance of environmental factors in carcinogenesis. Furthermore, penetrance of germline mutations may be modified by either environmental or other genetic factors. Examples of environmental factors that have been associated with increased cancer risk in the human population include chemical and physical mutagens (e.g. cigarette smoke, heterocyclic amines, asbestos and UV irradiation), infection by certain viral or bacterial pathogens, and dietary non-genotoxic constituents (e.g. macro- and micronutrients). Among molecular targets of environmental influences on carcinogenesis are somatic mutation (genetic change) and aberrant DNA methylation (epigenetic change) at the genomic level and post-translational modifications at the protein level. At both levels, changes elicited affect either the stability or the activity of key regulatory proteins, including oncoproteins and tumor suppressor proteins. Together, via multiple genetic and epigenetic lesions, environmental factors modulate important changes in the pathway of cellular carcinogenesis.

Introduction

We will focus the discussion on three issues: (i) the evidence that events impinging on the organism from the outside foster, or protect against, carcinogenesis; (ii) mechanisms underlying environmental factors' abilities to exert their effects; and (iii) the contribution of endogenous factors to the impact of environmental factors.

Evidence that environmental factors influence carcinogenesis

A large body of compelling evidence either confirms or implicates various environmental factors in the development of a wide range of malignancies. Among the key factors are chemical and physical carcinogens, infectious agents and life-style. A long list of chemicals that occur in the environment has been implicated in tumor formation (reviewed in ref. 1). An increasing number of studies are documenting the ability of chemical mutagens to elicit changes at both the genomic and the protein level (discussed below).

Environmental factors known to play important roles in the etiology of human cancer include chemical carcinogens, such as those found in cigarette smoke, dietary contaminants, such as the mycotoxin aflatoxin B1, and physical carcinogens, such as UV irradiation, asbestos and radon. Other environmental factors include pathogenic bacteria and viruses, such as *Helicobacter pylori*, human papilloma virus (HPV), and human hepatitis B and C virus (HBV/HCV). Life-styles that ignore known risk factors, such as smoking, excess exposure to sunlight, fat consumption and stress are themselves integral environmental factors that contribute to cancer development. Conversely, life-style elements thought to reduce certain cancer risk include fiber ingestion, antioxidants and exercise.

Signature mutations

A signature mutation reflects the nature of adducts and DNA lesions formed by a specific mutagen, as confirmed for several chemical and physical mutagens (reviewed in refs 2–4). The comprehensive analysis of the *p53* tumor suppressor gene has enabled the establishment of the existence of signature mutations. Classic examples for signature mutations are UV-related C→T and CC→TT conversion (5), G→T changes caused by dietary aflatoxin B1 exposure (6,7), G→T and G→C mutations associated with tobacco derived carcinogens (8,9) and the A→T and T→A alterations associated with vinyl chloride exposure (10). The identification of so-called signature mutations has provided evidence that links specific environmental factors with the mutation spectrum associated with the etiology of tumor development.

Epidemiological findings

Several lines of epidemiological evidence support the role of environmental factors in malignant disease. Non-genetic factors in cancer development have been implicated by epidemiological studies that have identified the differences in incidence and tumor type among different ethnic and geographical populations. Such studies have provided the foundation for investigating the role of environmental factors in tumor development (11,12).

Among the better-characterized examples are differences in frequency of certain types of cancer between Japanese and Western populations (1,11–13). The rate of gastric cancer in Japan is as much as six times higher than in Western populations (13). Conversely, the incidence of breast cancer is three to four times lower and that of prostate cancer, seven times lower in Japan than in Western countries.

Notably, changes in environment may be associated with major shifts in cancer prevalence. Thus the incidence of gastric cancer decreased markedly among Japanese people who migrated to Western countries (11). The risk of breast

Abbreviations: CREB, cyclic AMP response element binding protein; EGFR, epidermal growth factor receptor; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HPV, human papilloma virus; IGFR, insulin-like growth factor receptor; MAPK, mitogen activated protein kinase; NO, nitric oxide; PKA, protein kinase A; PKC, protein kinase C; ROS, reactive oxygen species; TFIIH, transcription factor IIH; TPA, 12-*O*-tetradecanoylphorbol-13-acetate.

cancer increases dramatically within only one generation upon moving to a higher-risk area, such as the USA (12,13). Such changes in tumor incidence within short time periods point to the contribution of environmental factors to tumor risk and tumor development.

Large databases based on extensive molecular analyses of tumors enable their comparison in different populations. Careful comparisons of cohorts within the same and among different populations reveal a diversity of mutational spectra. Recent analysis of the *p53* gene in breast tumors in 11 populations from five regions of Japan and six regions of the USA did not reveal a distinct pattern of mutation within either Japanese or American populations (14). Such inter-group diversity within a given ethnic population points to a regional environmental effect. Alternatively, such diversity could result from exposure to a mixture of environmental mutagens (multiple exogenous factors), which does not permit identification of the primary mutagen, nor would it coincide with a given signature mutation (14). Comparison of *p53* mutations in prostrate cancers of Japanese and Western populations have also led to identification of different mutation patterns, suggesting that different etiologic factors are involved (15).

In contrast, analyses of lung cancers among nine cohorts predominantly composed of smokers disclosed characteristic patterns among the diverse ethnic groups, suggesting that the response to mutagens in cigarette smoke overrides possible fluctuations in background mutation pattern within different ethnic groups (14).

Mutations in oncogenes have also been associated with environmental exposure. For example, the type of K-*ras* oncogene mutation has been widely associated with exposure to selective chemical and physical carcinogens (16–18).

Mechanisms whereby evironmental agents influence carcinogenesis and tumors

Development

Generally, the degree to which environmental factors affect tumor formation reflects variation in susceptibility to environmental factors, which depends on the makeup of an individual's defense mechanism, including detoxification and DNA repair enzymes. Differences in one's susceptibility could be attributed to the pattern of DNA methylation and possible polymorphism within detoxification genes. Indeed, altered activity of detoxification, and deaminating enzymes has been associated with the formation of DNA adducts as well as with the degree of DNA methylation. Hypo/hypermethylation of genes because of improper deamination reactions results in altered pattern of gene expression, as has been demonstrated for key cellular regulatory proteins, p53 and p16.

Primary targets (i.e. effectors) for environmental factors include cellular regulatory proteins, which are essential for control of cell growth, DNA repair and programmed cell death. Long-term changes elicited in those proteins occur both at the genomic level, through somatic mutations that alter protein makeup and function, and at the epigenetic level, through aberrations that affect the DNA methylation pattern at CpG sites in the promoter region of certain genes, which, in turn, affect the level of mRNA and protein expression. Environmental factors are also known to transiently modify proteins by phosphorylation and acetylation, affecting their stability and activity. The short-term effect of environmental factors on protein activity is in many cases sufficient to change the cell's ability either to enable repair of damaged DNA or to elicit programmed cell death. Prolonged exposure to environmental factors can also mediate long-term effects on the functions of cellular regulatory proteins.

To address mechanisms underlying the effect of specific environmental factors on carcinogenesis, we divide these factors into the following major groups.

Chemical and physical carcinogens

In principle, carcinogens of these types are frequently capable of eliciting pleiotropic cellular changes at the genetic and epigenetic levels and can be divided into two groups: (i) DNA-damaging agents that induce formation of DNA adducts and subsequent mutations, known as somatic mutations; and (ii) those that alter cellular signal transduction pathways and result in changes in post-translational modifications that affect conformation and/or activities of key cellular regulatory proteins. Changes in the first group (i.e. somatic mutations) are permanent; whereas those in the second group (post-translational) changes are transient. The effects of environmental factors at the protein level also are transient as a result of the limited life-span of a given protein. Both types can alter control of cell growth or death. For example temporary changes can override normal defense mechanisms and result in the incorporation and possible accumulation of somatic mutations. Accordingly, transient changes may suffice to determine a cell's capacity to undergo neoplastic transformation.

Concurrent with the well-documented activities of environmental genotoxic agents at the genomic level is their effect on cell surface receptors and various signaling cascades. The formation of reactive oxygen species (ROS) result in altered cellular redox potential and lead to respective activation of protein kinases and subsequent changes in transcription factors (Table I; reviewed in refs 19–21). The putative mechanisms by which changes in redox potential alter protein kinases include the formation of disulfide bonds between selective cysteines on signal-transducing molecules, which results in protein dimerization; such a mechanism leads either to protein activation or to inactivation (reviewed in refs 20,21).

ROS and redox potential can be considered the primary cytoplasmic changes that regulate protein kinases. The same kinases also can be activated by alterations within cell surface receptors. Cross-linking of receptors [e.g. epidermal growth factor receptor (EGFR), insulin-like growth factor receptor (IGFR)] (22,23) and subsequent trans-phosphorylation have been shown to occur in response to physical, chemical and cytokine stimuli.

A classic example of combined genetic and epigenetic changes is provided by the well-studied cellular response to UV irradiation, a potent etiologic agent in skin cancer development. While causing a signature mutation (5), post-translational modifications triggered by UV irradiation (22–29) have also been documented in the membrane, cytosol and nuclear compartments (30–33). In cellular plasma membrane, UV irradiation efficiently causes dimerization of receptors, as shown for IGFR and EGFR (22,23). In the nuclei, UV irradiation causes DNA lesions that lead to the formation of pyrimidine dimers and subsequent signature mutations, that coincide with activation of DNA-damage, related signaling cascades, as documented for c-*jun* N-terminal kinases (JNK) (34,35). Within the cytosol, UV irradiation has been implicated in the activation of various signaling cascades including protein kinase C (PKC) (36), mitogen activated protein kinase (MAPK)

Table I. Reactive oxygen species effect on protein kinases and transcription factors

Alters NF-κB activity (24,25)
Mediates apoptosis by TNFα via ASK1 (26)
Inhibits protein tyrosine phosphatases and activates MAPK and PLA2 cascades (27)
Activates p42 and p44 MAPK in hippocampus (28)
Combination with increased cytosolic calcium ROS activates ste 20 kinase 1 (29)
Regulates manganese superoxide dismutase (64)
Mediate cytokine activation of JNK (65)
Participates in lysophosphatidic acid stimulation of MAPK (66)
H_2O_2 mediated apoptosis involves extracellular signal-regulated protein kinases (67)
Level of intracellular glutathione is key regulator for JNK activation (68)
Liver cell necrosis via H_2O_2 is dependent on AP1 activation (109)
Oxidative stress regulates expression and activity of AP1 (110)
H_2O_2 role in expression of GADD153 and hemooxygenase-1 (111)
Induces IκB phosphorylation and subsequent degradation resulting in NFκB nuclear translocation and transcriptional activities (69,112)
Induces phosphoinositol 3 kinases (PI3K) and downstream effector PKB\Akt (113)
Changes in redox potential associate with altered de-acetylation of p53, p300 (114,115)

(37), and JNK (38) with changes in downstream effectors, as shown for transcription factors cyclic AMP-response element binding protein (CREB) (39), jun (40), fos (41), p53 (42) and NFκB (43).

Among the better-characterized stress kinases as per UV response is JNK. Activation of this stress kinase has been shown to occur within minutes of UV irradiation, and to last from 30 min to 24 h depending on the type (i.e. UVB, UVC) and dose (i.e. amount and dose rate) of irradiation (44). JNK activation by UV irradiation occurs as a result of JNK phosphorylation by its upstream kinases concurrent with inactivation of redox-sensitive JNK inhibitor (45). Activated JNK phosphorylate key regulatory transcription factors including c-*jun*, ATF2 and p53 (46–49). Such phosphorylation contributes to the activity and stability of JNK-associated proteins, which under non-stressed growth conditions are targeted by JNK for ubiquitination and subsequent degradation (50–52). It is the duration and magnitude of activity of stress-activated kinases and respective transcription factors that dictates whether the damaged cell will undergo growth arrest or apoptosis (53).

Dietary factors

An extensive and well-established database has been compiled that documents the relationship between micronutrients (vitamins, folic acid, beta carotene, calcium, selenium, isothiocyanates, dithiolthiones, indoles, phenols, protease inhibitors, plant sterols, limonene and phytoestrogens) and macronutrients (total energy, fiber, fat, protein, sodium chloride) and cancer risk (reviewed in 54–58). In general, dietary components relevant to cancer can be divided into three major categories: (i) dietary constituents that are carcinogenic including aflatoxins, heterocyclic amines, *N*-nitroso compounds, polycyclic aromatic hydrocarbons and trihalomethane (59–61); (ii) dietary factors that promote tumor development (tumor promoters) including diverse chemical classes, such as phorbol ester derivatives, non-TPA type tumor promoters (62), chlorinated hydrocarbons (from industrial or agricultural sources), alcohol and salt (sodium chloride). Investigations of dietary effects on experimental tumor promotion (e.g. skin, breast, colon, liver) indicate that increased ingestion of fats and/or calories markedly enhances tumor promotion in most tissues examined (58–63); and (iii) dietary components can also improve cellular defense mechanisms. For example, many bioactive compounds found in plants increase expression/induction of crucial detoxification enzymes, particularly glutathione synthetase, glutathione transferase and glucuonyl transferase, resulting in decreased bioavailability of potentially DNA-damaging carcinogens (64–71). Table II summarizes the effects of dietary factors according to their cellular targets.

It is only in recent years that the possible underlying mechanism for the effect of dietary components on tumor inhibition has begun to be better characterized. Dietary components mediate diverse effects on tumor development, including cell surface receptors, detoxification enzymes and various signaling cascades; these are summarized in Table II.

Bacterial infection

Helicobacter pylori and gastric cancer

Accumulating epidemiological and clinical data have identified *Helicobacter pylori* as a risk factor for gastric carcinogenesis (72,73). *Helicobacter pylori* infection is more prevalent in Asian populations than in Western populations, particularly in Japan and Korea where gastric cancer is the most frequently occurring malignancy. *H.pylori* infection could be a factor linking the etiologic sequence between salty food intake in Asian populations and development of gastric cancer (74).

From an etiologic standpoint, early acquisition of and long-term infection with *H.pylori* increase the risk of developing gastric cancer (72). The virulence of *H.pylori* is determined by its genotypes, particularly the cytotoxin-associated gene A (*cagA*), which encodes a high molecular weight immunodominant antigen, and *vacA* (vacuolating cytotoxin A). The carcinogenic potential of *Helicobacter pylori* infection is also implicated in the endogenous synthesis of nitric oxide (NO) in macrophages by the induction of NO synthase (74).

Viral infections

HPV

Infection with HPV, particularly types 16 and 18 (among >65 types), has been shown to be associated with most forms of uterine and cervical cancer (75). To exert its transforming potential, HPV integrates its viral dsDNA into the host genome (76). Possible mechanisms by which HPV participates in the development of cancer have been shown to depend on the activity of the two viral oncoproteins encoded by the *E6* and *E7* genes. E6 and E7 form complexes with several cellular proteins involved in cell cycle and growth control (77,78). *E6* binding to wild-type p53 promotes its degradation through the ubiquitination pathway (79,80) and abrogates its transcriptional activities (81).

Table II. Effect of dietary factors on key cellular targets

A. Carcinogen metabolism (detoxification) process
- Diet and nutritional status affect xenobiotic metabolism (70,71)
- Calorie restriction and selenium ingestion inhibit aflatoxin B1 metabolism (116,117)
- Casein inhibits hepatocellular carcinoma development in HBV-transfected mice (118)

B. Epigenetic changes leading to genetic damage
- Deficiency of methyl groups has been associated with DNA hypomethylation, altered expression of p53, impaired DNA repair and elevated mutation incidence (119–121)
- Deficiency of methyl groups increased expression of *ras* and *myc* oncogenes in rat liver (122)
- Folate deficiency induces mutations and causes break in chromosomes and single-strand DNA (123)

C. Promotion and progression
- Calorie restriction suppresses expression of the H-*ras* oncogene in rat pancreas (124) and development of spontaneous tumors in p53-null mice (125)
- Moderate deficiencies of methionine and choline enhance liver tumor development in rodents (126)
- Choline deficiency increases the hepatic concentration of diacylglycerol and proliferation of responsive cells (127)
- Specific fatty acids (ω-6) modulate the promotion of breast and prostate tumorigenesis through alterations in number of estrogen receptor in mammary gland of virgin adult mice (128)
- Responsiveness to epidermal growth factors (129–131) and activation of PKC (132)
- Sodium chloride increases oxidative damage and respective cellular regulatory proteins (133)

D. Alteration of cell cycle regulation leading to cancer prevention
- Volatile short-chain fatty acids induce apoptosis in colon cancer cell lines (134), and breast cancer cells (135)
- Retinoids induce G0/G1 arrest and apoptosis via increased expression of $p21^{WAF1/CIP1}$ and Bax, respectively, in cancer cells (136)
- Selenium-derived chemopreventive compounds potentiate activation of JNK (137) while inhibiting activities of PKC and PKA (138)
- Selenium derivatives inhibit cytosine methyltransferase (139), inhibit thymidine kinase (140), and induce apoptosis (141)
- Green tea and its constituent epigallactechin gallate (EGCG) suppress cell proliferation through EGF receptor (142), reduces AP1 (143), alters PKC and protein phosphatases (144) and inhibits physical/chemical carcinogen-induced tumor formation *in vivo* (145,146)

Table III. Mechanisms underlying HBV protein: HBx oncogenic potential

Induction of AP-1, by activating extracellular signal-regulated kinases and JNKs (147)
Activation of Ras via Ras–GTP complex, leading to transactivation of AP-1 and enhancement of cell proliferation (148)
Association with p53 tumor suppressor protein both *in vitro* and *in vivo* (149). HBx binding to p53 inhibits its sequence-specific DNA binding *in vitro*, and p53-mediated transcriptional activation of $p21^{WAF1\backslash CIP1}$ *in vivo (*150) and alters cell cycle (151)
Efficiently block p53-mediated apoptosis (152)
Association with the components of TFIIH and stimulation of the DNA helicase activity of TFIIH (153)
Regulation of expression of transforming growth factor-β 1 (154) and insulin-like growth factor I (IGF-I) receptor gene (155)
Binds damaged DNA and sensitize the cells to UV irradiation (156)
HBx inhibits nucleotide excision repair (157)

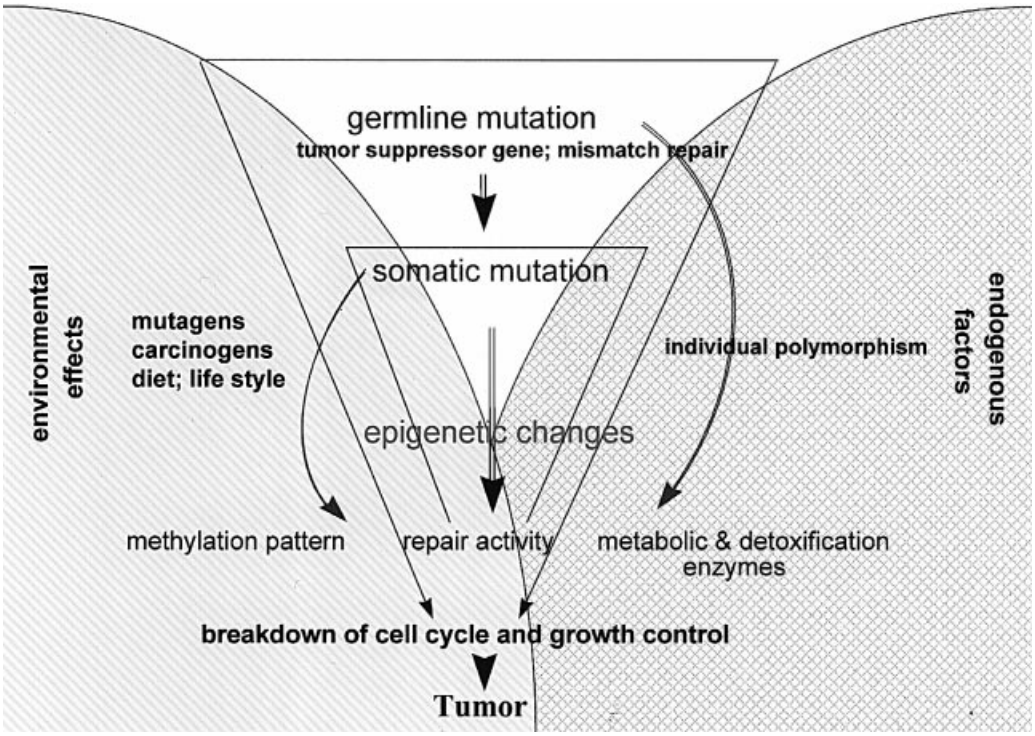

Fig. 1. When environmental-dependent and -independent changes converge.

E7 binds preferentially to unphosphorylated Rb, participates in cell growth regulation, and disrupts or alters cellular complexes that form between Rb and transcription factors E2F or *myc* (78). Importantly, continuous expression of HPV oncoproteins is required for inactivation of these tumor suppressor proteins (79).

The interaction between HPV genes and transcription factors, including AP1, NF1, Oct-1, Sp1, GRE and YY1, has been widely documented (reviewed in ref. 80). Molecular mechanisms that underlie E6 and E7 activities also include other cellular regulatory pathways.

HPV infection by itself is not sufficient for development of cervical cancer. It is the combination of HPV infection and accumulated genomic alterations that drives malignant progression (81).

Hepatitis virus

Epidemiological and clinical studies have linked HCV infection to the development of hepatocellular carcinoma (HCC), particularly in endemic area such as Korea, Japan and China (82). HCV sequences were detected in most HCV-related HCCs. The direct contribution of HCV to HCC was recently reported via the ability of HCV core protein to induce HCC in transgenic mice (83). Other regions that confer oncogenic potential include the 5′ end of the HCV genome, which encodes nonstructural protein 3; this protein is capable of mediating cell transformation *in vitro* (84). Genetic variants of HCV are determined by the nucleotide sequence corresponding to the hypervariable regions of the putative envelope protein. Whereas some variants have been shown to replicate in both malignant and non-malignant tissues, others replicate only in HCC tissue (85). Indirect evidence indicates that HCV induces genomic instability and increases the incidence of *in vivo* somatic cell mutations (86). Several genomic alterations of tumor suppressor genes, including p53, have been found in human HCC (87).

The prevalence of persistent HBV infection has been strongly correlated with the prevalence of HCC (88). Integration of HBV sequences in the host DNA is crucial for HCC development (88). The HBV genome contains the *HBx* gene, which encodes a 154 amino acid transcriptional transactivator considered to have oncogenic potential (89). *HBx* contains domains that share homology/similarity with several kinases (90,91). Of interest, the HBx protein independently, activates Ras in the cytoplasm and transcription factors in the nucleus (92). The oncogenic potential of *HBx* has been confirmed through its ability to induce HCC in *HBx* transgenic mice (93). The mechanisms that have been associated with *HBx* oncogenic potential are summarized in Table III.

Endogenous contributing factors

Germline mutations

Since they are fixed as part of the genetic makeup and thus obey rules of inheritance, germline mutations provide the foundation for a given person's predisposition to a certain cancer type. The extensive efforts to identify cancer genes via genetic and linkage analysis and the accumulating data from the human genome project have provided us with a fast growing list of genes that are mutated in the germline. So far, germline mutations in more than 20 different genes have been reported as hereditary traits increasing susceptibility to cancer. Among those are the tumor suppressor genes adenomatous polyposis coli (94,95) p53 (96–98), BRCA1 (99) and BRCA2 (100,101). In individuals with a family history [familial breast cancer (102), Li Fraumeni syndrome (97)] or those who have second malignancies, germline mutations are often present.

Gene polymorphism

Part of the wide variation in individual responses to exogenous agents is believed to result from the great diversity in responsiveness to risk factors in the environment. These variations, known as polymorphism, are caused by sporadic mutations caused by both endogenous and exogenous processes. In most instances, such mutations result in minor changes in the nucleotide sequence of the coding region as well as 5′ and 3′ untranslated regions, which are sufficient to alter expression or stability at both the RNA and protein levels. Efforts to identify functional polymorphism have been aimed primarily at enzymes associated with redox regulation and detoxification, such as glutathione *S*-transferase (103,104) and cytochrome p450 isozymes (105–107).

The recent development of high-throughput microchip-based PCR allows extensive analysis of polymorphic patterns in populations and comparisons between populations. It is expected that a wide range of polymorphism will be identified and point to different patterns in geographical ethnic groups.

Epilogue: when environment-dependent and -independent changes converge

The 'multi-hit' concept of carcinogenesis is becoming better understood as germline mutations, environmental factors and their cellular targets are identified. The interaction of any of these three major components can result in cancer (Figure 1).

Germline mutations play a key role in the relative risk of cancer predisposition, but for the most part, they are limited to those that meet the criteria of familial cases, a finding that allows better appreciation of the importance of changes influenced by environmental factors. An environmental factor's ability to cause cellular transformation hinges on an individual's genetic makeup, as on the activity of cellular defense protein (108). Polymorphism in metabolic activation and detoxification enzymes are believed to play important roles in the acquisition of susceptibility to environmental factors. It is further believed that genetic makeup, which differs among individuals, as reflected in the ability to cope with certain carcinogens, plays an important role in determining the susceptibility and development rate of the multistep carcinogenesis process. This view is well supported by findings regarding strain differences in animal model systems. Accordingly, the emerging concept is that the combined action of environmental factors and individual susceptibility determines an individual's likelihood of developing a tumor as well as its type and incidence.

Acknowledgements

We thank Ernest Wynder for inspiring the write-up of this review, Takashi Sugimura for discussions, Minako Nagao for comments and advice throughout the preparation of this review and Curtis Harris for helpful suggestions. Support by FPCR is kindly acknowledged.

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Received July 28, 1998; revised November 23, 1998; accepted December 1, 1998