Review Article

Chemical carcinogenesis: A brief review on mechanism & metabolism

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A B S T R A C T

Chemical carcinogens are supposedly considered to be the key etiological factor of malignancy. The covalent or non-covalent bonds between these chemical and the DNA, RNA, and proteins of human tissue help in the initiation of carcinogenesis wherein, genetic mutation and alteration in the genome transcription supervenes. These carcinogens behave as initiators or promoters of cancer cell growth. Alkylation of DNA, RNA, or proteins and the formation of covalent bonds with them begins initially followed by the promoting effect. Numerous molecular and cellular events causing the transformation of normal cells into neoplastic cells occur in the process. It is assumed though that endogenous molecular pathways could instigate mutations in respective genes with the support of reactive oxygen species thus leading to DNA damage. Thus, this review deals with the basic mechanism and metabolism of chemical carcinogenesis.

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1. Introduction

Human beings are persistently exposed to numerous physical, chemical and biological agents that can cause deleterious effects on the DNA and also trigger specific oncogenic pathways leading to inflammation. These specific effects damages could provide the foundation for certain precancerous and cancerous lesions.¹ Head-and-neck squamous cell carcinomas (HNSCC) typically encompassing the oral cavity, symbolizes the 6th most common cancer across the globe epitomizing approximately 3% of all types of cancer.² ³ Curtis C Harris (1991) defined Carcinogenesis as – “a multistage process driven by carcinogen-induced genetic and epigenetic damage in the population of target cells and involves the activation of protooncogenes and inactivation of tumor suppressor or anti-metastasis genes”.⁴ Oral cancer is reputedly a multifarious and intricate process which occurs when squamous epithelium is disturbed by numerous genetic alterations.³ There are unambiguous carcinogenic factors that can either be categorized as exogenous or endogenous which are responsible for cancer development.⁵ Some of the exogenous factors incorporate means related to food preparation, socio-economic status, lifestyle, ionizing and non-ionizing radiation, chemical compounds, xenobiotics, alcohol consumption and tobacco smoking. Few of the endogenous factors encompasses definite disorders and mediators that disrupts the immune system and ensuing inflammation.⁶ Chemical carcinogens bring about the process of carcinogenesis by covalently or non-covalently attaching to DNA, RNA, and proteins. Cancer initiation engulfs processes like metabolic alteration, alkylation, oxidation or dealkylation and bring about genetic mutation.⁷

2. Historical Perspective

It is implied through various researches that DNA is the cellular focus for stimulated chemical carcinogens. It is also believed that mutation is an extremely vital step of cancer
thus, outlining the structure of the major adducts in DNA by benzo (a) pyrene and aflatoxin B1.8 A pathologist named Dr. Katsusaburo Yamagiwa along with his assistant Koichi Ichikawa were considered to be the first to implement experimental work on chemical carcinogenesis in 1915.9

3. Chemical Carcinogens

Chemical carcinogens can have antagonistic effects when concurrently portrayed in different metabolic ways. Chemical carcinogens can be classified into several groups (Figure 1).10

![Fig. 1: Classification of chemical carcinogens](image)

4. Multistage Carcinogenesis

The development of cancer encompasses multifactorial etiology, multistep and multigenetic alterations, and is a multipath disease. The process of carcinogenesis consists of several molecular and cellular events and includes the three major steps - initiation, promotion, and progression to bring about transformation in a normal cell to a malignant cell.6 Initiation occurs due the exposure of cells to an adequate quantity of carcinogenic agent and cause DNA damage permanently and promoters are help to induce the tumors in initiated cells but are non-tumorigenic themselves.11

5. Mechanisms of Chemical Carcinogenesis

5.1. Initiation

Initiation is a fast, irreversible process that is transmitted to daughter cells. The development of neoplasia depends on the carcinogenic quantity wherein, the incidence and the array of neoplastic process increases with increased dosage and decreases when dose is decreased.10 The chemicals that help to initiate carcinogenesis are: (a) direct acting compounds (does not entail chemical transformation) and (b) indirect acting compounds or procarcinogens (involve metabolic conversion).9 The damaged DNA does not get repaired as the proliferating cells have less time and consequently the covalent bonds that chemicals establish with the DNA (adducts) are not removed. Thus this process verifies that cellular division stays symmetrical due to the two new initiated cells.10 The process of initiation encompasses a non-lethal and hereditary mutation in cells by interaction of a chemical with DNA. Mitogenic stimulation leads to an increased number of new cells and inhibits apoptosis through intrinsic and/or extrinsic factors thus, resulting in the clonal expansion of initiated cells that survives later.13 Reactive Oxygen Species (ROS) are considered to help in the activation of such carcinogens through hydroperoxide-dependent oxidation which is mediated by peroxyl radicals. The chemicals include aflatoxin B, aromatic amines and polycyclic aromatic hydrocarbon dihydrodiols. ROS or their byproduct of lipid peroxidation directly reacts with DNA to produce oxidative DNA adducts. Hence, this indicates an interactive function of ROS in the initiation process.10 The amount of increased DNA damage is especially important in stem cells because the damaged stem cells can endure for a longer time in the tissues, and may remain unknown for a little longer.13

5.2. Promotion

Clonal expansion of the initiated cells occurs due to the promotional influences. Reversibility is thought to be one of the essential features of the promotion response. This implies that removal of the promoting agent causes no further proliferation of the initiated cell population.14 The promotion stage comprises of epigenetic processes accountable for the development of the malignant phenotype and tumor cells survival.15 The following products such as phorbol esters, hormones, phenols and drugs are by themselves non-tumorigenic but intensifies the carcinogenicity of chemicals. These promoters helps to proliferate and leads to clonal expansion of initiated or mutated cells.11 The promoting agents thus increase cell proliferation in vulnerable tissues, donate towards fixing mutations, augment genetic and cause changes in cellular growth control. These promoters could indirectly damage the DNA by oxidation.10 ROS production is directly associated to P450 enzyme activity wherein oxidative stress could aid in the clonal expansion of the mutated cells.12 A tumor promoter can occasionally encourage neoplastic effect even without initiation stimuli if there is long term or high dose exposure. This is attributed to the genotoxicity of such compounds which may not be detected, thus, leading to a lack of repair, or the initiated cells may automatically develop because of the insult. There is an escalation in the incidence and frequency of cell division that can enrich the DNA replication errors as well as mutations. It is observed that not all the cells exposed to a tumor promoter experience promotion, and only cells that are encouraged to divide and evade apoptosis go on to the next step i.e. “progression”; 6,16
5.3. Progression

Genetic heterogeneity in a promoted cell population takes place when the initiated or mutated cell population is extended during promotion and attains further genetic damage. This is accredited to either agent mediated or spontaneous pertaining to irreversible and progressive changes. In the step of progression, a neoplastic phenotype is attained due to genetic and epigenetic means. Here, the proliferation is a self-governing process in spite of the presence or absence of progression-related stimuli. It is exemplified by irreversibility, genetic instability, growth factor production, invasion, metastasis, and alterations in the biochemistry, metabolism, and morphology of disturbed cells.

6. Epigenetic Mechanism & Molecular Targets

The most well comprehended epigenetic mechanisms encompasses DNA methylation and histone acetylation, methylation and phosphorylation. A liaison between DNA methylation and histone modifications occurs. The patterns of histone deacetylation and histone methylation are connected with DNA methylation and gene silencing. Hence, these epigenetic changes in chromatin can also modify the DNA sensitivity sequences to thus, making the genes more predisposed to toxic insult.

It is well accepted now that protooncogenes, tumor suppressor genes and cell cycle regulator genes adopt an unambiguous importance. DNA is the major target for chemical carcinogens but there is no exceptional and exclusive alteration that can be related to the initiation of chemical carcinogenesis. The picture of specific type of DNA damage in human tumors can postulate certain molecular evidences to their etiology. This is exhibited with the help of research works on mutations in RAS and p53 genes. Each carcinogen yields a molecular ‘fingerprint’ that relates to specific chemicals along with the mutational outcomes. The tumor suppressor proteins p53; p21 and Retinooblastoma protein (pRb) play vital roles in cellular protection as they tend to support and augment the blocking of cells at G1 phase of cell cycle. The loss of pRb protein function aggravates and there is enhanced cell proliferation rate. Absence of terminal differentiation p53 can disrupt the cell cycle at G1 phase and bring about repair mechanisms for the damaged DNA.

6.1. DNA damage & repair

It is imperative to note that aberrations at the primary sequence may not principally result in cancer irrespective of the particular nature of the carcinogen damage to DNA. Hence, there are at least three possible fates for such carcinogen damage (summarized in Figure 3). The typical form of DNA damage brought about by carcinogens governs the mechanism of its repair. DNA repair is a process which allows a cell to preserve its genome reliability. There are different means towards DNA repair e.g. excision repair, (which consists of both nucleotide excision repair and base excision repair), mismatch repair (MMR) and double strand break (DSB) repair. Each pathway embraces certain distinctive enzymatic mechanism. It is well established by authors that all DNA adducts and damage are repaired, with only the rare exception leading to the change in sequence and mutation.

7. Metabolism of Chemical Carcinogens

There are countless chemicals that employ metabolic activation in order to apply their carcinogenic potential. Elizabeth and James Miller showed in their studies that metabolic activation of azo dyes led to the covalent binding to cellular macromolecules. They also demonstrated the model carcinogen 2-acetylaminofluorene (2-AAF) wherein, hydroxylation of the amide nitrogen produced a metabolite that was more carcinogenic than the parent molecule. Chemical carcinogens may be absorbed in many ways (oral, inhalator, cutaneous and injection) and are dispersed among
various tissues. This absorption rely on the physicochemical properties of the substance and occur through active or passive transport mechanism. The substances that are absorbed orally pass through the liver and then are they dispersed in the body; those absorbed in the lungs are distributed by the blood before reaching the liver at a later stage. It has been established that approximately all chemicals undergo metabolism through different enzyme pathways, with differences in kinetics and saturation levels. Such metabolic pathways also preferably help to process and detoxify noxious chemicals. These reactions have been categorized into phase I and phase II metabolism. Phase I can be separated into oxidation, reduction and hydrolytic reactions and phase II involves a series of conjugation reactions wherein, an endogenous molecule is added to the xenobiotic chemical.

Generally, phase I reactions expose and introduce a functional group into the molecule and phase II metabolism conjugates the derivative with a polar, water-soluble and endogenous acidic molecule. However, these pathways of detoxication metabolism have proficiency to fortuitously bioactivate chemical carcinogens. The enzymes produced in phase I contribute in the reactions of oxidation, reduction and hydrolysis, and are thus cataloged as oxidoreductases (cytochrome P450 dependent monooxygenases, flavine monooxygenases, cyclooxygenases and alcohol dehydrogenase) and hydrolases (epoxide hydrolases). Phase II enzymes partake in the conjugation and inactivation of chemical carcinogens and comprise of transferases (glutathione S transferases, N-acetyltransferases, UDP-glucuronosyltransferases, sulphotransferases). Cytochrome P450 isoenzymes are the most common group of enzymes that indulges in carcinogen metabolism. Although, several other enzyme systems have been also recognized in the process. Though some of these metabolic processes lead to activation to reactive electrophiles, many other cause inactivation of chemicals by enhancing the aqueous solubility and causing increased excretion.

Peroxidations also occur analogous to metabolic reactions with the constant production of ROS that are correlated with many chronic diseases and with chemical carcinogenesis. The ROS damage DNA, RNA and proteins by specific chemical reactions like oxidation, nitration/nitrosation and halogenation which causes an increase in mutation and alteration in the functions of important enzymes and proteins. The preponderance of procarcinogens are activated by mechanisms encompassing two-electron-mediated metabolic reactions primarily catalyzed by the mixed-function oxidase enzyme systems, frequently including cytochrome P-450 (CYP) enzymes. Mutations in the equivalent and corresponding genes promote carcinogenesis and progression of tumors. Other enzyme systems that can contribute in these one-electron activation reactions incorporate constitutive peroxidises such as myeloperoxidase and lactoperoxidase (both can activate xenobiotics).

8. Conclusion

Chemical carcinogenesis thus encompasses numerous stages that are correlated with genetic alterations. The etiology of carcinogenesis is extremely complicated and difficult to comprehend easily, thus encompassing innumerable levels of regulation. It is thus clear that endogenous molecular pathways can cause mutations in certain important genes along with ROS and can bring about DNA damage. The various research and study work
on chemical carcinogenesis includes data pertaining to the biology, cancer risk evaluation, public health policy, determining of lifestyle and several cancer chemoprevention means.

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References

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