Advances in Nanomedicine and Nanotechnology Research
ANNR, 2(2): 123-126
www.scitcentral.com

ISSN: 2688-5476

Original Research Article: Open Access

Mutation by Base Pair Substitution

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Received March 02, 2020; Revised March 26, 2020; Accepted March 28, 2020;

ABSTRACT

In this paper chronic toxic effects of carcinogenesis are studied. In carcinogenesis, the first stage initiation includes a genotoxic event such as binding of an electrophilic xenobiotic to DNA, causing a premutagenic lesion in a single cell. In the next stage promotion finally resulting in tumor formation. In this paper, multistep model of tumor formation was illustrated. Reproductive toxicity, which including any detrimental effect on the male or female reproductive system due to exposure to toxic effects and DNA replication was studied.

Keywords: Induced toxicity, Embryotoxicity, DNA repair, Promotion, Genotoxic event, Tumor formation

Abbreviations: DNA: Deoxyribonucleic acid; RNA: Ribonucleic acid; mRNA: Messenger RNA; rRNA: Ribosomal RNA; tRNA: Transfer RNA; UV: Ultraviolet light

INTRODUCTION

Chronic effects are those that appear after repetitive exposure to a substance, many compounds require several months of continuous exposure to produce adverse effects. Often, the chronic effects of chemicals are different from those seen after acute exposure. Carcinogenic effects of chemicals usually have a long latency period. Tumors may be observed years, in rodents, or even decades, in humans, after exposure.

The induction of cancer by chemicals is a complex multistep process involving interactions between environmental and endogenous factors. Tumors are formed as a result of aberrant tissue growth due to loss of control mechanisms of cell division. A model traditionally used for an operational description of carcinogenesis is the initiation-promotion model. The first stage initiation requires a genotoxic event such as binding of an electrophilic xenobiotic to DNA, causing a premutagenic lesion in a single cell. After DNA replication, the premutagenic lesion may be transformed into a heritable mutation i.e., by base pair substitution. In the stage of promotion, several primarily nongenotoxic mechanisms facilitate (promote) the preferential proliferation of the initiated cell, finally resulting in tumor formation.

Initiators are usually genotoxic agents whereas promoters act generally by interfering with extranuclear sites and processes, most promoters increase cell growth and cell proliferation. In this paper mutation by base pair substitution was studied.

INITIATORS AND PROMOTERS

Initiators are resulting in irreversible changes in the cellular genome without threshold exposure levels. Promoters show some reversibility and threshold exposure levels for promoters were discussed [1-7]. This stepwise nature of carcinogenesis was first shown in mouse skin and this model has now been well characterized. In a typical experiment, an initiating chemical such as dimethylbenzanthracene is applied to mouse skin at a low dose so that very few tumors, if any, are produced in the animal's lifetime. After an interval of one week to one year, the treated (initiated) skin is exposed to multiple applications of a promoter, such as the phorbol esters found in croton oil. Tumors begin to appear within 5 to 6 weeks after application of the promoter, and all mice carry tumors by 10-12 weeks after the start of application.

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Citation: Savkovic-Stevanovic J. (2020) Mutation by Base Pair Substitution. Adv Nanomed Nanotechnol Res, 2(2): 123-126.

The initiation-promotion experiments on mouse skin and similar experiments in rodent liver have led to the following general rules of carcinogenesis:

- The initiator must be given first; no tumors or very few tumors result if the promoter is administered first.
- The initiator, if given once at a sub carcinogenic dose, does not produce tumors during the time of observation, however, repeated doses of the initiator may cause tumors even in the absence of promoter the initiator is a complete carcinogen in this case.
- The action of the initiator is irreversible, tumor result in nearly the same yield if the interval between initiation and promotion is extended from one week to one year.
- The initiator is an electrophile, which binds covalent to DNA causing a mutation after DNA replication.
- In contrast, no evidence exists of covalent binding of promoters or their metabolites to DNA.
- The action of the promoter is reversible at an early stage and usually requires repeated exposure, thus, a threshold level of exposure to promoters probably exists. However, threshold levels cannot be reliably defined, as long as the biochemical mechanism involved in tumor promotion is not known precisely. In contrast to the established target of the initiation process DNA, the molecular mechanisms of tumor promotion are still largely unknown.

In addition to the promotion of skin carcinogenesis by phorbol esters, promoters for tumors in other organs are known or suspected. Bile acids are promoters of colon carcinogenesis in experimental animals. In humans, a strong association exists between high intake of dietary fat and cancer of the colon, since ingestion of fat increases the amount of bile acids in the colon, the increased incidence of colon cancer may be due to the promoting effect of bile acids on intestinal epithelia. In rat bladder, saccharine and cyclamate are promoters of tumors initiated by a single dose of dimethylnititrosourea, tryptophan is a promoter of urinary bladder tumors in dogs treated with an initiating dose of 4-aminobiphenyl or 2-naphthylamine. Hormones are also known modifiers of chemical carcinogenesis. An oral or intravenous injection of dimethyl benzanthracene produces mammary tumors in susceptible female mice. Prolactin increases and accelerates tumor development, whereas ovariectomy results in reduced tumor yield **(Figure 1)**.

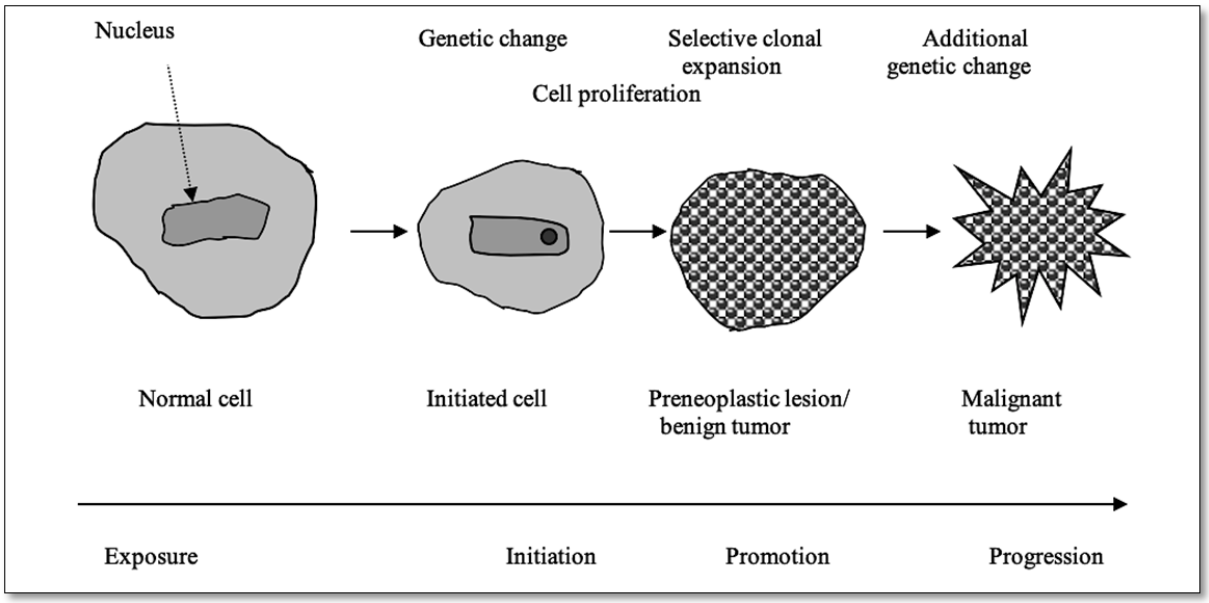

Figure 1. Model of tumor formation.

In eurocaritic cells, the initial mRNA copy contains homologues of both the intron and the exon regions. The intron regions are removed, and the exon regions are spliced together to form the active mRNA molecules, which are then transported through the pores of the nuclear membrane to the cytoplasm.

The next process involves the translation of mRNA molecules into polypeptides. This procedure requires many enzymes and two further types of RNA, transfer RNA (tRNA) and ribosomal RNA (rRNA). A specific tRNA exists for each amino acid. The tRNA molecules are involved in the transport and coupling of amino acids into the resulting polypeptide. Each tRNA molecule has two binding sites one for the specific amino acid, the other containing an inlet of bases that is complementary to the appropriate codon on the mRNA.

Genotoxic events resulting in heritable mutations cause the formation of an initiated cell (initiation). In the following stage of promotion, nongenetic (epigenetic) events contribute to preferential proliferation of the initiated cell. In the third stage of progression, additional genetic events increase the malignancy of the tumor tissue, its growth becomes increasingly destructive and metastases are formed in other organs.

The toxic effects from prenatal exposure observed at the time of birth are embryolethality, malformations and growth retardation. The relationship among embryo lethality, malformations and growth retardation is quite complex and depends on the type of agent, the time of exposure and the dose. Some developmental toxins may cause malformations of the entire litter at exposure levels that do not cause embryolethaly.

DNA STRUCTURE AND REPLICATION

DNA structure and function determine translation and replication of DNA. The linkage between DNA in the cytoplasm is not direct. Information contained in the DNA molecule is transferred to the protein-synthesizing procedure of the cell messenger RNA (mRNA), which is synthesized complementary to involve the translation of mRNA the relevant DNA sequence by RNA polymerase. The mRNA molecules act as transport vehicles for information contained in the genes being expressed.

The tRNA is complexed with protein to form subcellular globular organelles called ribosomes. Ribosomes can be regarded as the reading heads, which allow the linear array of mRNA codons to base pair with an anti-codon of an appropriate incoming tRNA-amino acid complex.

All cells possess the same genetic information, however, different types of cells exhibit distinct gene transcription patterns [8,9]. These differences in gene expression are critical to the morphological and biochemical properties of the many thousands of cell types in the human and animal body. Hence mechanisms are required that regulate gene expression, determine which genes are expressed and to what extent and which genes are not expressed in a certain cell type at a particular time. The mechanisms involved in regulation of gene transcription are not entirely understood. The transcription of structural genes is regulated by a special set of codons, in particular, promoter sequences, the initial binding sites for RNA polymerase before transcription begins. Different promoter sequences have different affinities for RNA polymerases.

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The mechanisms involved in regulation of gene transcription are not entirely understood [10-16]. The transcription of structural genes is regulated by a special set of codons, in particular, promoter sequences, the initial binding siters for RNA polymerase before transcription begins. Different promoter sequences have different affinities for RNA polymerases. Additional regulatory genes called operators regulate the activity of several genes or gene groups (operons). The activity of the operator itself is further controlled by a repressor protein, which stops transcription of the whole operon by binding to the operator sequence. Because of these regulatory mechanisms, cells are able to express only the genes required at a given moment for their specialized function. This not only helps to converse cellular energy but also is decisive for correct cellular differentiation, tissue pattern formation and function and maintenance of the physiological integrity of the entire organism.

All living cells possess several efficient DNA repair processes. DNA repair is crucial in protecting cells from spontaneous and exogenous lethal and mutating effects such as heat-induced DNA hydrolysis, UV light, ionizing radiation, DNA-reactive chemicals, free radicals and reactive oxygen species. Among the various existing DNA repair mechanisms, the most comprehensively studied mechanism in eukaryotes is the excision repair pathway. The mechanism includes a group of enzymes acting cooperatively to recognize DNA.

Lesions, remove them, and correctly replace the damaged sections of DNA [17-20].

The excision repair pathway is regarded as error free and does not lead to mutations [21-23]. However, this pathway may become saturated after excessive DNA damage. In this case, the cell may be forced to activate other repair mechanisms that are not error free. Several of these mechanisms, such as error-prone repair, have been well characterized in bacteria, but their counterparts, if any, in mammalian cells have not been identified.

XENOBIOTIC BIOTRANSFORMATION

Although the human placenta contains most of the important enzymes of xenobiotic biotransformation, the activities of these enzymes are negligible compared to the liver. Hence, no significant metabolism is expected to occur in the placenta unless the mother has been exposed to enzyme inducers.

Xenobiotics that are lipophilic, nonionized at physioloc pH and have molecular masses <500 readily cross the human placenta.

Important for the human situation is the fact that smoking appears to increase significantly the activity of aryl hydrocarbon hydroxylase (AHH, cytochrome P4501A1) in the human placenta. Xenobiotic biotransformation does not occur or is negligible in the embryo or fetus. Also, the majority of experimental evidence available so far does not

indicate inducibility of xenobiotic metabolism in the fetus until late in gestation.

CONCLUSION

This paper considers toxic effects to genesis system. Some developmental toxins may cause malformations. Embryotoxic effects can lead to overall growth retardation or delayed growth of certain organs.

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