
# FACULTY OF ENGINEERING & TECHNOLOGY

# LT. 17 Chemical Carcinogenesis

**Content outline**

1. Chemical carcinogenesis

# Chemical carcinogenesis

•Chemicals appear to be of major importance in the induction of human cancers. The known chemical carcinogens include a wide range of structures. Their common feature is that their ultimate forms are electrophilic reactants; in most cases, these reactants arise through metabolism in vivo.

•Carcinogenesis by chemicals is a multistage process.

**Cancer arise in 3-steps**

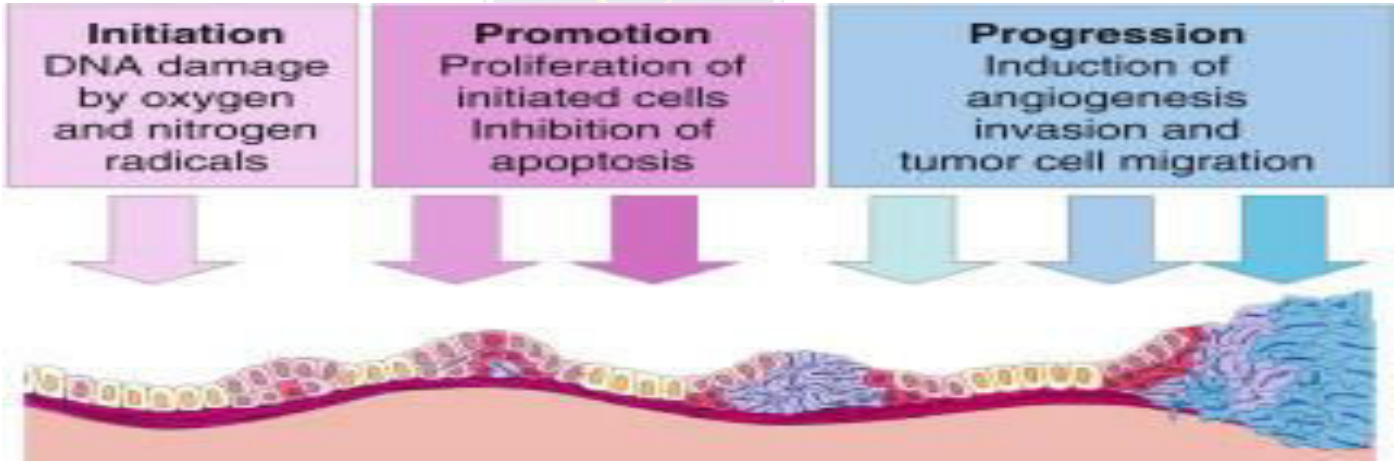
i. Initiation (the process of acquisition of genetic and epigenetic changes that sets the cell on path to cancer),

ii. Promotion (a step during which the primed cells express altered responses that provide a selective advantage allowing them to survive and develop locally),

iii. Progression (a series of steps during which the now established cancer cells accumulate further changes on the path to malignancy

•Chronic inflammation contributes to each of these mechanisms. First, inflammation generates an overload in reactive oxygen species (ROS) and reactive nitrogen species (RNS) that damage DNA and enhance several mutagenic processes, thereby accelerating the acquisition of mutations that drive the cancer process. Second, chronic inflammation involves the production of a complex combination of factors, some of which promote cell proliferation and survival, while others induce cell death.

•Third, inflammation profoundly alters the relationships between cells and their stroma, and also enhances angiogenesis, thus facilitating local invasion and distal dissemination of cancer cells.




•The role of inflammation in initiation, promotion, and progression stages of cancer development. The sequence of development of an epithelial tumor is represented and divided in three steps: initiation, promotion, and progression. The contribution of inflammatory mechanisms to each step is summarized.

**Different type of electrophilic reactant generated *invivo*.**

The main DNA-damaging reactive species produced during inflammation are hydrogen peroxide ($H_2O_2$), nitric oxide ($NO^{\cdot}$), and reactive intermediates such as hydroxyl radicals ($OH^{\cdot}$), superoxide ($O_2^{-\cdot}$), and peroxynitrite ($ONOO^-$).During inflammatory response, $NO^{\cdot}$ is also produced inside cells through the activation of the transcription of inducible nitric oxide synthase (NOS)-2 in response to cytokines. The promoter of NOS-2 contains binding sites for nuclear factor kappa B (NFκB). Overproduction of $NO^{\cdot}$ causes two main mechanisms of mutagenesis. One is direct DNA damage through radical attack of DNA (generating DNA strand break, base damage, and chromosome damage). The second is enhanced deamination of 5-methylcytosine (5mC), the most common methylated form of cytosine representing about 3% of all cytosines in the genome. Deamination of 5mC into thymine generates a DNA mismatch (G:T) whichif not repaired, may result in a mutation (from a G:C base pair to an A:T base pair) Since 5mC preferentially occurs at CpG dinucleotides, this type of mutation is often found within this particular sequence context. Mutations at CpG dinucleotides are the most frequent form of single base substitutions in inflamed tissues and in cancers arising in an inflammatory context. For example, about 50% of mutations in the TP53 tumor suppressor gene occur at CpG dinucleotides in colon cancer and in adenocarcinoma of the esophagus – two cancers with well-defined inflammatory precursors.

# References & Further reading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