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Carcinogenesis: Molecular mechanisms, risk factors, and emerging therapeutic target

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ABSTRACT

Carcinogenesis is a multistep biological process in which normal cells transform into malignant ones due to genetic, epigenetic, and environmental influences. This review explores the fundamental mechanisms of carcinogenesis, including the initiation, promotion, and progression phases. It delves into the roles of oncogenes, tumor suppressor genes, DNA repair mechanisms, and the tumor microenvironment. Additionally, the article examines carcinogenic agents such as chemicals, radiation, and infectious organisms. Emphasis is also placed on emerging molecular targets and therapeutic approaches in cancer prevention and treatment. Understanding the complex interplay of cellular and molecular events in carcinogenesis is vital for developing more effective cancer diagnostics and interventions.

KEYWORDS

Hereditary; Carcinogenesis; Immunotherapy; Vaccination; Early screening; Macrophages

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Introduction

Cancer continues to be among the primary reasons for illness and death globally. Although progress has been made in early diagnosis and therapy, the worldwide impact of cancer is still increasing. Carcinogenesis, the transformation of normal cells into cancerous ones, is key to comprehending cancer biology and creating effective treatment approaches. It entails an active interplay between genetic tendencies and environmental factors that result in the conversion of a normal cell into a cancerous phenotype.

The Multistep Model of Carcinogenesis

Carcinogenesis is commonly categorized into three overlapping yet distinct phases: initiation, promotion, and progression.

Initiation

This stage includes permanent genetic alterations frequently triggered by carcinogen exposure, resulting in mutations in vital genes such as proto-oncogenes or tumor suppressor genes. DNA damage happening during initiation may arise from direct contact with mutagens or from the metabolic activation of procarcinogens [1].

Promotion

During this reversible phase, activated cells are prompted to multiply. Promoters don't directly induce DNA damage but promote the clonal proliferation of mutated cells. Persistent inflammation, hormonal influences, and specific dietary elements frequently serve as contributors [2].

Progression

This concluding phase involves further genetic and epigenetic changes that promote cell growth, invasiveness, blood vessel formation, and spread to other sites. Genomic instability becomes more evident, and tumor cells frequently develop resistance to apoptosis and immune detection [3].

Molecular Mechanisms in Carcinogenesis

Oncogenes and proto-oncogenes

Proto-oncogenes produce proteins that play a role in cell growth and survival. When altered, they turn into oncogenes, promoting uncontrolled cell growth. Examples consist of RAS, MYC, and HER2. Mutations can arise from point mutations, gene amplification, or chromosomal rearrangements [4].
Tumor suppressor genes

Genes like TP53, RB1, and BRCA1/2 function as cellular "brakes" to regulate growth and encourage DNA repair or cell death. Loss-of-function mutations in these genes create a conducive environment for tumor growth [5].

DNA repair mechanisms

Effective DNA repair mechanisms are crucial for maintaining genomic stability. Deficiencies in mismatch repair (MMR), nucleotide excision repair (NER), or homologous recombination repair (HRR) are associated with several hereditary cancers, including Lynch syndrome and breast/ovarian cancers linked to BRCA [6,7].

Epigenetic modifications

Epigenetic alterations, such as DNA methylation, modifications to histones, and expression of non-coding RNAs, affect gene expression without changing DNA sequences. Irregular hypermethylation of tumor suppressor genes and overall hypomethylation play roles in cancer development (Table 1) [7,8].

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Table 1. Overview of carcinogenesis: mechanisms, factors, and implications.

Category	Key Components	Role in Carcinogenesis
Phases of Carcinogenesis	Initiation, Promotion, Progression	Sequential stages leading to malignancy; initiation involves genetic mutations, promotion involves clonal expansion, and progression includes invasion/metastasis.
Genetic Alterations	Oncogenes (RAS, MYC), Tumor suppressor genes (TP53, RB1), DNA repair genes (BRCA1/2, MSH2)	Mutations in these genes disrupt cell cycle control, DNA repair, and apoptosis, promoting uncontrolled cell growth.
Epigenetic Modifications	DNA methylation, Histone modification, non-coding RNAs	Modify gene expression without altering DNA; involved in silencing tumor suppressors or activating oncogenes.
Tumor Microenvironment (TME)	Fibroblasts, Immune cells (TAMs, Tregs), Extracellular matrix, Cytokines	Supports tumor survival, immune evasion, angiogenesis, and metastasis through complex interactions.
Carcinogenic Agents	Chemical: PAHs, nitrosamines, aflatoxins, Radiation: UV, ionizing radiation, Infectious agents: HPV, HBV, H. pylori	External agents that initiate or promote carcinogenesis through DNA damage, inflammation, or immune modulation.
Hereditary Syndromes	BRCA1/2 (breast/ovarian), APC (colorectal), TP53 (Li-Fraumeni)	Inherited mutations increase lifetime cancer risk; early screening and prophylactic measures often recommended.
Molecular Biomarkers	EGFR (lung), KRAS (colorectal), HER2 (breast), PSA (prostate)	Aid in early detection, prognosis, and guiding targeted therapies.
Emerging Therapies	Targeted therapy, Immunotherapy (Checkpoint inhibitors, CAR-T), Epigenetic drugs	Personalized and molecular-based treatments showing improved specificity and efficacy.
Prevention Strategies	Lifestyle modifications, Vaccination (HPV, HBV), Early screening	Essential for reducing cancer incidence and detecting precancerous conditions early.

Role of the Tumour Microenvironment (TME)

The TME consists of cancer-associated fibroblasts, immune cells, endothelial cells, and extracellular matrix components. These elements interact with tumor cells to promote angiogenesis, immune evasion, and metastasis. Chronic inflammation and hypoxia in the TME further exacerbate tumor progression. For example, tumor-associated macrophages (TAMs) often support tumor growth and suppress cytotoxic T-cell activity [9,10].

Carcinogenic Agents

Chemical carcinogens

Chemical carcinogens can be classified as genotoxic (direct DNA-damaging agents) or non-genotoxic (promoters of proliferation). Examples include polycyclic aromatic hydrocarbons (PAHs), aflatoxins, and tobacco-specific nitrosamines. Many require metabolic activation by cytochrome P450 enzymes [11].

Radiation

Ionizing radiation causes DNA strand breaks and oxidative stress, contributing to mutations and chromosomal abnormalities. Ultraviolet (UV) radiation, particularly UVB, induces pyrimidine dimers and is a major risk factor for skin cancers [10,12].

Infectious agents

Oncogenic viruses such as human papillomavirus (HPV), hepatitis B and C viruses (HBV/HCV), and Epstein–Barr virus (EBV) are implicated in various cancers. These pathogens interfere with cell cycle regulation and immune responses [13].

Lifestyle and environmental factors

Diet, alcohol consumption, obesity, and physical inactivity have also been linked to increased cancer risk. Environmental pollutants like asbestos and arsenic are well-established carcinogens.

Genetic and Hereditary Factors

Approximately 5–10% of cancers are due to inherited genetic mutations. Hereditary syndromes such as Li-Fraumeni syndrome (TP53 mutation), Familial adenomatous polyposis (APC mutation), and Hereditary breast and ovarian cancer syndrome (BRCA1/2 mutations) significantly increase lifetime cancer risk [14].

Emerging Biomarkers and Therapeutic Targets

Molecular biomarkers

Biomarkers for early detection and prognosis are critical. Examples include KRAS mutations in colorectal cancer, EGFR mutations in non-small cell lung cancer, and PSA in prostate cancer [15].

Targeted therapy

Molecular understanding of carcinogenesis has led to targeted therapies, including tyrosine kinase inhibitors (e.g., imatinib,

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erlotinib), monoclonal antibodies (e.g., trastuzumab), and immune checkpoint inhibitors (e.g., nivolumab, pembrolizumab) [16].

Immunotherapy

Harnessing the immune system to combat cancer has revolutionized oncology. Checkpoint blockade, CAR-T cell therapy, and cancer vaccines show promise in hematological malignancies and solid tumors [17].

Epigenetic therapy

Drugs targeting DNA methylation and histone deacetylases are used in certain hematological cancers, with ongoing research into their broader application [18].

Prevention and Early Detection

Lifestyle modifications

Smoking cessation, weight management, physical activity, and a balanced diet are key to reducing cancer risk. Vaccination against HPV and HBV has shown significant success in reducing virus-related cancers [19].

Screening programs

Screening tools such as mammography, colonoscopy, Pap smears, and low-dose CT scans for high-risk individuals facilitate early detection and improved outcomes [20].

Challenges and Future Directions

Despite progress, cancer heterogeneity, drug resistance, and metastasis remain major challenges. Future directions include: Precision oncology provides personalized cancer treatment tailored to an individual's genomic and proteomic profile, enhancing therapeutic efficacy and minimizing side effects. Liquid biopsies offer a non-invasive method to detect circulating tumor DNA (ctDNA), enabling real-time monitoring of cancer progression and treatment response [21]. Nanotechnology enables targeted drug delivery and advanced diagnostic tools, improving treatment precision and reducing systemic side effects in cancer therapy. Artificial Intelligence (AI) enhances diagnostic accuracy and optimizes treatment planning by analyzing complex medical data with greater speed and precision [22].

Conclusions

Carcinogenesis is a complex, multistep process driven by genetic mutations, epigenetic changes, and environmental exposures that transform normal cells into cancerous ones. Understanding these mechanisms is crucial for improving early detection, prevention, and treatment strategies. Advances in molecular biology have revealed key pathways and biomarkers involved in cancer development, enabling the rise of personalized medicine. As research progresses, targeted therapies and precision oncology offer promising approaches to reduce cancer incidence and improve patient outcomes, marking a significant shift toward more effective and individualized care in oncology.

Disclosure statement

No potential conflict of interest was reported by the authors.

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