MOLECULAR BASIS OF TUMOR DEVELOPMENT: THE ROLE OF GENETIC MUTATIONS AND ONCOGENES

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Annotation: This article examines the molecular basis of tumor (oncological) diseases. It focuses on genetic mutations, the conversion of proto-oncogenes into oncogenes, the interaction between oncogenes and tumor suppressor genes, as well as molecular mechanisms and signaling pathways. The research methodology includes literature review, comparative analysis, and synthesis of scientific data. The main part discusses types of mutations, molecular mechanisms of oncogenes (point mutations, gene amplification, translocations, gene fusions), signaling pathways (RAS/MAPK, PI3K/AKT, JAK/STAT, etc.), tumor suppressor genes (e.g., TP53, RB, BRCA) and their loss, genomic instability, examples of cancer types, and recent discoveries. The analytical section discusses “driver” and “passenger” mutations, tumor clonality, and mechanisms of rapid progression. The conclusion summarizes the role of oncogenes and mutations and offers recommendations for future directions.

Keywords: oncogene, proto-oncogene, genetic mutation, tumor suppressor gene, signal transduction, genomic instability, driver mutation, passenger mutation

INTRODUCTION

Tumors (oncological diseases) are a major health problem for humanity, with significant genetic and molecular contributions. Traditionally, oncology focused on macroscopic and cellular levels, but in the last half-century, molecular biology and genetic analysis have revealed the root of these diseases — genetic alterations and signaling pathway disruptions within the cell.Today, one of the most promising directions in oncology is the identification of tumor mutations, understanding their molecular mechanisms, and developing targeted therapies based on this knowledge. Tumor development is a complex, multistep process that requires several molecular “hits” for a normal cell to transform into an autonomously growing oncogenic cell. Each “hit” is usually associated with a genetic mutation or a change in gene expression levels. Additionally, loss of tumor suppressor genes, genomic instability, epigenetic modifications, and chromosomal aberrations play essential roles.The aim of this article is to analyze in depth the molecular pathways of tumor development, the role of genetic mutations and oncogenes, and their interrelations.

RESEARCH METHODOLOGY

This paper is a review-type scientific article, based on published literature. The methodology includes:

1. Literature Collection

Searches were conducted in databases such as PubMed, Google Scholar, and Web of Science using keywords like "oncogene mutations cancer molecular basis review," "tumor suppressor gene mutations," and "cancer genomics driver passenger."

Articles were evaluated for content and relevance to the topic.

Both recent studies (last 10–15 years) and classical theoretical papers were included.

2. Data Analysis and Synthesis

Data from different sources were compared and systematized.

Topics were divided by signaling pathways, molecular mechanisms, and gene types, with examples such as RAS mutations, BCR-ABL fusion gene, and TP53 mutations.

3. Structural Organization

The article is organized step by step: mutation types, oncogenes and suppressor genes, signaling pathways, analysis, and conclusion.

Comparative discussions and examples were used to expand the topic.

Thus, this article does not present new experimental data but synthesizes and analyzes existing scientific knowledge.

MAIN BODY

1. Genetic Mutations: Types and Mechanisms

A mutation is a change in the DNA sequence that can affect gene function. In oncogenesis, mutations alter gene expression and protein function, driving tumor formation. Major types include:

a) Point mutations — single-nucleotide substitutions, insertions, or deletions. For example, a single base change in the RAS gene may cause constant GTP activation, resulting in permanent signaling and oncogenic transformation.

b) Gene amplification — an increase in the copy number of a genomic region, leading to overexpression of a proto-oncogene, such as HER2 amplification in breast cancer.

c) Chromosomal translocations — DNA segments break and rejoin in different positions, creating fusion genes with abnormal functions (e.g., BCR-ABL in chronic myeloid leukemia, MYC translocation in Burkitt's lymphoma).

d) Microdeletions/insertions — small sequence changes causing frameshift mutations that lead to loss or gain of gene function.

e) Epigenetic modifications — DNA methylation or histone modification that silences genes without changing the DNA sequence, e.g., methylation of tumor suppressor gene promoters.

f) Large structural aberrations — deletions, duplications, inversions, or aneuploidy affecting entire chromosomes or large regions, promoting instability and mutation accumulation.

2. From Proto-Oncogenes to Oncogenes

Proto-oncogenes regulate normal cell growth and differentiation. When mutated or overexpressed, they become oncogenes, promoting uncontrolled proliferation.

Mechanisms of activation:

Point mutations (e.g., RAS, BRAF V600E)

Gene amplification (HER2/neu in breast cancer)

Promoter/enhancer mutations (TERT promoter)

Chromosomal translocations and fusion genes (BCR-ABL, EML4-ALK, PML-RARA)

Rearrangements within or between genes.

Classes of oncogenes:

Growth factors

Receptor tyrosine kinases (EGFR, HER2)

Intracellular signaling proteins (RAS, RAF, PI3K, AKT)

Transcription factors (MYC, FOS, JUN)

Adaptor proteins (SHC, GRB2, SOS)

Genes regulating angiogenesis or metastasis.

3. Tumor Suppressor Genes

Tumor suppressor genes inhibit cell division, repair DNA damage, or induce apoptosis. Their inactivation removes growth control.

Key examples:

TP53 ("guardian of the genome") — induces cell cycle arrest or apoptosis after DNA damage. Mutated in >50% of cancers.

RB1 — regulates G1→S transition; loss leads to uncontrolled cell cycle progression.

BRCA1/2 — DNA repair genes; mutations increase breast/ovarian cancer risk.

PTEN, CDKN2A (p16), APC — regulate cell cycle arrest, signaling inhibition, or apoptosis.

Mechanisms of inactivation:

Point mutations or deletions

Loss of heterozygosity (LOH)

Epigenetic silencing (methylation)

microRNA regulation

Chromosomal deletions.

4. Major Signaling Pathways in Cancer

RAS/MAPK pathway: mutations in RAS or BRAF cause constant activation, promoting proliferation.

PI3K/AKT/mTOR pathway: mutations in PI3K or loss of PTEN sustain growth and survival.

JAK/STAT pathway: mutations maintain permanent activation of STAT-mediated transcription.

Notch, Wnt/β-catenin, Hedgehog pathways regulate differentiation and growth; mutations cause abnormal activation.

Apoptosis pathways: BCL-2 family and caspases are often dysregulated to avoid cell death.

Genomic instability: events such as kataegis (localized hypermutation) or chromothripsis (chromosomal shattering and reassembly) accelerate oncogenesis.

Driver mutations actively promote tumor development, while passenger mutations have minimal impact but accumulate over time.

5. Clinical Examples

Lung cancer: EGFR, KRAS, ALK, ROS1, MET mutations — targets for specific inhibitors.

Chronic myeloid leukemia (CML): BCR-ABL fusion gene — treated effectively with tyrosine kinase inhibitors (e.g., imatinib).

Breast cancer: HER2 amplification and BRCA1/2 mutations — treated with HER2-targeted drugs and PARP inhibitors.

Melanoma: BRAF V600E mutation — sensitive to BRAF inhibitors (e.g., vemurafenib).

ANALYSIS AND RESULTS

1. Tumor mutations are diverse — point, structural, and epigenetic types all play roles.

2. Only a few driver mutations are critical for tumor initiation; others are passengers.

3. Mutations in signaling pathways are central to uncontrolled growth and survival.

4. Genomic instability increases mutation accumulation and tumor heterogeneity, complicating treatment.

5. Targeted therapies against known oncogenic mutations have strong clinical significance.

6. Challenges:

Tumor heterogeneity reduces therapy effectiveness.

Many cancer-related genes remain unidentified.

Epigenetic dysregulation is underexplored.

Combined molecular and immunotherapy holds promise.

CONCLUSION

Tumor development is a multistage genetic process involving various mutations — point mutations, gene amplifications, chromosomal translocations, and epigenetic changes. Mutated or overexpressed proto-oncogenes become oncogenes, driving proliferation. Loss of tumor suppressor genes (e.g., TP53, RB, BRCA) removes growth control.Signaling pathways such as RAS/MAPK, PI3K/AKT, and JAK/STAT are key molecular mechanisms disrupted in oncogenesis. Genomic instability, driver/passenger mutations, and clonal diversity complicate disease progression and treatment response.Clinically, identifying oncogenic mutations enables personalized targeted therapy. Future research should focus on deeper mutation profiling, combined therapies (molecular + immunotherapy), and epigenetic regulation.

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