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MOLECULAR MECHANISMS OF APOPTOSIS AND ITS ROLE IN HUMAN DISEASES

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ABSTRACT

Apoptosis, or programmed cell death, is a highly regulated biological process essential for normal development, tissue homeostasis, and immune regulation. Dysregulation of apoptosis contributes to a wide range of human diseases, including cancer, neurodegenerative disorders, autoimmune conditions, and cardiovascular diseases. Apoptosis occurs through intrinsic (mitochondrial) and extrinsic (death receptor-mediated) pathways, involving caspases and regulatory proteins such as Bcl-2 family members and p53. Understanding the molecular basis of apoptosis provides insight into disease pathogenesis and therapeutic targets. This article reviews the molecular mechanisms of apoptosis, its physiological significance, and its involvement in major human diseases.

Keywords: apoptosis, programmed cell death, caspases, Bcl-2, p53, medical biology

INTRODUCTION

Apoptosis is a genetically controlled process of cell death that plays a critical role in embryonic development, immune system regulation, and tissue homeostasis. Unlike necrosis, which is uncontrolled and inflammatory, apoptosis is a highly organized process characterized by cell shrinkage, chromatin condensation, membrane blebbing, and formation of apoptotic bodies.

The term "apoptosis" was first introduced by Kerr, Wyllie, and Currie in 1972. Since then, extensive research has revealed that apoptosis is mediated by complex molecular signaling pathways. Disruption of apoptotic regulation may lead to pathological conditions. Excessive apoptosis contributes to neurodegenerative diseases, while insufficient apoptosis promotes tumor development.

This article aims to analyze the molecular pathways of apoptosis and discuss their clinical significance in human diseases.

METHODS

A narrative review of scientific literature was conducted using databases such as PubMed, ScienceDirect, and Google Scholar. Publications between 2000 and 2024 were prioritized, including review articles, experimental studies, and clinical research papers.

Search terms included: *apoptosis*, *caspase activation*, *intrinsic pathway*, *extrinsic pathway*, *Bcl-2 family*, *p53*, *cancer apoptosis*, and *neurodegeneration*. Only peer-reviewed English-language sources were included.

RESULTS

Molecular Pathways of Apoptosis. Apoptosis occurs through two main pathways:

1 Intrinsic (Mitochondrial) Pathway

The intrinsic pathway is activated by intracellular stress signals such as:

- DNA damage
- Oxidative stress
- Hypoxia
- Growth factor deprivation

The tumor suppressor protein **p53** plays a central role in sensing DNA damage. It promotes expression of pro-apoptotic proteins such as Bax and Bak.

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Mitochondrial outer membrane permeabilization (MOMP) results in release of **cytochrome c**, which binds Apaf-1 and procaspase-9 to form the apoptosome. This leads to activation of **caspase-9**, followed by effector caspases (caspase-3, -6, -7), resulting in cell death.

The balance between pro-apoptotic (Bax, Bak) and anti-apoptotic (Bcl-2, Bcl-XL) proteins determines cell survival.

2 Extrinsic (Death Receptor) Pathway

The extrinsic pathway is initiated by binding of ligands such as:

- Fas ligand (FasL)
- Tumor necrosis factor (TNF-α)
- TRAIL

These ligands bind death receptors on the cell surface, leading to formation of the death-inducing signaling complex (DISC). This activates **caspase-8**, which subsequently activates effector caspases.

The intrinsic and extrinsic pathways may interact through Bid protein cleavage.

Apoptosis in Human Diseases

1 Cancer

Cancer cells often evade apoptosis through:

- Overexpression of Bcl-2
- Mutation of p53
- Reduced caspase activation

Targeted therapies, such as Bcl-2 inhibitors (e.g., Venetoclax), aim to restore apoptotic signaling in malignant cells.

2 Neurodegenerative Diseases

Excessive neuronal apoptosis contributes to:

- Alzheimer’s disease
- Parkinson’s disease
- Huntington’s disease

Mitochondrial dysfunction and oxidative stress play key roles.

3 Autoimmune Disorders

Defective apoptosis of autoreactive lymphocytes may result in autoimmune diseases such as systemic lupus erythematosus.

4 Cardiovascular Diseases

Ischemia-reperfusion injury triggers apoptosis in cardiomyocytes, contributing to heart failure.

DISCUSSION

Apoptosis is essential for maintaining cellular equilibrium. Its dysregulation disrupts tissue homeostasis and contributes to various diseases. Understanding molecular regulators such as caspases, Bcl-2 family proteins, and p53 has opened new therapeutic avenues.

Targeted modulation of apoptosis represents a promising strategy in oncology and degenerative diseases. However, therapeutic manipulation must be carefully balanced to avoid unintended consequences.

Future research focuses on gene therapy, mitochondrial-targeted drugs, and personalized medicine approaches.

CONCLUSION

Apoptosis is a fundamental biological process essential for development and tissue homeostasis. Molecular pathways regulating apoptosis are complex and tightly controlled.

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Dysregulation contributes to cancer, neurodegeneration, autoimmune, and cardiovascular diseases. Continued research into apoptotic mechanisms will enhance therapeutic innovation and improve clinical outcomes.

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