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Progress of the Molecular Mechanism of Genistein against Colorectal Cancer

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Abstract: As a highly prevalent malignant tumor worldwide, the development of therapeutic agents for colorectal cancer has been a hot spot of medical research. Genistein, as a natural isoflavone compound, has attracted much attention in recent years for its remarkable anti-tumor activity. Studies have shown that genistein can regulate the proliferation, apoptosis and metastasis of colorectal cancer cells through multi-targets and multi-pathways, demonstrating a unique molecular mechanism of action. In-depth analysis of the molecular mechanism of genistein against colorectal cancer will not only help to elucidate the material basis of its efficacy, but also provide a theoretical basis for the design of new targeted drugs, which is of great scientific value and clinical translation significance.

1. Introduction

In the field of natural product antitumor research, genistein has become a key research target because of its low toxicity and broad-spectrum anticancer properties. For colorectal cancer, a common malignant tumor in the digestive system, genistein has demonstrated multidimensional antitumor effects, such as regulating epigenetics and influencing the tumor microenvironment. With the development of molecular biology technology, its targets and signaling pathways have been revealed, which opens up new ideas for the development of safer and more effective therapeutic strategies for colorectal cancer. The systematic combing of the research progress on the molecular mechanism of genistein against colorectal cancer has an important guiding value for promoting the clinical application of plant active ingredients.

2. Overview of chemical properties and biological activities of genistein

Genistein is a natural isoflavonoid, chemically named 4',5,7-trihydroxyisoflavone, with the molecular formula C15H10O5, and has a typical benzo-γ-pyrone backbone structure. The presence of multiple phenolic hydroxyl groups in its molecule provides it with strong antioxidant activity, and at the same time endows it with amphiphilic character, which allows it to be moderately soluble in both aqueous and lipid phases. Genistein is stable under alkaline conditions, but is susceptible to degradation in strong acids or high temperature environments. As a representative substance of

phytoestrogens, its structure is similar to that of mammalian estrogens, and it is able to selectively bind to estrogen receptors, showing bidirectional regulation. In terms of biological activities, genistein has a wide range of pharmacological effects, including antioxidant, anti-inflammatory, anti-tumor and cardiovascular protective effects. Its anti-cancer mechanism involves multi-target regulation, such as inhibiting tyrosine kinase activity, blocking NF-κB signaling pathway, and regulating cell cycle-related protein expression. In addition, genistein can affect gene expression through epigenetic modification and exhibits the ability to regulate the tumor microenvironment. These properties make them important lead compounds for natural product drug development and have broad application prospects in the fields of functional food and tumor adjuvant therapy.

3. Molecular pathological features of colorectal cancer and current status of treatment

3.1 Molecular pathologic features of colorectal cancer

The development of colorectal cancer involves abnormal alterations in multiple genes and pathways, mainly including the continuous activation of signaling pathways such as Wnt/β-catenin, RAS-MAPK, PI3K-AKT and so on. Microsatellite instability (MSI) and chromosomal instability (CIN) are the two core molecular subtypes characterized, in which MSI-H type is often accompanied by mismatch repair gene (MMR) defects, while CIN type is dominated by mutations of oncogenes, such as APC and TP53, as well as copy number variations. Epigenetic alterations (e.g., aberrant DNA methylation) also play a key role in the carcinogenesis process, especially in the silencing of tumor suppressor genes. In addition, the heterogeneity of immune cell infiltration and dysregulation of cytokine networks in the tumor microenvironment further promote malignant progression and immune escape in colorectal cancer [1].

3.2 Current status of colorectal cancer treatment

Current colorectal cancer treatment is based on surgical resection, combined with a comprehensive strategy of chemotherapy (e.g., FOLFOX, FOLFIRI regimens), targeted therapy (anti-EGFR, anti-VEGF drugs) and immune checkpoint inhibitors (for MSI-H/dMMR patients). However, the problem of drug resistance is becoming increasingly prominent, especially in patients with RAS mutations that do not respond to EGFR-targeted therapy, while the BRAFV600E mutation portends a worse prognosis. Immunotherapy, although effective in the MSI-H subtype, accounts for only ~15% of all patients and some patients still face secondary resistance. Emerging combination therapies (e.g., targeted agents in combination with immunotherapy) and individualized dynamic monitoring based on liquid biopsy are gradually becoming the research direction to break through the therapeutic bottleneck.

4. Optimization scheme for genistein combination therapy regimen

4.1 Precise design of chronotropic dosing regimen

The combination of genistein with conventional antitumor drugs requires strict consideration of chronotropic effects to maximize synergism. Studies have shown that pretreatment of genistein (e.g.,administration 24 hours in advance) can make tumor cells more sensitive to subsequent chemotherapeutic drugs through epigenetic modulation; while its immune microenvironmental modulation can produce immediate synergistic effects when used in tandem with immune checkpoint inhibitors. For different therapeutic means (chemotherapy/targeting/immunity), timing optimization schemes based on pharmacokinetic (PK) and pharmacodynamic (PD) models need to

be established, and the optimal dosing window should be verified through animal experiments, so as to provide a scientific basis for clinical regimen design [2].

4.2 Balance of dose ratio and toxicity control

The dose ratio of genistein and conventional drugs in combination therapy directly affects the efficacy and safety. Although genistein itself has low toxicity, it may affect the metabolism of the combined drug by inhibiting the CYP450 enzyme system, resulting in abnormally high blood drug concentration. In vitro liver microsomal experiments and preclinical toxicology studies are needed to determine the dose safety thresholds of different combinations. For example, when combined with paclitaxel, the dosage of genistein should be controlled below 50 mg/kg to avoid enhanced neurotoxicity, while the dosage of genistein can be appropriately increased in combination with PD-1 inhibitors to enhance the immunomodulatory effect. The establishment of a dose-effect relationship database is a key basis for optimizing the combination regimen.

4.3 Synergistic effect of nano-delivery system

Traditional genistein suffers from poor water solubility and low bioavailability, which restrict its combined therapeutic effect. Novel nano-delivery technologies (e.g., liposomes, polymer micelles, metal-organic frameworks, etc.) can simultaneously encapsulate genistein and chemotherapeutic drugs to achieve co-delivery and tumor-targeted release. For example, pH-responsive nanoparticles can release genistein and oxaliplatin simultaneously in the microacidic environment of tumors, improving efficacy through the dual mechanism of enhancing DNA damage and inhibiting repair. Such systems can also increase drug accumulation at the tumor site through the EPR effect and reduce toxicity to normal tissues, providing technical support for combination therapy.

4.4 Biomarker-guided individualized combination therapy

The heterogeneity of patients' tumor molecular characteristics requires individualization of combination therapy regimens, and screening for predictive biomarkers can accurately identify populations sensitive to genistein combination therapy: e.g., patients with EGFR-mutant colorectal cancers may benefit from the combination of genistein and cetuximab, while patients with MSI-H phenotype are more suited to the combination of genistein and PD-1 inhibitors. Dynamic monitoring of treatment response by circulating tumor DNA (ctDNA) allows real-time adjustment of the combination strategy. The establishment of a multi-omics (genomic, epigenomic, microenvironmental immune profiling) based predictive modeling will drive the shift of combination therapy from empirical dosing to precision medicine.

4.5 Exploration and validation of novel combination modalities

Beyond traditional drug combinations, the synergistic potential of genistein with emerging therapeutics deserves to be explored in depth. In lysosomal virus therapy, genistein may enhance viral replication by inhibiting the IFN-β pathway; in CAR-T cell therapy, its role in modulating the depletion properties of T cells may prolong the duration of efficacy. In addition, when combined with tumor electric field treatments (TTFields), genistein's effect on cell cycle synchronization may enhance electric field sensitivity. These innovative combinations need to be mechanistically validated by advanced platforms such as organoid models and human organ microarrays, and gradually translated to clinical trials to expand the boundaries of combination therapy.

5. Challenges and Prospects for Clinical Application of Genistein

5.1 Bottleneck breakthrough in bioavailability and formulation technology

The primary obstacle to the clinical application of genistein lies in its poor pharmacokinetic properties, including low oral bioavailability (<10%) and short plasma half-life (~7 hours). Conventional formulations are difficult to maintain effective blood concentrations, and existing nano-delivery systems still face stability challenges for large-scale production. In the future, new delivery technologies need to be developed, such as pre-drug design based on the activation of intestinal flora, self-microemulsification drug delivery system, etc., as well as exploring the feasibility of non-oral routes of administration (e.g., inhalation dosage forms, transdermal patches). Breaking through the formulation bottleneck will significantly enhance the drug accumulation in target tissues and lay the foundation for clinical application [3].

5.2 Systematic assessment of drug interactions

As a multi-target modulator, genistein's complex interactions with conventional drugs (e.g., anticoagulants, antidepressants) pose clinical safety risks. Its potential to alter the metabolic process of co-administered drugs through inhibition of CYP3A4 and P-glycoprotein has led to a lack of comprehensive drug interaction databases. A systematic assessment system covering in vitro metabolizing enzyme inhibition experiments, clinical PK/PD studies, and the development of intelligent drug monitoring software are needed to provide real-time warnings for different combined drug scenarios. The improvement of this assessment mechanism is a key component to ensure safe clinical drug use.

5.3 Systematic construction of evidence-based medicine evidence

Current clinical studies of genistein have limitations such as small sample size (most trials <100 cases) and single study endpoints (mostly safety rather than efficacy). There is an urgent need to conduct multi-center, large-sample randomized controlled trials, focusing on verifying its clinical value in adjuvant therapy (e.g., prevention of recurrence and metastasis), and efficacy enhancement of combination therapy. At the same time, a standardized biomarker detection system should be established to objectively assess the efficacy of treatment by means of ctDNA dynamic monitoring and other means. Only by accumulating high-quality evidence-based medicine evidence can we promote its identity change from dietary supplement to clinical therapeutic drug.

5.4 Precise Development of Individualized Therapeutic Strategies

Tumor heterogeneity determines that genistein requires differentiated clinical application strategies, and future research should focus on: 1) molecular typing-based screening of beneficiary populations (e.g., patients with high ERβ expression); 2) pharmacogenomics-guided dosage optimization (e.g., the effect of polymorphisms in the UGT1A1 gene); and 3) precise grasp of the treatment timing (e.g., the time window for postoperative adjuvant therapy). Combining liquid biopsy and artificial intelligence prediction models to develop a closed-loop individualized protocol of “detection-treatment-monitoring” will maximize its clinical value and provide new therapeutic options for precision oncology [4].

5.5 Improvement of regulatory standards and clinical application guidelines

The current regulatory positioning of genistein as a natural product is ambiguous, and its dual attributes of drugs and health products have led to a lack of uniform standards for clinical application. It is necessary to establish a special review pathway for plant-derived antitumor components, with clear purity requirements (e.g., total isoflavone content ≥95%), quality control indexes (e.g., the proportion of specific active ingredients), and clinical efficacy evaluation criteria [5]. At the same time, professional societies should formulate evidence-based hierarchical application guidelines to standardize their indications, contraindications and dosing regimens in different treatment scenarios (e.g., adjuvant therapy, palliative care) to provide an authoritative basis for clinical decision-making and promote standardized application.

6. Conclusion

In summary, the study of the molecular mechanism of genistein against colorectal cancer has provided an important paradigm for the development of natural product anticancer drugs. With the continuous discovery of targets and in-depth analysis of molecular pathways, the synergistic effects of genistein are becoming clearer and clearer. Future studies should focus on improving the bioavailability, optimizing the drug delivery system, and strengthening the clinical translational research, so that this natural active ingredient can better serve the precision treatment of colorectal cancer and provide a new choice path for tumor prevention and treatment.

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