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Colorectal Cancer Pathogenesis and Treatment Strategies: Insights into the Role of p53

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Colorectal cancer (CRC) is a major cause of cancer-related morbidity and mortality worldwide. Its development results from cumulative somatic and genetic alterations that disrupt normal cell division and promote uncontrolled proliferation. Genetic and epigenetic modifications, particularly mutations in tumor suppressor genes such as *TP53*, are key drivers of CRC. Most CRCs are adenocarcinomas, and the CMS4 molecular subtype is characterized by enhanced stromal invasion and epithelial-mesenchymal transition (EMT), mainly regulated through the TGF-β signaling pathway.

This narrative review aims to highlight the molecular mechanisms underlying CRC pathogenesis, with a specific focus on the Role of *p53*, and to explore emerging gene therapy strategies targeting these pathways.

This study is a narrative review based on a comprehensive search of articles published from 2000 to 2024 in PubMed, Scopus, and Web of Science. Keywords included "colorectal cancer," "p53," "gene therapy," "CMS4," "WNT/β-catenin," and "angiogenesis." Selected articles were reviewed for relevance to the pathogenesis and targeted treatment approaches in CRC.

Alterations in WNT/β-catenin signaling, cell cycle regulators, and apoptotic pathways are commonly observed in CRC. *p53* mutations significantly affect tumor progression and response to therapy. Gene therapy approaches using adeno-associated virus (AAV) vectors to deliver anti-angiogenic genes such as *angiostatin* and *endostatin* offer novel therapeutic potential, with reduced side effects and improved targeting of tumor pathways.

Targeting molecular abnormalities, especially those involving *p53*, may enhance CRC treatment efficacy. Gene-based strategies represent a promising direction in personalized CRC therapy.

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INTRODUCTION

Cancer remains a paramount global health challenge, with an estimated 19.3 million new cases and 10 million cancer-related deaths projected in 2020, underscoring its significant burden across both sexes. Colorectal cancer (CRC) ranks as the second leading cause of cancer mortality worldwide, surpassed only by lung cancer, and exhibits a higher incidence in developed countries [1]. Conventional treatment strategies for CRC primarily involve surgical resection combined with chemotherapy [2]. However, despite considerable advances in therapeutic modalities and heightened efforts for early detection, a substantial proportion of CRC cases continue to be diagnosed at advanced stages, which is associated with poor clinical outcomes [3, 4].

Carcinogenesis is driven by the accumulation of somatic mutations and genetic alterations that disrupt normal regulatory mechanisms governing cell division, resulting in uncontrolled cellular proliferation and tumor development. The acquisition of fundamental biological capabilities characterizes this process, referred to as the hallmarks of cancer, which enable malignant cells to evade growth suppressors and resist cell death [5]. In CRC, both genetic mutations and epigenetic modifications play critical roles in tumor initiation and progression, with frequent alterations observed in pivotal genes such as the tumor suppressor TP53 [6]. Nevertheless, conventional chemotherapy is often accompanied by substantial adverse effects, highlighting the urgent need for more efficacious and less toxic therapeutic approaches [7].

In this context, targeted gene therapy has emerged as a promising and innovative strategy aimed at improving patient survival rates and reducing cancer recurrence. This therapeutic modality involves the introduction of exogenous genes into cancer cells or their microenvironment to induce apoptosis or inhibit tumor growth. The versatility of gene therapy, combined with the expanding repertoire of genetic targets and delivery vectors, has demonstrated encouraging efficacy in numerous clinical trials. These advances suggest the potential for gene therapy to be utilized either as a standalone treatment or in synergy with traditional modalities to enhance clinical outcomes [8, 9].

CRC originates from the epithelial lining of the colon or rectum and progresses through a well-defined multistep process involving the transformation of benign intestinal polyps—most notably adenomatous polyps—into malignant adenocarcinomas. This progression is driven by the sequential accumulation of genetic alterations in key oncogenes and tumor suppressor genes at various stages of tumorigenesis [10-13].

Despite extensive research elucidating the molecular and genetic underpinnings of CRC, significant challenges remain in early diagnosis, prognostication, and the development of effective targeted therapies. Therefore, the present study aims to provide a comprehensive overview of the genetic alterations and molecular pathways involved in colorectal carcinogenesis and to critically evaluate the emerging Role of targeted gene therapy as a novel and promising therapeutic approach. This investigation seeks to bridge existing knowledge gaps and contribute to the advancement of personalized medicine in CRC management.

METHODS

This study is a narrative review. Relevant articles published in English between 2000 and 2025 were identified through databases such as PubMed, Scopus, and Web of Science using keywords including "colorectal cancer," "p53," "gene therapy," "pathogenesis," and "therapeutic targets." Studies were selected based on their relevance to the molecular mechanisms of CRC and the therapeutic relevance of *p53*.

Molecular Classification and Genetic Drivers of Colorectal Cancer: Implications for Targeted Therapy

CRC represents a highly heterogeneous malignancy at the molecular level, characterized by a spectrum of genetic, epigenetic, and transcriptomic alterations that collectively influence tumor initiation, progression, therapeutic response, and clinical prognosis. Advances in high-throughput sequencing and integrative genomic analyses have elucidated distinct molecular subtypes of CRC, facilitating precision oncology approaches tailored to individual tumor biology [14-18].

A robust framework for CRC molecular taxonomy is provided by the Consensus Molecular Subtypes

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(CMS), which classify CRC into four biologically and clinically relevant categories. CMS1 (MSI Immune) is typified by defects in the DNA mismatch repair (MMR) system, including loss or mutation of key genes such as *MLH1* and *MSH2*, culminating in microsatellite instability-high (MSI-H) tumors. This hypermutated phenotype engenders a high neoantigen load, eliciting vigorous immune infiltration dominated by cytotoxic T lymphocytes and increased expression of immune checkpoint molecules such as PD-1 and PD-L1, rendering these tumors exquisitely sensitive to immune checkpoint blockade therapies [14,17,18]. The clinical relevance of CMS1 lies in its favorable response to immunotherapy, a breakthrough that has redefined therapeutic paradigms for this CRC subset.

In contrast, CMS2 (Canonical) tumors exhibit pronounced epithelial differentiation and are molecularly characterized by the upregulation of the WNT/β-catenin and MYC signaling pathways, which drive aberrant proliferation and tumor growth. The canonical activation of these pathways underscores the critical oncogenic mechanisms sustaining tumor cell survival and expansion in this subtype [14].

CMS3 (Metabolic) represents a distinct molecular phenotype marked by profound dysregulation of metabolic pathways. Alterations in glycolysis, lipid metabolism, and nucleotide biosynthesis contribute to metabolic reprogramming, enabling tumor cells to adapt to microenvironmental stress and nutrient scarcity, thereby promoting tumorigenesis and progression [14].

Finally, CMS4 (Mesenchymal) is associated with an aggressive clinical course, characterized by extensive stromal infiltration, activation of TGF-β signaling, angiogenesis, and epithelial-mesenchymal transition (EMT). These features facilitate enhanced invasiveness, metastatic potential, and resistance to conventional therapies, correlating with poor prognosis [14].

At the genomic level, CRC development is orchestrated by the sequential acquisition of driver mutations—genetic alterations that confer selective growth advantages by perturbing key cellular pathways involved in proliferation, apoptosis, DNA repair, and differentiation. These drivers contrast with passenger mutations, which accumulate stochastically and may modulate tumor heterogeneity and therapeutic response without directly initiating oncogenesis [15, 16].

Among the pivotal genetic alterations, tumor suppressor genes such as *APC* and *TP53* play essential roles in maintaining genomic integrity and regulating cell cycle checkpoints. *APC* mutations, often truncating, disrupt the β-catenin destruction complex, resulting in constitutive activation of WNT signaling and early adenoma formation—a critical initiating event in CRC carcinogenesis [17, 18]. Loss of *TP53* function, predominantly via missense mutations in its DNA-binding domain, impairs the cellular DNA damage response and apoptosis, facilitating malignant progression and genomic instability [17, 18].

Oncogenes, including *KRAS* and *BRAF*, harbor activating mutations that perpetually stimulate the MAPK/ERK signaling cascade, fostering uncontrolled proliferation and survival. The presence of *KRAS* mutations is also a well-established predictive biomarker of resistance to anti-EGFR therapies, emphasizing their clinical significance [17, 18].

Deficiencies in mismatch repair (MMR) genes, such as *MLH1* and *MSH2*, underlie the MSI pathway. MSI-high tumors accumulate extensive insertion-deletion mutations in microsatellite regions, resulting in a hypermutated genotype and heightened immunogenicity that sensitizes these tumors to immune checkpoint blockade [17,18].

It is critical to recognize that CRC pathogenesis encompasses both inherited (germline) and acquired (somatic) mutations. Familial cancer syndromes, exemplified by Lynch syndrome, arise from germline mutations in MMR genes and confer markedly elevated lifetime CRC risk. However, the majority of CRC cases (~70%) are sporadic, reflecting a complex interplay between environmental exposures, lifestyle factors, and somatic genetic alterations [17,18].

In sum, the intricate molecular heterogeneity of CRC, delineated by CMS classification and key genetic drivers, underscores the necessity for comprehensive molecular profiling. Such approaches enable the stratification of patients for tailored therapeutic

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regimens, optimizing clinical outcomes and paving the way for precision oncology in CRC management.

Therapeutic Implications

The molecular classification and genetic landscape of CRC have direct implications for therapy:

Targeting Driver Mutations: Therapies aimed at oncogenic drivers (e.g., anti-EGFR antibodies ineffective in KRAS-mutant tumors) require molecular profiling for patient selection [16-18].

Exploiting MSI Status: MSI-high tumors respond favorably to immune checkpoint inhibitors, highlighting the importance of MMR status in treatment planning [14,17, 18].

Addressing Tumor Heterogeneity: CMS classification informs prognosis and guides combination therapies tailored to tumor biology, such as targeting metabolic pathways in CMS3 or TGF-β signaling in CMS4 [15,17,18].

Personalized Medicine: Integration of molecular subtype and mutation profiling enables precision oncology approaches, improving treatment efficacy and minimizing toxicity [17,18].

Signaling Pathways and Genetic Factors in CRC

CRC develops as a consequence of sequential alterations in cellular signaling pathways and genetic factors that govern cell growth, differentiation, and apoptosis. These changes allow cells to escape normal regulatory mechanisms, leading to tumorigenesis. Signaling pathways, comprising complex networks of proteins, facilitate the cellular response to extracellular and intracellular cues. In CRC, several key signaling cascades become dysregulated, playing pivotal roles in the aberrant regulation of cellular processes such as proliferation, survival, programmed cell death, and metastasis.

The β-catenin/WNT Signaling Pathway

One of the most frequently disrupted CRCs in pathways is the WNT/β-catenin signaling pathway, which normally regulates the growth and differentiation of intestinal epithelial cells. When activated, β-catenin avoids degradation by the proteasome and moves into the nucleus, where it triggers the transcription of genes responsible for cell growth and survival. In CRC, mutations in the APC gene, a crucial suppressor of the WNT pathway, are often detected. These mutations cause constant activation of the WNT pathway, leading to an abnormal buildup of β-catenin in the nucleus and promoting uncontrolled cell proliferation. This pathway dysregulation is considered a key early event in colorectal tumor development［19,20].

The Signaling Pathway of RAS/RAF/MEK/ERK (MAPK)

he RAS/RAF/MEK/ERK pathway, also referred to as the MAPK signaling cascade, is another critical pathway implicated in CRC. This pathway governs key cellular processes, including growth, differentiation, and migration. Mutations in KRAS or BRAF, two essential components of this pathway, are frequently identified in CRC cases. Oncogenic mutations in KRAS lead to constitutive activation of the MAPK signaling cascade, driving unchecked cell proliferation and survival. Similarly, mutations in BRAF, notably the V600E substitution, result in hyperactivation of the pathway, further promoting tumor growth. These mutations are associated with poor clinical outcomes and resistance to certain targeted therapies, underscoring their importance in CRC pathogenesis [21, 22].

The mTOR/PI3K/AKT Signaling Pathway

CRC is characterized by the deregulation of the PI3K/AKT/mTOR pathway, a key axis in the control of cell metabolism, growth, and survival. This pathway is constitutively activated by mutations in PIK3CA, which codes for the catalytic subunit of phosphatidylinositol 3-kinase (PI3K), which are commonly observed in CRC. Through the inhibition of pro-apoptotic signals, AKT activation in this pathway enhances cell survival. Thereby confers resistance to apoptosis in cancer cells. Additionally, aberrant signaling through the mTOR complex leads to enhanced protein synthesis and cellular growth. The dysregulation of this pathway not only facilitates tumor progression but also contributes to chemotherapy resistance, making it a critical target for therapeutic intervention in CRC [23, 24].

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The Signaling Pathway of TGF-β

The TGF-β signaling pathway exhibits a dual function in CRC, serving as a tumor suppressor during the early stages and transforming into a tumor promoter in later stages. In normal cells, TGF-β signaling restricts cell growth and triggers apoptosis. However, mutations in pathway components like SMAD4 or disruptions in the regulation of TGF-β signaling result in its shift towards an oncogenic role in advanced CRC. At this stage, TGF-β drives processes like epithelial-mesenchymal transition (EMT), which aids in tumor invasion and metastasis. EMT involves the loss of epithelial traits and the gain of a mesenchymal phenotype, empowering cancer cells to spread and establish themselves in distant organs [25, 26].

Microsatellite instability and DNA mismatch repair pathways (MSI)

Deficiencies in the DNA mismatch repair (MMR) system represent a key feature of CRC, particularly in tumors with microsatellite instability (MSI). The MMR system corrects replication errors that occur during DNA synthesis. When MMR genes such as MLH1, MSH2, MSH6, or PMS2 are mutated or epigenetically silenced, the result is MSI, marked by an accumulation of replication errors, especially in microsatellites, which are short, repetitive DNA sequences. MSI-high tumors, found in roughly 15-20% of CRC cases, often have a higher mutation rate, driving tumor progression. Notably, MSI-high tumors tend to respond better to immunotherapy, likely due to their elevated mutational burden, which increases tumor immunogenicity [27, 28].

Colorectal Carcinogenesis: Molecular Pathways and Therapeutic Significance

CRC arises from a multifactorial interplay of genetic, epigenetic, and microenvironmental influences that collectively drive malignant transformation and tumor progression. The molecular pathogenesis of CRC is principally governed by three well-characterized pathways: chromosomal instability (CIN), microsatellite instability (MSI), and the CpG island methylator phenotype (CIMP), each contributing distinct genetic and epigenetic aberrations that define CRC heterogeneity and therapeutic responsiveness [25, 27-31].

The CIN pathway, accounting for approximately 80% of advanced CRC cases, is hallmarked by extensive chromosomal alterations, including loss of heterozygosity (LOH), aneuploidy, and sequential mutations in critical tumor suppressors such as *APC* and *TP53*, as well as oncogenes like *KRAS* [25, 27, 29]. Loss-of-function mutations in *APC* disrupt the β-catenin destruction complex, resulting in constitutive activation of Wnt/β-catenin signaling, which promotes uncontrolled proliferation and initiates adenoma formation. Subsequent accumulation of genetic insults within this pathway drives progression from benign adenoma to invasive carcinoma [25, 27, 29].

The MSI pathway emerges from defects in the DNA mismatch repair (MMR) system, leading to the accumulation of mutations in repetitive DNA microsatellite regions. MSI is the molecular hallmark of Lynch syndrome and occurs in 15–20% of sporadic CRCs. Tumors exhibiting high microsatellite instability (MSI-H) manifest a hypermutated genotype, resulting in elevated neoantigen burden and heightened immunogenicity. This underlies their notable responsiveness to immune checkpoint inhibitors, establishing MSI status as a pivotal predictive biomarker for immunotherapy [25].

The CIMP pathway is defined by widespread hypermethylation of CpG islands in promoter regions of tumor suppressor genes, causing their transcriptional silencing. CIMP-positive CRCs often co-occur with activating mutations in *BRAF*, representing a distinct molecular subtype with characteristic clinical features, including a generally poorer prognosis and unique therapeutic sensitivities [27].

Beyond these intrinsic molecular mechanisms, the tumor microenvironment (TME) plays a critical role in CRC progression. The dynamic crosstalk between tumor cells and stromal constituents—such as cancer-associated fibroblasts (CAFs), infiltrating immune cells, and vascular endothelial cells—facilitates tumor invasion, metastasis, angiogenesis, and evasion of immune surveillance [28–31]. Additionally, host genetic polymorphisms, particularly single-nucleotide polymorphisms (SNPs)

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in genes regulating inflammation, immune responses, and DNA repair pathways, modulate individual susceptibility to CRC and influence therapeutic outcomes [28-31].

Therapeutically, these pathways offer actionable targets: pharmacologic agents aiming to inhibit the Wnt/β-catenin axis or restore *APC* function are under development for CIN-driven tumors [25, 27]; MSI-H status directs the use of immune checkpoint blockade therapies with significant clinical efficacy [25, 27]; epigenetic modifiers such as DNA methyltransferase inhibitors hold promise to reverse CIMP-associated gene silencing and sensitize tumors to conventional treatments [25]; and strategies targeting components of the TME—including CAFs, angiogenesis, and immune checkpoints—are actively pursued to disrupt the tumor-supportive niche and enhance anti-tumor immunity [28-31].

In summary, delineating the molecular and microenvironmental underpinnings of CRC enables precision medicine approaches tailored to each tumor's unique profile, optimizing therapeutic efficacy and minimizing adverse effects [27].

Genetic Alterations in Colorectal Cancer: Key Drivers and Therapeutic Implications

CRC represents a paradigmatic model of multistep carcinogenesis driven by the accumulation of genetic and epigenetic alterations that disrupt cellular homeostasis and promote malignant transformation. Comprehensive genomic analyses, notably through initiatives like The Cancer Genome Atlas (TCGA), have delineated a complex genetic landscape dominated by mutations in tumor suppressor genes, oncogenes, and signaling pathway components, with the chromosomal instability (CIN) pathway accounting for approximately 80% of CRC cases [27, 35-44].

Central to CRC initiation is the inactivation of the *APC* gene, a gatekeeper tumor suppressor mutated in 80–90% of sporadic cases. *APC* encodes a critical component of the β-catenin destruction complex; loss-of-function mutations prevent β-catenin ubiquitination and degradation, resulting in its nuclear accumulation and constitutive activation of Wnt/β-catenin target genes. This dysregulated Wnt signaling orchestrates uncontrolled proliferation, stemness maintenance, and adenomatous polyp formation, marking the earliest molecular event in CRC pathogenesis [27, 38-40, 42].

Complementing *APC* mutations, activating mutations in *CTNNB1* (β-catenin) further potentiate aberrant Wnt pathway signaling, reinforcing oncogenic transcriptional programs [40-42].

Progression from benign adenoma to invasive carcinoma is heavily influenced by disruption of the *TP53* tumor suppressor pathway. *TP53*, mutated in approximately 60% of CRCs, encodes the p53 protein, a transcription factor pivotal in maintaining genomic integrity via induction of cell cycle arrest, senescence, DNA repair, and apoptosis in response to genotoxic stress. Missense mutations frequently localize to the DNA-binding domain, abrogating p53's transcriptional activity and enabling clonal expansion of genomically unstable cells. Furthermore, loss of heterozygosity (LOH) at the *TP53* locus amplifies this effect, facilitating malignant transformation and poor clinical outcomes [27, 35-40].

Oncogenic activation of the RAS-RAF-MAPK pathway constitutes another hallmark of CRC molecular pathology. Mutations in *KRAS* (~30–40%) and less commonly *NRAS* (~1–5%) lock RAS proteins in a constitutively GTP-bound active state, driving persistent downstream MAPK signaling independent of upstream receptor tyrosine kinases such as EGFR. This results in enhanced cell proliferation, survival, and metabolic adaptation, and is a major determinant of resistance to anti-EGFR monoclonal antibodies, a cornerstone of targeted CRC therapy [37,38,39,40,41,42]. Similarly, activating mutations in *BRAF*, particularly the V600E substitution (~5–15%), cause hyperactivation of MAPK signaling, correlating with aggressive tumor phenotypes, poor prognosis, and differential therapeutic responses [37, 38-41].

Parallel to MAPK pathway aberrations, mutations in *PIK3CA* (10–20%) hyperactivate the PI3K/Akt/mTOR axis, fostering cell survival, growth, and metabolic reprogramming. This pathway also modulates the tumor microenvironment and contributes to therapy resistance [36–40]. Loss-of-function mutations in *SMAD4*, a central mediator of

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TGF-β signaling, turn off the pathway's tumor-suppressive effects on epithelial proliferation and promote tumor progression. Notably, TGF-β signaling exhibits a paradoxical role by suppressing tumorigenesis at early stages but facilitating epithelial-mesenchymal transition (EMT), invasion, and metastasis in advanced CRC [40–43].

Further genetic insults include mutations in *FBXW7*, an E3 ubiquitin ligase that targets multiple oncoproteins (e.g., cyclin E, c-Myc, Notch) for proteasomal degradation. Loss of *FBXW7* function leads to stabilization and accumulation of these substrates, contributing to increased proliferation and genomic instability [40-44]. Mutations in chromatin remodelers such as *ARID1A* disrupt epigenetic regulation, are associated with microsatellite instability (MSI), and modulate tumor immunogenicity and microenvironment, influencing both tumor behavior and response to immunotherapy [40-42].

Moreover, overexpression of matrix metalloproteinases (MMPs) degrades extracellular matrix components, facilitating tumor invasion and dissemination, a key step in CRC metastasis [37-41].

Therapeutic Implications

The identification of these genetic alterations has profound clinical significance:

Targeted therapies such as EGFR inhibitors require KRAS and NRAS wild-type status for efficacy [37-41]. TP53 mutations influence response to chemotherapy and are being explored as targets for novel agents that restore p53 function. BRAF-mutant CRCs may benefit from combined MAPK pathway inhibitors. PIK3CA mutations suggest potential for PI3K/Akt pathway inhibitors. MSI status and associated mutations guide immunotherapy use. Understanding the complex interplay of driver mutations and their downstream pathways enables precision oncology approaches, improving patient stratification and therapeutic outcomes [37,40-43].

Gene Therapy Strategies in Colorectal Cancer: Innovative Approaches and Targeting p53

Gene therapy has emerged as a promising therapeutic strategy for CRC, offering the potential for increased treatment specificity and reduced systemic toxicity. Several innovative modalities have been developed to improve the precision and efficacy of gene-based treatments [44-46].

One prominent approach is Gene-Directed Enzyme Prodrug Therapy (GDEPT), which employs the targeted delivery of genes encoding enzymes capable of converting non-toxic prodrugs into cytotoxic agents selectively within tumor cells. This strategy significantly reduces the side effects typically associated with conventional chemotherapy [46].

Another strategy involves cancer drug-resistance gene transfer, designed to enhance the tolerance of healthy tissues to chemoradiotherapy. By conferring resistance to normal cells, this method allows for intensified treatment of tumor cells while minimizing collateral damage [46].

Additionally, the advent of theranostic systems, which integrate diagnostic and therapeutic capabilities, has revolutionized personalized medicine. These systems enable real-time monitoring of therapeutic responses, facilitating timely adjustments to treatment protocols [46].

Beyond directly targeting cancer cells, gene therapy also addresses the tumor microenvironment (TME), which plays a crucial role in CRC progression. Anti-angiogenic gene therapy, delivered via adeno-associated virus (AAV) vectors, has demonstrated efficacy in inhibiting tumor vascularization. Genes encoding proteins such as angiostatin and endostatin have shown potential in reducing tumor growth with minimal adverse effects [47, 48].

Among the key genetic drivers of CRC, TP53 mutations are among the most prevalent and influential. The TP53 gene encodes the p53 tumor suppressor protein, which regulates apoptosis, DNA repair, and cell cycle arrest. Mutations in TP53 disrupt these processes and contribute to tumorigenesis and resistance to therapy [49].

To counter this, gene therapy targeting p53 has gained substantial interest. Approaches include the restoration of wild-type TP53 function via viral

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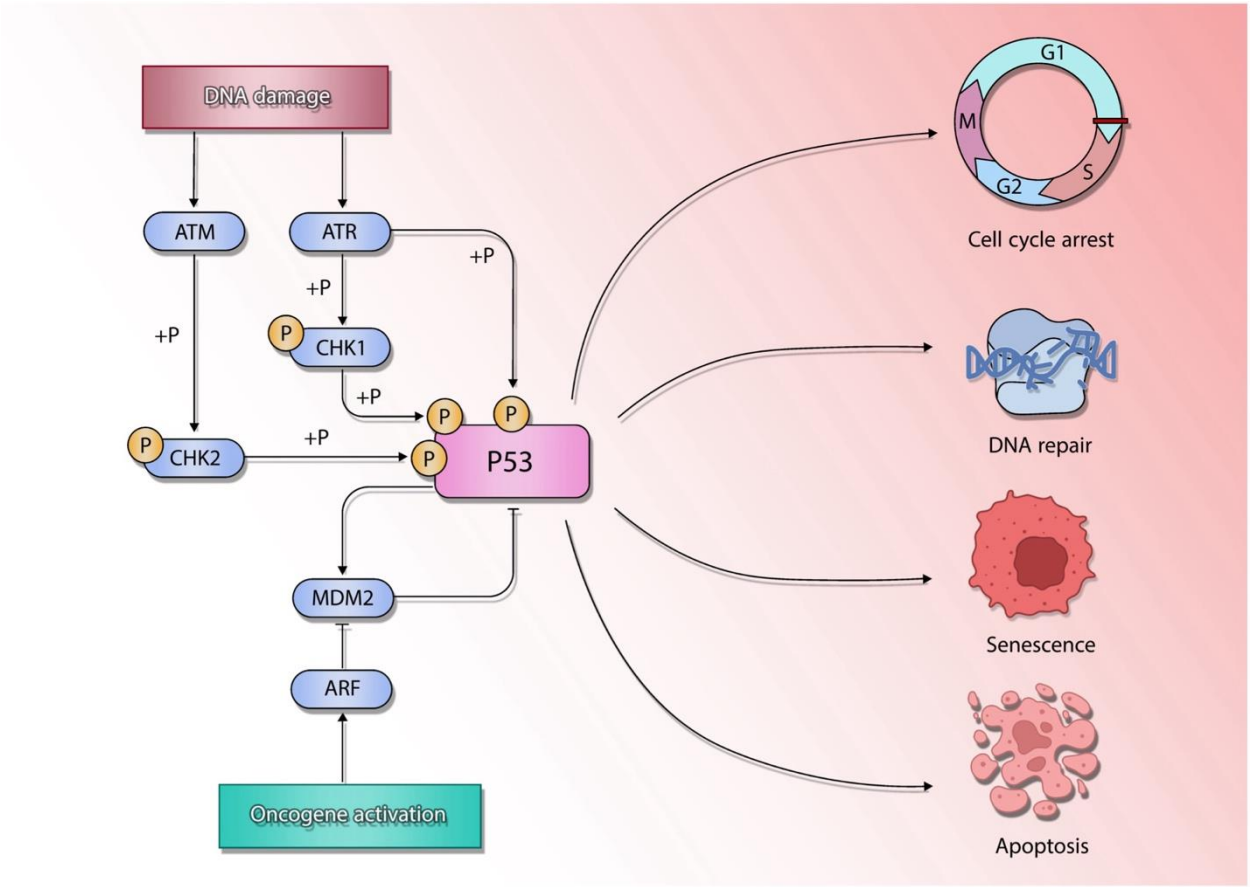

Figure 1. Schematic representation of the p53 signaling pathway and its regulatory Role in cell cycle arrest and apoptosis in colorectal cancer. This figure illustrates how p53 responds to cellular stress, such as DNA damage, by activating transcription of target genes involved in cell cycle arrest (e.g., p21) and apoptosis (e.g., BAX). In colorectal cancer, mutations in TP53 disrupt these protective mechanisms, allowing uncontrolled proliferation and tumor progression.

vectors, the suppression of mutant p53 expression using RNA interference technologies, and genome editing tools like CRISPR/Cas9. These methods aim to correct or neutralize the effects of dysfunctional p53, thereby reinstating tumor-suppressive mechanisms [46-49].

Given the high frequency of TP53 mutations in CRC, targeting p53 offers a tailored approach with the potential to improve patient outcomes significantly. When integrated with other gene therapy strategies and approaches targeting the TME, p53-directed therapies may form a cornerstone of future personalized cancer treatments [46-49].

Restoring Tumor Suppression: Targeting p53 in Colorectal Cancer Gene Therapy

The TP53 gene, often referred to as the *"guardian of the genome,"* is frequently mutated in CRC, leading to the loss of its tumor-suppressive functions such as apoptosis induction and cell cycle regulation [50-52]. Gene therapy efforts have focused on restoring wild-type p53 activity or inhibiting the effects of mutant forms.

Gendicine**,** a recombinant adenovirus delivering wild-type p53, was the first gene therapy approved (China, 2003). It has shown promising results in over 30,000 patients, especially when combined with chemotherapy or radiotherapy, including applications in advanced CRC [53-55].

Additionally, other viral vectors like VB-111 are being explored for targeting tumor vasculature, and combination therapies (e.g., p53 gene therapy plus chemotherapy) have enhanced tumor suppression in solid tumors [55-58].

A 2020 French study by Thierry André et al. demonstrated the effectiveness

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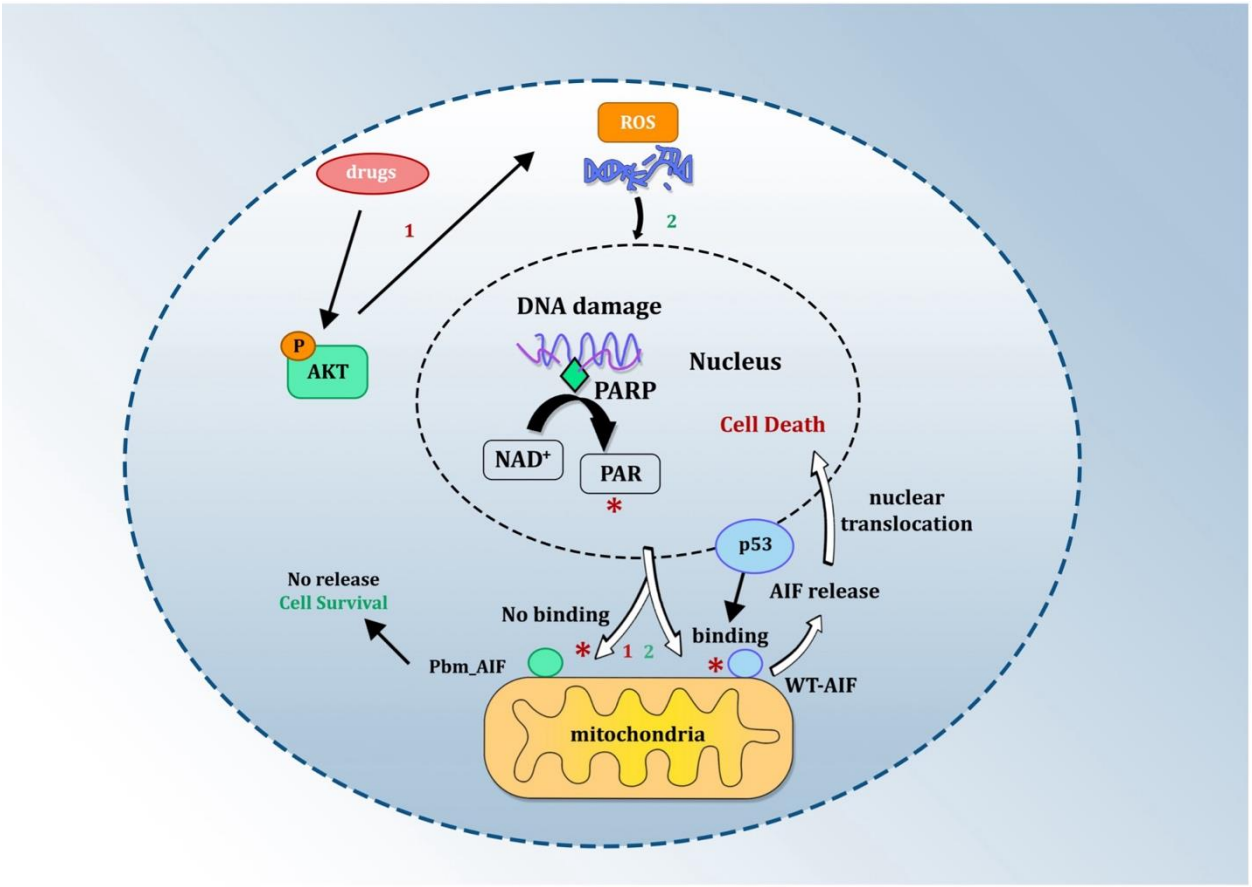

Figure 2. Mechanistic illustration of p53-induced apoptosis via AIF release from PAR and the effect of TP53 mutation on autophagy. Under normal conditions, p53 promotes apoptosis by facilitating the release of apoptosis-inducing factor (AIF) from PAR polymers, leading to caspase-independent cell death. However, in mutated p53, this apoptotic pathway is impaired, shifting the cellular response toward autophagy, which may contribute to tumor cell survival in CRC.

of Pembrolizumab as a first-line therapy for metastatic MSI-H/dMMR CRC, highlighting the growing Role of immune- and gene-based therapies in improving outcomes [9].

Emerging Promoter Systems and Nanoparticle-Based Gene Delivery

Advances in gene therapy for CRC are increasingly focused on improving specificity and efficiency through emerging promoter systems and nanoparticle-based gene delivery, with particular attention to p53-targeted therapies.

Tumor-Specific Nanosystems: Tumor-specific promoters are genetic elements engineered to activate gene expression specifically in cancer cells but not in normal tissues, thereby minimizing off-target effects and enhancing therapeutic precision. In CRC, several promoters show promise for driving selective p53 expression. For example, promoters linked to genes overexpressed in colon cancer, such as survivin, hTERT, or carcinoembryonic antigen (CEA), have been studied for their tumor specificity. Research also indicates that dual tumor suppressor gene delivery, combining p53 with other suppressors like PTEN under tumor-specific promoters, yields synergistic anti-cancer effects, including enhanced apoptosis and chemotherapeutic sensitivity in CRC cells. Such promoter systems enable targeted p53 gene activation that triggers cell cycle arrest and apoptosis primarily in cancerous cells, improving the safety and efficacy of the therapy [60].

Nanoparticle-Based Gene Delivery: Nanoparticles (NPs)—especially mesoporous silica nanoparticles (MSNs)—are emerging as highly effective gene delivery vehicles for CRC therapy due to their biocompatibility, high loading capacity, controlled release, and modifiable surfaces for targeted delivery [61]. MSNs can be functionalized with ligands

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targeting receptors overexpressed on CRC cells, facilitating selective uptake. Recent studies have demonstrated MSN platforms co-delivering p53 genes alongside chemotherapeutic drugs to overcome multidrug resistance and induce apoptosis more effectively. These hybrid nanosystems enable combination therapeutic strategies by simultaneously delivering gene therapy agents and traditional drugs, with enhanced penetration and reduced immunogenicity compared to viral vectors [61-65].

Satapathy et al. (India, 2013) systematically investigated the anti-cancer potential of starch-capped silver nanoparticles (AgNPs) against human colon cancer HCT116 cells. Their findings demonstrated that AgNPs inhibited cell growth and viability, induced apoptosis marked by increased apoptotic nuclei, elevated expression of p53, p21, BAX/BCL-XL ratio, cleaved PARP, and activation of caspases 3, 8, and 9, while reducing AKT and NF-κB levels. Cell cycle analysis showed a decrease in G1 phase cells with accumulation in S phase. DNA damage and impaired interaction between p53 and NF-κB were also reported. These effects were absent in p53-knockout HCT116 cells, indicating that AgNPs exert anti-cancer effects in a p53-dependent manner [66].

Challenges and Potential Solutions in p53 Gene Therapy for Colorectal Cancer

The challenges and potential solutions in p53 gene therapy for CRC reflect a broad spectrum of biological, technical, ethical, and economic issues, each requiring carefully designed strategies:

Limited Availability of Genetic Testing

Many settings, especially low-resource ones, face restricted access to comprehensive genomic profiling needed to identify TP53 mutations crucial for patient selection in p53-targeted therapies [1, 67, 68].

Solution: Expanding the use of liquid biopsy techniques, such as circulating tumor DNA analysis, and implementing low-cost next-generation sequencing panels can enhance mutation screening accessibility. The development of point-of-care diagnostics further promotes early detection and enables personalized therapy planning [1, 67, 68].

Therapeutic Resistance and Variable Efficacy

Challenge: Intratumoral heterogeneity, redundancy in the p53 pathway, anti-apoptotic resistance mechanisms, inefficient gene delivery, and immune clearance of vectors all limit consistent therapeutic success [1, 2].

Solution: Multimodal delivery platforms, such as polymeric or lipid-based nanoparticles combined with gene-editing tools like CRISPR/Cas9 or mRNA constructs, help improve gene expression efficiency and evade immune detection. Combining p53 gene therapy with sensitizing agents (e.g., BCL-2 inhibitors, immune checkpoint inhibitors) also addresses resistance and enhances efficacy [1, 2].

Safety and Off-Target Effects

Challenge: Overexpression of p53 in normal tissues risks unwanted apoptosis or senescence; viral vectors, especially adenoviral types, may cause strong immune reactions or insertional mutagenesis [1, 69].

Solution: Using tumor-specific promoters (e.g., survivin, hTERT, carcinoembryonic antigen (CEA) promoters) selectively targets p53 expression in cancer cells. Inducible gene expression systems (e.g., Tet-On) permit temporal and controlled p53 activation. Advances in non-integrating vectors and immune-evasive formulations further minimize off-target risks [1, 69, 70].

Ethical and Regulatory Challenges

Challenge: Gene therapy poses ethical issues, including informed consent for gene editing, long-term monitoring for safety, and equitable access, particularly among underserved populations [1, 71, 72].

Solution: Establishing strong ethical frameworks, transparent clinical trial protocols, and harmonized global regulatory standards can uphold safety and public confidence. Partnerships between pharmaceutical companies and public health systems may improve therapy access and affordability [1, 71-73].

High Economic Burden

Challenge: The substantial costs of vector production, personalized treatment development, and regulatory compliance hinder widespread clinical implementation [69, 70].

Solution: Advances in scalable manufacturing techniques (e.g., microfluidic nanoparticle synthesis, cell-free mRNA production) and value-based

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reimbursement models can reduce expenses. Economic studies demonstrating long-term cost-effectiveness versus conventional chemotherapy may also support broader adoption [70-73].

Overall, while these solutions are scientifically promising, further clinical studies and robust evidence are needed to validate their effectiveness and safety in CRC. Integration of emerging technologies and collaborative frameworks can enhance the development and accessibility of p53 gene therapy for CRC, addressing the current gaps in examples and study-backed evidence.

p53 Gene Therapy in Colorectal Cancer: Recent Advances and Clinical Trials

The tumor suppressor gene p53 plays a pivotal role in regulating cell cycle arrest, DNA repair, and apoptosis. Given its frequent mutation in CRC, restoring p53 function through gene therapy has been a promising therapeutic strategy. Recent clinical trials and preclinical studies have explored various approaches, including viral vector-mediated p53 delivery, small molecules that reactivate mutant p53, and combination therapies (Table 1).

Table 1. This table integrates recent clinical data and corresponding peer-reviewed articles published mostly in 2025, providing a comprehensive and up-to-date overview of p53 gene therapy clinical developments and their scientific backing.

Study / Trial Name	Cancer Type	Therapy Type	Phase / Status	Key Characteristics	Summary of Results / Status
APR-246 (Eprenetapopt) + AZA + VEN (NCT04214860)	TP53-mutated AML	Small molecule reactivating mutant p53 + azacitidine + venetoclax	Phase I/II	Frontline triple therapy for AML with TP53 mutation	CR/CRi rate 53% (CR 37%); promising efficacy but increased toxicity; biomarker-driven patient selection needed
APR-246 + Carboplatin + PLD (NCT02098343)	TP53-mutated high-grade serous ovarian cancer	APR-246 + chemotherapy	Phase Ib/II	Platinum-sensitive ovarian cancer	Improved complete response rate; higher toxicity and PD rate; need for optimized patient selection
APR-246 + PLD (NCT03268382)	Platinum-resistant recurrent HGSOC	APR-246 + chemotherapy	Phase II	TP53-mutated ovarian cancer	Disease control rate 69.6%; grade ≥3 adverse events 39.29%
Gendicine® (rAd-p53)	Head and neck squamous cell carcinoma and others	Recombinant adenoviral p53 gene therapy	Marketed in China; multiple clinical trials	The first approved p53 gene therapy, combined with radiotherapy and chemotherapy	Demonstrated safety and improved tumor control; enhanced outcomes vs. standard therapy alone
SGT-53 (scL-53)	Advanced solid tumors	Nanoparticle cationic liposome delivering wtp53 DNA	Phase I	Tumor-targeted delivery via transferrin receptor	Successfully delivered TP53 transgene to metastatic sites; demonstrated anti-cancer effects.
PC14586 and JAB-30355	Solid tumors with the TP53 Y220C mutation	Mutation-specific p53 reactivation agents	Recruiting	Targeting specific TP53 mutation for precision therapy	Trials are ongoing to assess safety and efficacy
Adenoviral p53 + Immune Checkpoint Inhibitors	Various solid tumors	Combination gene therapy and immunotherapy	Phase II	Intra-tumoral delivery of Ad-p53 with checkpoint blockade	Safety and efficacy under evaluation
General p53 gene therapy research	Various tumors	Various viral and nanoparticle delivery systems	Preclinical /early clinical	Development of novel delivery vectors and combination strategies	Promising preclinical results; clinical efficacy pending

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DISCUSSION

Recent advancements in gene therapy, particularly those targeting the TP53 gene, present promising opportunities for the treatment of CRC. TP53 plays a fundamental role in maintaining genomic stability by regulating processes such as cell cycle arrest, apoptosis, and DNA repair, which makes it a prime candidate for therapeutic intervention. Given the frequent mutations in TP53 observed in CRC, restoring or enhancing its function through gene therapy could offer significant clinical benefits. Over the past two decades, research into TP53-targeted therapy has produced encouraging preclinical data, with numerous studies showing tumor regression and restored p53 signaling in CRC cell lines and animal models. However, the translation of these results to the clinical setting has been less straightforward. Early-phase trials, such as those using adenoviral-mediated p53 delivery, demonstrated safety and biological activity, but objective response rates were often modest. Comparatively, immunotherapy—particularly immune checkpoint inhibitors—has shown more dramatic clinical benefits in specific CRC subtypes, such as microsatellite instability-high (MSI-H) tumors, setting a high efficacy benchmark for any novel therapeutic approach. One of the key limitations in TP53 gene therapy is the complexity of the p53 pathway itself. As a central node in numerous cellular processes, p53 interacts with multiple upstream and downstream regulators. This means that simply restoring wild-type p53 expression may not always result in therapeutic benefit, especially if other tumor-suppressive pathways are also compromised.

Moreover, some TP53 mutations produce dominant-negative proteins that can interfere with the function of wild-type p53, complicating the therapeutic strategy. Delivery methods remain another critical challenge. Viral vectors, such as adenoviruses and lentiviruses, have been the mainstay of gene delivery, offering high transduction efficiency, but they raise concerns regarding immunogenicity and off-target effects. Non-viral approaches, including lipid nanoparticles, polymeric carriers, and exosome-based systems, are emerging as promising alternatives that could improve tumor specificity and safety profiles. Interestingly, recent studies have explored CRISPR/Cas9-mediated gene editing to correct TP53 mutations directly in CRC cells, with encouraging in vitro results. However, these approaches require further refinement to ensure precision and minimize unintended genome modifications. Another important consideration is treatment integration. Given the heterogeneity of CRC, TP53-targeted therapy may be most effective as part of a combination regimen, potentially with immune checkpoint inhibitors, chemotherapy, or targeted drugs such as EGFR or KRAS inhibitors. Combination strategies could not only enhance tumor suppression but also overcome resistance mechanisms that often limit the efficacy of monotherapies. Economic and logistical barriers also hinder the widespread adoption of TP53-based gene therapy. These treatments are currently complex, expensive, and personalized, requiring specialized manufacturing facilities and delivery platforms. Reducing production costs, simplifying delivery systems, and establishing scalable manufacturing protocols will be essential for their transition into mainstream clinical use.

CONCLUSION

TP53-targeted gene therapy represents a novel and potentially transformative approach to CRC treatment. While the preclinical evidence is compelling, clinical translation will require overcoming significant scientific, technical, and economic challenges. The future of this therapeutic strategy likely lies in precision medicine frameworks, where patient-specific molecular profiles guide the integration of TP53-targeted therapy with other modalities. As our understanding of CRC biology deepens and delivery technologies improve, TP53-based interventions could become an integral part of personalized oncology, offering renewed hope for patients with this challenging malignancy.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ETHICS APPROVAL

Not applicable.

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