EDITORIAL

Colorectal Cancer and p53

Colorectal Cancer (CRC) is one of the most common malignancies with high prevalence and low 5-year survival. CRC is a heterogenous disease with complex, genetic and biochemical background. Development of CRC is a multifactorial and multi-stage process involving the activation of oncogenes and inactivation of tumor suppressor genes. Confirmed by numerous studies, p53 is a key tumor suppressor gene and one of the most important elements of our body's anticancer defense[1]. p53 is the most commonly mutated gene in human cancer[2].

Dysregulation of p53 tumor suppressor gene is one of the most frequent events contributing to the transformation of colorectal cancer (CRC), as well as the aggressive and metastatic features of CRC. Tp53 mutation occurs in approximately 40%-50% of sporadic CRC[3]; 34% in proximal colon and 45% in distal colorectal cancer[4]. Patients with mutated p53 CRC appear more chemo-resistance and have poorer prognosis than those with wild-type p53 patients[4].

It is much more frequently mutated in high-grade dysplastic polyps, which are thought to mark the transition from adenoma to carcinoma, than in early adenomas. This finding implies that most TP53 mutations probably occur before metastasis[5].

P53-based gene therapy presents a compelling strategy for combating cancer, particularly in the context of CRC. This approach typically focuses on two main objectives: administering wild-type p53 to restore its normal tumor-suppressive functions or suppressing the expression of mutant p53 in p53-defective cancer cells[6]. By targeting the dysfunctional p53 pathway, this therapy aims to inhibit malignant development and progression in CRC, potentially leading to improved treatment outcomes. As research advances, p53-based gene therapy holds promise as a robust method to combat tumor growth and develop more effective interventions for patients suffering from this aggressive cancer type.

Emerging evidence from laboratories and clinical trials highlights the promising potential of small molecules, such as PRIMA-1 and its methylated derivative APR246, in targeting mutant p53 proteins. These compounds have been shown to refold the incorrectly folded mutant p53 into a functional conformation, thereby enabling it to regain its tumor-suppressive activities[7]. In parallel, gene therapy approaches are being developed to deliver a functional copy of the p53 gene directly into cancer cells, offering a potential pathway to restore the normal function of p53 in tumors that have lost its activity due to mutations8. Together, these strategies represent a significant advancement in the fight against cancer, targeting one of the most critical players in tumor biology and providing hope for more effective therapeutic options.

p53 mutations confer resistance to classical chemotherapy but, on the other hand, they open the door for immunotherapy, as p53-mutated tumors are rich in neoantigens.

CRC patients with mutant p53 can benefit from enrolling in clinical trials investigating novel therapies or combination treatments, as this provides access to cutting-edge treatments and may improve outcomes. Moreover, these patients require rigorous follow-up and monitoring for recurrence or progression of the disease due to the higher risk associated with this mutation.

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