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From polyp to carcinoma: The molecular progression of colorectal neoplasia and its clinical implications.

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Introduction

Colorectal cancer develops gradually, often beginning as a non-malignant polyp that transforms over years or decades into invasive adenocarcinoma. This evolution—known as the adenoma-carcinoma sequence—is driven by progressive molecular abnormalities that disrupt normal colonic epithelial homeostasis. Understanding the underlying mechanisms of this progression is crucial for early intervention and reducing CRC-related mortality.[1].

Colorectal polyps are generally categorized into three types: hyperplastic polyps, which are typically benign with minimal malignant potential; adenomatous polyps (adenomas), the most common precancerous lesions; and serrated polyps, including sessile serrated adenomas/polyps (SSAs/Ps), which have malignant potential via the serrated pathway. Among adenomas, those with villous histology, larger than 1 cm, or exhibiting high-grade dysplasia carry a higher risk of progressing to cancer. The traditional adenoma-carcinoma sequence, as outlined by Fearon and Vogelstein, describes the stepwise accumulation of genetic mutations leading to colorectal cancer.[2].

This sequence begins with the inactivation of the APC gene, a tumor suppressor, resulting in β-catenin accumulation and uncontrolled cell growth through the Wnt signaling pathway. It is followed by activating mutations in the KRAS gene, which enhance proliferation and inhibit apoptosis, contributing to the growth of small adenomas into larger, dysplastic forms. Later events include the mutation or loss of the TP53 gene, impairing DNA repair and apoptosis, thus enabling malignant transformation, and the loss of chromosome 18q and inactivation of SMAD4, a critical regulator in the TGF-β pathway, which further compromises tumor suppression and facilitates progression to invasive cancer. [3].

A significant proportion of colorectal cancers (CRCs) arise through an alternative route known as the serrated neoplasia pathway, which is characterized by BRAF mutations that activate the MAPK pathway, the CpG island methylator phenotype (CIMP) leading to epigenetic silencing of tumor suppressor genes, and MLH1 promoter methylation resulting in microsatellite instability (MSI), particularly common in proximal colon cancers and more frequently observed in older women with right-sided tumors. In addition to genetic mutations, epigenetic alterations also play a crucial role in CRC development, including promoter methylation of tumor suppressor genes such as MLH1 and p16, histone modifications, and non-coding RNA dysregulation. These epigenetic changes alter gene expression without modifying the DNA sequence, thereby contributing to cancer progression [4].

Understanding the molecular timeline of colorectal cancer (CRC) progression has significantly influenced clinical practices, especially in screening and early detection. Colonoscopy enables the identification and removal of polyps before they become malignant, while fecal DNA tests like Cologuard detect methylated DNA and KRAS mutations in stool, and MSI testing aids in diagnosing Lynch syndrome and guiding immunotherapy. Regular surveillance, based on polyp size, number, and histology, plays a crucial role in reducing CRC incidence and mortality [5].

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Conclusion

The transformation from polyp to carcinoma in colorectal neoplasia is a well-characterized process marked by genetic and epigenetic alterations. Understanding these molecular events has revolutionized CRC screening, surveillance, and treatment. With the integration of genomics and personalized medicine, early intervention strategies are poised to become e ven more precise and impactful.

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