Colorectal Neoplasia Pathways: State of the Art

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KEYWORDS

• Colorectal cancer • Chromosomal instability • Microsatellite instability
• Serrated neoplasia pathway • Colonoscopy • Colorectal polyps

KEY POINTS

- Colorectal cancer (CRC) is a very heterogeneous disease resulting from multiple overarching neoplasia pathways, of which the chromosomal instability, the microsatellite instability, and the serrated neoplasia pathways are the most significant.
- Besides conventional adenomas, serrated polyps also seem to be precursor lesions of CRC, arising via the serrated neoplasia pathway.
- Accurate endoscopic characterization of premalignant colonic lesions would enable the implementation of targeted treatment in the near future, resulting in effective, safe, as well as cost-effective CRC prevention.

INTRODUCTION

Colorectal cancer (CRC) is a very heterogeneous disease with regards to tumor development as well as clinical tumor behavior. Due to the presence or absence of diverse genetic and epigenetic alterations, each CRC appears to possess a unique molecular tumor profile.[1] The oncogenesis of CRC is extensively evaluated compared to other solid tumors in the human body (**Fig. 1**). This is partly due to its high priority because CRC has high morbidity and mortality rates in the Western world.[2] Other factors are the slow progression of disease and the possibility to sample CRC precursor lesions, enabling the assessment of molecular changes in consecutive steps of tumorigenesis.[3]

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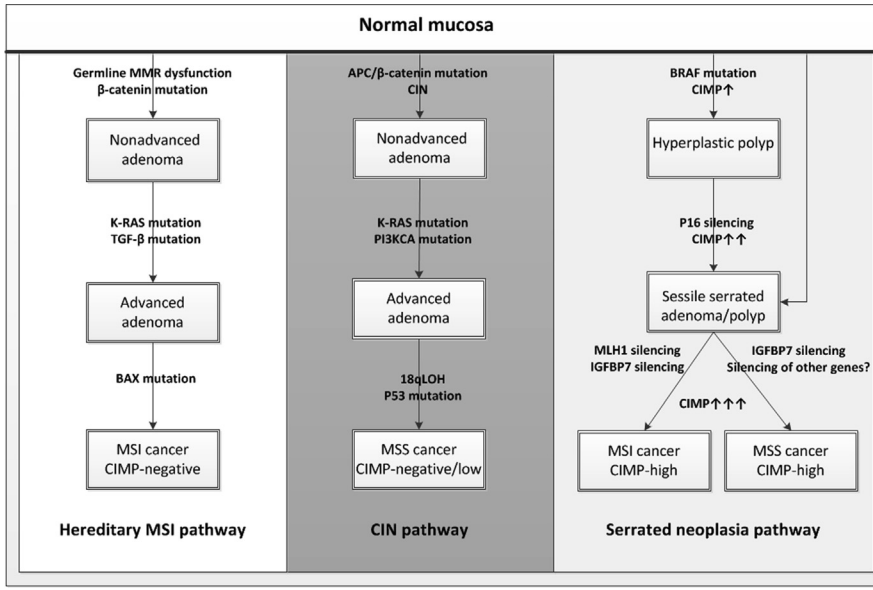

Fig. 1. Model of CRC oncogenesis presenting a global and simplified insight in the 3 most studied colorectal neoplasia pathways.

Until recently, conventional adenomas (further referred to as adenomas) were regarded as the only precursors of CRC, developing into cancer via the adenoma-carcinoma pathway.[4] A multistep molecular sequence responsible for the adenoma-carcinoma pathway was first described by Fearon and Vogelstein.[5] Although more recent literature has demonstrated that a minority of CRCs arise exactly via the pathway described by Fearon and Vogelstein,[5] the model has long been a prominent paradigm for research concerning the origin of CRC and other solid tumors.[6] Currently, multiple colorectal neoplasia pathways are distinguished, of which the chromosomal instability (CIN) pathway; the microsatellite instability (MSI) pathway; and the CpG island methylator pathway (CIMP), also referred to as the serrated neoplasia pathway, are the best studied.[7–9] Oncogenesis occurring via these pathways may, however, not be completely separated. Crossover, or even overlap, between the pathways is likely to exist. Serrated polyps (SPs), rather than adenomas, are suggested to be the precursor lesions of CRC arising via the serrated neoplasia pathway, responsible for approximately 15% to 30% of CRC.[10–12] This finding has led to an important paradigm shift in daily practice for colonoscopies because it has become apparent that adenomas as well as premalignant SP subtypes should be detected and resected to effectively prevent CRC.[13]

Only a small percentage of polyps seem to develop into CRC, whereas most polyps remain stable over time or even regress.[14,15] However, for adenomas as well as for SPs, it is unclear which molecular alterations induce the final transition toward invasive growth. As a result, it is still largely unknown which lesions will develop into CRC and which lesions will have a benign course. Profound knowledge of the colorectal neoplasia pathways is essential for each endoscopist to optimize current prevention strategies. Ongoing research could, it is hoped, lead toward the targeted resection of truly premalignant colorectal lesions in the near future.