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Lynch syndrome: new tales from the crypt

C Richard Boland

GI Cancer Research Laboratory, Division of Gastroenterology, Department of Internal Medicine, Sammons Cancer Center and Baylor Research Institute, Baylor University Medical Center, Dallas, TX, USA rickbo@baylorhealth.edu

Lynch syndrome is a hereditary disease that predisposes to cancer and is caused by germline mutations in DNA mismatch repair (MMR) genes.¹ The disease is inherited in a classic Mendelian dominant way, but tumours act like a recessive disease—a somatic mutation is needed to inactivate the uninvolved allele. Individuals with Lynch syndrome are phenotypically normal at birth, but carry a silent germline mutation. At some point in the individual's development, the so-called second hit occurs, which initiates the progression towards neoplasia. In the case of familial adenomatous polyposis, the germline mutation occurs in the *APC* gene. A somatic mutation in the wild-type *APC* allele leads to the emergence of a dysplastic aberrant crypt focus, which is a very small adenoma. However, Lynch syndrome is different. The paired mutations do not create a neoplastic phenotype directly, but rather they create a deficiency in DNA MMR, which allows the accumulation of mutations and microsatellite instability.²

One unanswered question in Lynch syndrome regards what is the timing and sequence of genetic events through which colorectal cancers evolve. One theory is that adenomatous polyps develop as they do in sporadic neoplasia, MMR deficiency occurs within the adenoma, which accelerates the accumulation of mutations, and is followed by step-wise neoplastic progression. An alternative idea is that deficiency of MMR occurs first, and the adenoma evolves from the MMR-deficient cell. Data exist to support either model but no consensus has been reached on which one is most representative. Matthias Kloor and colleagues³ in *The Lancet Oncology* provide new insights, and show that MMR-deficient crypts can be found in Lynch syndrome before the affected cells seem to be neoplastic. Kloor and colleagues³ did immunohistochemistry for MMR proteins on non-neoplastic colonic tissues that were resected along with colorectal cancer tissue. The investigators identified colonic crypts that were near-normal in appearance and did not express MMR proteins. Moreover, the DNA showed microsatellite instability, suggesting strongly that mismatch repair activity was functionally deficient in these crypts. The absent MMR protein matched the germline mutation, and no MMR-deficient crypts were found in the colons of individuals with sporadic colorectal cancer.

MMR-deficient crypts are prevalent in colons of patients with Lynch syndrome. About one MMR-deficient crypt was recorded per cm² of mucosa, or about one per 10 000 crypts in the colon, and slightly fewer were recorded in the small intestine of patients with Lynch syndrome. At least one MMR-deficient crypt was noted in eight of ten colons of patients with Lynch syndrome. Subtle nuclear abnormalities were noted at the bottoms of these crypts, but the architecture was not identifiably neoplastic. MMR-deficient crypts are not the equivalent of dysplastic aberrant crypt foci, which already have a neoplastic phenotype.⁴ In fact, what happens to all the MMR-deficient crypts is not yet apparent. Unfortunately, these lesions are too small and subtle to be relied upon clinically to suggest a diagnosis of Lynch

syndrome. Importantly, the investigators acknowledge that, although they noted these lesions occurred frequently, most patients with Lynch syndrome will develop zero to two cancers, and typically only a few adenomatous polyps, through their lifetimes.⁵ Small bowel cancers occur in no more than 1–4% of patients with Lynch syndrome,⁶ yet that organ has one MMR-deficient crypt per 2 cm² of mucosa. Obviously, most of these lesions do not develop into cancer. So, what happens to them?

Kloor and colleagues³ speculate that immunoediting detects and eradicates these lesions because microsatellite instability permits frameshift mutations and predictable types of cancer-associated neoantigens.^{7,8} The authors propose that the generation of these neoantigens sensitise the immune system against tumours, and that patients with Lynch syndrome auto-vaccinate themselves against cancer.

What are the limitations of this work? First, the authors have clearly found MMR-deficient crypts, and the data strongly suggest they are Lynch syndrome-specific, but they did not show that these lesions can grow, are neoplastic, or are precursors to neoplasms. They could be irrelevant to tumour formation. Something restrains or eliminates these lesions, and it might be that MMR-deficient cells simply migrate up the crypt and are eliminated like their MMR-proficient siblings. MMR-deficient crypts do not populate the entire colon, so some mechanism must therefore limit their expansion. In a study,⁹ MMR-deficiency was uniformly present in adenomatous polyps >9 mm in diameter in Lynch syndrome patients, but was frequently absent in smaller lesions, suggesting that the MMR defect occurs after the evolution of the adenoma in some instances, rather than as a primary event.⁹

The authors did not report immune infiltrates in the MMR-deficient crypts, so one might thus anticipate future studies to determine if an immunological reaction exists against these lesions. The missing link in this work is the contrast between the large number of MMR-deficient crypts and the relatively small number of clinically relevant neoplasms in this disease. That said, this work is highly novel, underscores the differences between Lynch syndrome and sporadic colorectal cancers, and raises a fresh group of important questions to be addressed.

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