Lynch syndrome: much progress but many questions remain

John Keating

Finding and correcting mismatched nucleotide base pairs in newly formed DNA strands during cell division is the role of the four mismatch repair (MMR) genes and their encoded proteins. This mechanism follows on from the proofreading exonuclease function of DNA polymerase that acts as the initial check on the fidelity of replication of the over three billion nucleotides in human DNA.

MMR deficient colorectal cancers (dMMR CRCs) account for 15% of the colorectal cancer burden. As a consequence of defective MMR function these tumours exhibit multiple abnormal repeats of mono and dinucleotides at characteristic sites throughout the genome (microsatellites) and are thus said to show microsatellite instability or be MSI high (MSI or MSI-H). In the majority of cancers that are microsatellite unstable and that show loss of expression (LOE) of one or more of the MMR proteins on immunohistochemistry, the cause is an acquired loss of MMR function in the tumour from hypermethylation induced inactivation of the corresponding gene. MLH1 and PMS2 LOE is the usual pattern and can be confirmed as an acquired event by testing the MLH1 gene promoter directly for methylation or indirectly by confirmation of the v-600e mutation in the BRAF gene, which is usually present in this setting. In less than a third of patients with a CRC with LOE a dominantly inherited germline mutation in one of the four MMR genes MLH1, MSH2, MSH6 and PMS2 is the cause. This group of patients has Lynch syndrome (LS). Additionally, an inherited mutation in the EPCAM gene can silence the expression of an otherwise normal MSH2 gene leading to LS. Lynch syndrome predisposes to a range of tumours with colorectal and endometrial being the most important numerically, but less commonly ovarian, small bowel, urological, gastric and small bowel tumours are encountered. The picture is further complicated by patients who have LOE of an MMR protein in their tumour without evidence of hypermethylation, but in whom no pathogenic mutation can be identified on sequencing of the corresponding gene. Such patients are referred to as being “Lynch like” or having “possible Lynch” but in practice are screened along the lines of patients having a confirmed germline mutation as they carry a similar risk of cancer to LS patients. Somatic mutation in the MMR genes is responsible for a proportion of these cases while others remain unexplained.

The great majority of the population with LS are unaware that they carry the condition in part due to a lack of robust tumour testing. Recent population-wide genome studies have revealed that LS is surprisingly common with an incidence of 1 in 226, making it among the commonest inherited cancer predisposition genes. These data suggest that ascertainment bias may have overestimated the cancer risk for mutation carriers. This is especially true for PMS2 carriers who have a much lower cancer penetrance in contrast to MLH1 and MSH2. Mutation in one of the latter two genes carries a risk of CRC to the age of 70 of 34 to 47%. The risk of CRC in all four genes is higher in men than women for reasons that are unclear. Also unclear are the factors responsible for the huge variation in risk between carriers of the same mutated gene, with some having a risk close to the population risk and others being at very high risk.

Another fundamental question in LS-associated CRC is the nature of the precursor lesion. Until recently it was assumed that a dMMR adenoma was the precursor lesion, however, isolated dMMR crypt foci have been shown to occur in LS patients and it
is posited that these may proceed directly to cancer without the development of an intermediate adenoma. The distinction is important as more frequent colonoscopy may not reliably prevent CRC if the latter is an important mechanism. Recent data from a prospective multinationa screening programme for LS patients demonstrates that colorectal cancer still occurs frequently but is associated with very few deaths.

The current New Zealand Familial Gastrointestinal Cancer Service (NZFGCS) recommendations for cancer surveillance in Lynch syndrome are for yearly colonoscopy from age 25 to 75 for mutation carriers, or 10 years younger than the earliest CRC in the family. Upper gastrointestinal endoscopy is now recommended as a one-off examination at age 35 for MLH1 and MSH2 carriers with eradication of H. pylori if identified. Examination should be performed to the distal duodenum with repeat examination if there are significant findings such as extensive intestinal metaplasia. Gynaecological consultation and consideration of screening is advised for women from the age of 30 with the option of hysterectomy and oophorectomy on completion of their family. There is no evidence to support routine urological screening.

Patients with LS who develop CRC and undergo an extended colonic resection as opposed to a segmental resection have a significantly lower risk of developing a metachronous cancer. In patients with a CRC in whom LS is suspected based either on the family history or the age of diagnosis it is therefore important to request immunohistochemistry on the tumour biopsy taken at colonoscopy to allow informed preoperative discussion of the relative merits of the extent of surgical resection.

Aspirin use reduces the incidence of sporadic CRC, and long-term follow-up of LS patients in a randomised controlled trial of aspirin has demonstrated a significant reduction in CRC risk. Further dosing studies are underway to determine whether smaller doses than the 600mg a day used in the initial trial are equally effective. The results of these dosing trials are some years away. Aspirin use is, however, currently advised for proven mutation carriers, especially for the high cancer penetrance genes MLH1 and MSH2.

The defective DNA mismatch repair in LS CRC leads to the generation of frameshift peptides that are recognised by the immune system as foreign and as such are accompanied by a prominent immune response. This marked immune response is thought to be an important factor in the better prognosis in LS-associated CRC compared to sporadic disease. Important differences in treatment response are exhibited by dMMR CRCs. Mismatch repair deficient CRCs are poorly responsive to 5FU-based chemotherapy, indeed in the adjuvant setting, chemotherapy results in a worse survival in stage two disease and only a marginal benefit in stage three disease.

Perhaps the most important recent finding is the responsiveness of advanced dMMR CRCs, either germline or acquired, to pd-1 inhibition. This is not observed in MMR proficient CRC. The timing and combination of Pd-1 inhibitors, either alone or in combination, as well as their integration into conventional chemotherapy schedules for advanced disease is a source on multiple ongoing trials. What is clear is that these uncommon tumour syndromes look set to continue to further our knowledge of fundamental tumour biology.

Competing interests: Nil.

Author information: John Keating, Medical Advisor, Wellington Office, NZFGCS.

Corresponding author: Dr John Keating, Colorectal and General Surgeon, Southern Cross Specialist Centre, 90 Hanson Street, Newtown, Wellington. keating.john40@gmail.com

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