Mismatch repair gene abnormalities in tumours

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High levels of microsatellite instability (MSI-H), also known as deficient mismatch repair (D-MMR), occur as a result of germ line mutations or acquired somatic events in the MMR genes (MLH1, MSH2, MSH6 and PMS2). The former is referred to as Lynch syndrome (previously known as hereditary non polyposis colorectal carcinoma) and is an autosomal dominant condition with predisposition to colorectal, gynaecological and other tumours (often at an early age). Summary box 11.17 Microsatellite instability and mismatch repair genes /uni25CF for MMR mutations, although some centres use PCR-based microsatellite testing for screening. Loss of immunohistochem - ical staining by neoplastic cells is a marker for a gene defect, an indication for further testing and may lead to genetic testing for Lynch syndrome (Figure 11.30). In most patients, a detectable MMR abnormality is sporadic and does not represent Lynch syndrome . MMR gene defects in CRC also identify sporadic tumours with di ff erent phenotypic and genetic characteristics. For example, BRAF V600E mutations are frequent in these cases and such cancers develop via the serrated polyp pathway rather than from adenomas (see Chapter 77). MMR abnormalities generally predict lower recurrence rates, better survival rates and a lack of need for 5-fluorouracil.

Microsatellite instability (MSI) Regulated by four main genes: MLH1, PMS2, MSH2, MSH6 Genetic changes responsible for MSI Sporadic hypermethylation of MLH1 (more common; 85%) Germline mutation, i.e. Lynch syndrome (less common) Microsatellite unstable (MSI-H) tumours 15% of colorectal carcinoma (CRC) 30% of endometrial carcinoma Tests Immunohistochemistry Recommended for all newly diagnosed CRCs The preferred initial test in most centres PCR-based microsatellite testing NGS Clinicopathological correlation: MSI-H CRC Typically right sided More likely to have mucinous element histologically Likely to have BRAF V600E mutation Clinical value Phenotypic classi /f_i cation, e.g. medullary CRC is typically MSI-H Prognosis, e.g. MSI-H better prognosis overall Selection of drug therapy, e.g. MSI-H CRC responds better to ICIs and has no response to 5- /f_l uorouracil Screening for germline mutation, i.e. Lynch syndrome

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