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Genomic Study on Molecular Pathways of Cancer Development and Its Relevance to Cancer Precision Medicine

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Colorectal cancers (CRC) develop through two major molecular pathways. The majority goes through the adenoma-carcinoma sequence, with stepwise mutation of APC, KRAS and TP53 genes. A smaller proportion (around 15%) develops through inactivation of the DNA mismatch repair (MMR) system leading to an accelerated mutation rate and microsatellite instability (MSI). Some of these molecular alterations are emerging as biomarkers for prognostication, guiding patient treatment as well as prediction of genetic predisposition for focused preventive screening. CRC with MSI are sensitive to immune checkpoint inhibition. Furthermore, MSI CRC are more likely to progress through the serrated pathway with RNF43 mutation or R-spondin fusions, thus these patients may be candidate for clinical trials involving WNT upstream inhibitor treatment. Whilst most late onset CRC with MSI are sporadic due to biallelic inactivation of MLH1 by promoter methylation in somatic cells, majority of early-onset MSI CRCs are due to hereditary predisposition by way of germline MMR gene mutation (Lynch Syndrome). Genetic diagnosis to distinguish between germline versus somatic alterations can identify high risk group for prophylactic screening, and has proven highly effective in cancer prevention. Emerging technologies including next generation sequencing can facilitate the discovery of novel genes or pathways that contribute to development of inherited or sporadic gastrointestinal cancers. Finally, emerging organoid culture technology enables direct culture of patients' cancer cells for drug sensitivity testing, which coupled with genomic analysis, holds great potential for advancement of cancer precision medicine through tailored targeted therapy to specific subgroup of patients.