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The Microsatellite Instability Phenotype

in Human Colorectal Carcinoma

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CHAPTER 1

Outline of the Thesis

Outline of the Thesis

Colorectal cancer (CRC) is the second to the fourth most common cancer in industrialized countries. Baseline mutation rates are insufficient to account for the multiple mutations that are required for cancer to develop. As highlighted in **Chapter 2**, genomic instability is now recognized as an essential cellular feature that accompanies the acquisition of these mutations. In colon cancer, at least 3 distinct pathways of genomic instability have been described, the chromosomal instability (CIN), microsatellite instability (MSI), and the so-called CpG island methylator phenotype (CIMP) pathways, each with distinctive tumor genotypes and phenotypes. MSI is commonly caused by loss of the DNA mismatch repair (MMR) system, which normally recognizes and repairs mismatched nucleotides and insertion/deletion loops caused by slippage of DNA polymerase. MSI occurs in hereditary as well as sporadic CRC. In Lynch syndrome (LS), responsible for 2-5% of all CRC cases, a germline mutation in a MMR gene accounts for more than 90% of cases, whereas in 10-15% of sporadic CRCs MSI is due to loss of expression of a MMR gene (most commonly *hMLH1*) caused by epigenetic silencing.

In **Chapter 3**, the clinical features, cancer risks, diagnostic strategies, and surveillance and management of LS are discussed. The timely recognition of LS is essential to identify patients at high-risk who will require intensive cancer surveillance. A significant patient survival advantage and reduction in the incidence of colorectal tumors has been observed following colonoscopic screening and polypectomy. In LS, carcinogenesis proceeds through the adenoma-carcinoma sequence. Although the number of polyps in Lynch patients appears to be similar to the general population, the polyps are more likely to occur at a younger age, have a predilection for the proximal colon, be larger, display villous

features or high-grade dysplasia, and most importantly, grow rapidly and progress to invasive cancer in less than 3 years. As the recognition of LS is increasing in the population, many individuals with suspected LS now undergo routine colonoscopic screening with polypectomy. In such a scenario, there is no colon cancer tissue available for MSI and IHC testing. In **Chapter 4**, we present the results of a study that was undertaken to test the hypothesis that MSI testing and IHC analysis in pre-cancerous colorectal adenomas instead of colorectal cancers may be an alternative approach to screen for LS.

The clinical behavior of MSI tumors is distinctive, and the most intriguing and consistently described feature is the enhanced survival benefit that does not appear to be attributable to differences in therapeutic response. The molecular basis for the prognostic advantage due to MSI is not clearly established. The most commonly mutated gene in tumors with MSI is the transforming growth factor-β receptor II (*TGFBR2*) gene, which harbors an $(A)_{10}$ repeat that undergoes a frame shift. This mutation leads to a disruption in the function of TGF-β. As described in **Chapter 5**, TGF-β signaling plays a dual role in tumorigenesis: in early stages it mediates tumor-suppressive effects whereas, paradoxically, at later stages TGF-β signaling may enhance tumor progression due to its ability to inhibit cell death from growth factor deprivation, suppress immune function, and induce an epithelial to mesenchymal transition (EMT). In **Chapter 6**, we present the results of a study in which we tested, *in vitro* and in human samples, the hypothesis that the favorable natural history seen in MSI tumors, carrying a mutant *TGFBR2*, is due to the impaired ability of TGF-β to induce EMT.