WHITEPAPER

Let's Get Clinical: Understanding Mismatch Repair and Microsatellite Instability

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Cancer, a complex and multifaceted disease, arises from the uncontrolled growth of abnormal cells. While advancements in medical science have significantly improved cancer treatment and survival rates, the underlying mechanisms driving carcinogenesis remain a subject of clinical significance and intense research. Central to this understanding is the intricate interplay between DNA repair systems and genetic instability. A key player in this complex biological dance is known as Mismatch Repair (MMR).

By understanding these mechanisms and the associated laboratory tests, healthcare providers can make informed decisions, leading to improved patient outcomes and advancing the field of pathology and oncology.

Note: This overview provides a foundational understanding of MMR and MSI and their relations to certain cancers. It's crucial to incorporate the latest findings and expert opinions with in-depth analysis of specific cancer types, clinical trials, and emerging research.

MMR and MSI: A Comprehensive Overview

Mismatch Repair (MMR) is a cellular process crucial for maintaining genomic stability. Simply put, it corrects errors that occur during DNA replication, and regulates different processes of cellular function. Key MMR genes include MLH1, MSH2, MSH6, and PMS2. When these genes are mutated, the MMR system becomes dysfunctional, leading to an accumulation of errors and increased risk of cancer, sometimes called MMR deficiency (dMMR). In some rare cases, there have been patient findings with a mutated EpCAM gene, which can lead to loss of MSH2 or MSH6 expression.[1] We can use immunohistochemistry (IHC) to detect gene and protein expression from MLH1, MSH2, MSH6, and PMS2.

MMR protein expression is not necessarily a conclusive measure of MMR function. There can be a loss in the function of these proteins without a corresponding loss of the protein in the cell, with 5–10% of proteins retaining antigenicity when they are not functional.[2] This is why labs typically test for Microsatellite Instability with MMR.

Microsatellite Instability (MSI) is a direct consequence of dMMR and causes instability of microsatellites of the genome, affecting cells to accurately replicate short, repetitive DNA sequences. Testing for MSI is typically reflexed after MMR-IHC in certain tumors and can be done by a variety of lab testing methods with the most common being Polymerase Chain Reaction (PCR). There are also Next Generation Sequencing (NGS) tests that can measure and detect the mutations within microsatellite sequences of a tumor sample.[3]

These lab methods can be used to determine if a patient's sample is MSI-High (MSI-H), where more than 30% of the typically used repeats are unstable, MSI-Low (MSI-L), where less than 30% of the typically used repeats are unstable, or MSI-Stable where 0 (or 0%) of the typically used repeats are unstable.[1]

Clinical Significance of MMR and MSI

1. Colorectal Cancer

- **Lynch Syndrome:** Historically called hereditary nonpolyposis colorectal cancer, it is caused by germline mutations in MMR genes. Lynch Syndrome is known to be a hereditary condition that give patients an increased risk of developing colorectal, endometrial, ovarian, gastric, and other cancers.[4] Studies of Lynch syndrome-associated adenomas suggest a slightly lower rate of MSI compared to invasive cancers, with approximately 80% of adenomas being MSI-H. Adenomas with high-grade dysplasia are more likely to exhibit MSI than early polyps.[5]

2. Endometrial Cancer

- dMMR deficiency can be associated with some endometrial cancers. Approximately 20%-30% of endometrial cancers exhibit MSI, and as with colorectal cancers, the majority are the result of somatic MLH1 promoter methylation.[6]

3. Other Cancers and Tumors

- In a recent study testing many cancers outside of colorectal and endometrial cancers, less than half (46.1%) of the tumors tested were found to have almost 62% loss of co-expression of MLH1/PMS2, and close to 25% would have loss of co-expression of MSH2/MSH6.[3]

Prognostic Implications

- A lot of dMMR and MSI-H cancer cells look "foreign" to the immune system. This makes them easier for immune cells to find and some checkpoint inhibitor drugs are more likely to work, potentially making these cancers easier to treat as they will respond well to immunotherapy. In March 2023, a drug called pembrolizumab was fully approved by the U.S. Food and Drug Administration for any advanced cancer found anywhere in the body if the cancer is dMMR or MSI-H.[7]

Conclusion

The intricate relationship between Mismatch Repair (MMR) and Microsatellite Instability (MSI) underscores their role in the landscape of cancer. As shown in this whitepaper, MMR serves as a guardian of genomic integrity, while its deficiency, dMMR, precipitates MSI and a heightened risk of numerous colorectal, endometrial, and other cancers.

The clinical implications of MMR and MSI are profound. Their detection and characterization have transformed cancer diagnosis, prognosis, and treatment paradigms. From identifying hereditary cancer syndromes like Lynch syndrome to informing therapeutic strategies, particularly immunotherapy, MMR and MSI have emerged as indispensable biomarkers.

While this whitepaper provides a foundational overview, the field of MMR and MSI research likely demands continuous exploration. Delving deeper into specific cancer types, unraveling the molecular mechanisms underlying MMR dysfunction, and evaluating the efficacy of novel therapeutic interventions will be instrumental in advancing cancer care. By harnessing the power of MMR and MSI insights, we can predict a future where cancer is more effectively prevented, detected, and treated.

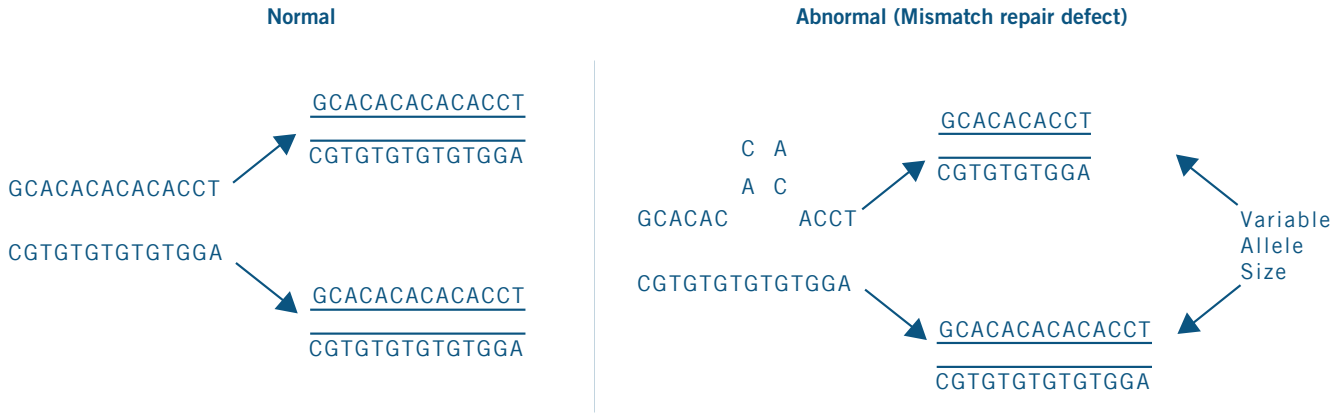

Figure 1: MSI testing is used to identify tumors caused by dMMR by comparing the number of nucleotide repeats in a panel of MSI markers in normal tissue with the number from tumor tissue from the same individual.

Microsatellite stability (MSS) is present if the same number of repeats is present in each marker in both the tumor and the normal tissue. Microsatellite instability (MSI) is present if the number of repeats in the tumor and the normal tissue differs.[8]

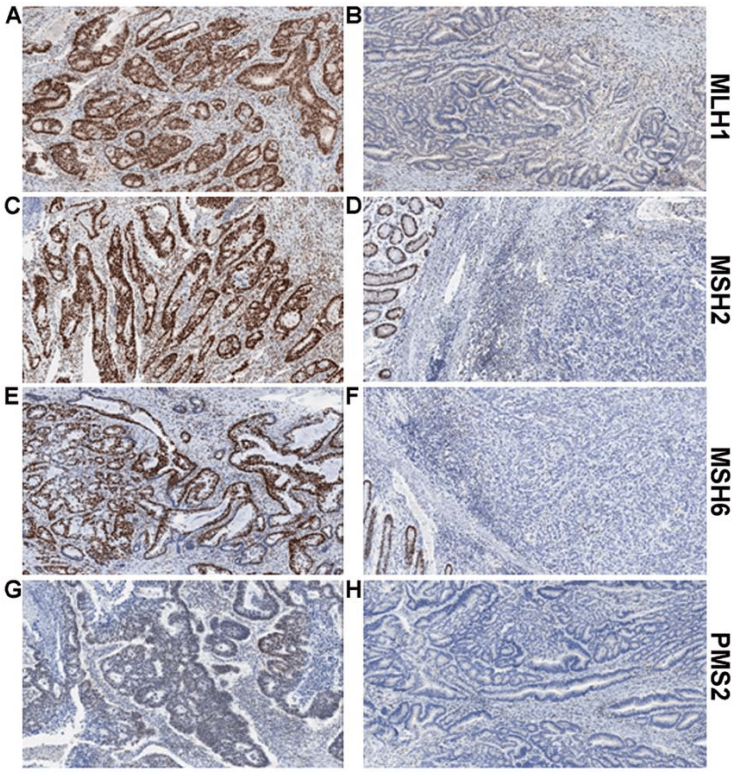

Figure 2: Examples of MLH1, MSH2, MSH6 and PMS2 immunohistochemistry. (A) Positive MLH1 staining and (B) absence of MLH1 staining in tumor epithelium yet showing the positive internal control staining of lymphocytes in the stroma. (C) Positive MSH2 staining and (D) absence of MSH2 staining in tumor epithelium yet showing positive staining in the adjacent normal colonic epithelium. (E) Positive MSH6 staining and (F) absence of MSH6 staining in tumor epithelium yet with positive staining in the adjacent normal colonic epithelium. (G) Positive PMS2 staining and (H) absence of PMS2 staining in tumor epithelium yet with positive internal control staining of lymphocytes in the stroma.[9]

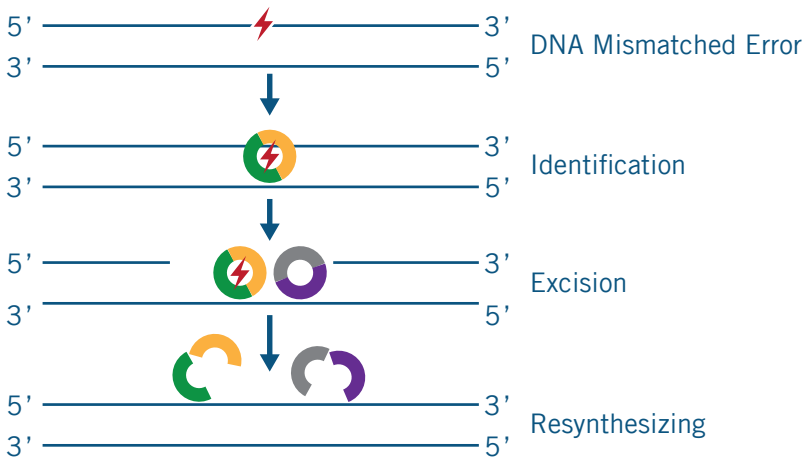

Figure 3: MSH2/MSH6 heterodimers handle binding to the initial DNA mismatched base errors, while MLH1/PMS2 heterodimers are in charge of the excision and synthesis of corrected DNA chains in the mismatch site[10]

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