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Review Article

Microsatellite Instability: Its Role in Carcinogenesis, and in Malignant Brain Neoplasms Development in Adults – A Contemporary Review

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Abstract

Microsatellite instability (MSI) is a critical molecular event in carcinogenesis and is associated with impaired maintenance of genetic stability. Microsatellites are short, repetitive DNA sequences, e.g., repeated 1-6 base pairs such as, -CACACA - During normal DNA replication, errors may occur in the mentioned regions. Under normal conditions, these errors are corrected by the DNA repair system, which is known as Mis-match Repair (MMR) System. When this system is impaired leads to errors accumulation, which in turn results in MSI. MSI leads to mutations in genes which are responsible for regulation of cell proliferation, DNA repair, and apoptosis (programmed cell death). The mentioned molecular events result in uncontrolled cell growth, accumulation of additional mutations, and eventually, cancer development. Crucial genes which are involved concern defects in MMR genes such as MLH1, MSH2, MSH6, and PMS2, which are frequently associated with Lynch syndrome. MSI is observed mainly in Colorectal Cancer (CRC), especially in proximal colon, Endometrial Cancer (EMC), and less frequently involve Gastric, Ovarian, Small intestine cancer, and certain Urothelial cancers. On the other hand, MSI is not one of the primary mechanisms in most primary malignant brain tumours. However, MSI may be observed in Glioblastomas (GBs), in rare cases, Paediatric tumours with MMR deficiency (dMMR), and tumours in patients with Lynch syndrome (rare CNS involvement), and Turcot syndrome. The presence of MSI has clinical significance as it has major therapeutic implications. To be more specific, MSI-high (MSI-H) tumours have a high mutational burden, and respond better to immunotherapy, eg., PD-1 inhibitors, such as pembrolizumab. The current study presents a contemporary review of modern knowledge regarding the molecular biology of MSI in the development of malignant tumours, and especially in malignant brain tumours in adults.

Key Words: microsatellite instability; brain neoplasms; DNA mismatch repair system; molecular biology; genetics

Introduction

Microsatellites are short, repetitive DNA sequences that are broadly distributed through-out the genome and are closely associated with many functionally significant genes [1]. Microsatellites, also referred to as simple sequence repeats (SSRs), are repeat units typically consist of one to six nucleotides [2]. Despite their abundance, microsatellites are not randomly distributed. In eukaryotic genomes, they are more frequently localized in non-coding regions than in coding ones, whereas microsatellites located within coding regions are particularly prone to generating frame-shift mutations, thereby contributing to genomic instability and carcinogenesis [3]. Moreover, microsatellites are believed to contribute to the organization and restructuring of chromosomal architecture, thereby influencing gene replication and expression [4], therefore are widely utilized as markers in the study of genetic diseases and as predictive biomarkers across multiple cancer types [5,6]. During DNA replication, microsatellites are particularly susceptible to insertion or deletion errors due to DNA polymerase slippage. Under normal conditions, these errors are associated with the Mismatch Repair (MMR) System [7].

The DNA MMR System plays a critical role in maintaining genomic integrity by identifying and correcting base-pair mismatches that arise during DNA replication, particularly within repetitive sequences such as microsatellites [8]. MMR-associated proteins include at least seven key components, hMLH1, hMLH3, hMSH2, hMSH3, hMSH6, hPMS1, and hPMS2. These proteins form specific heterodimeric complexes that recognize and repair mismatched bases, including small insertion-deletion loops involving one to four nucleotides generated during DNA replication [9]. The MMR pathway is a highly conserved intracellular mechanism involving coordinated interactions among multiple proteins to ensure replication constancy. During DNA replication, errors may occur as a result of recombination events or physical and chemical damage to DNA bases. Under normal conditions, the MMR system detects and corrects these errors. However, mutations or epigenetic alterations in MMR-related genes can impair their function, leading to reduced or absent production of MMR proteins. This deficiency compromises DNA repair capacity and ultimately results in the accumulation of replication errors, leads to variations in microsatellite repeat length giving rise to microsatellite instability (MSI) [10].

MSI is defined as a change in microsatellite length resulting from the insertion or deletion of repeat units, leading to the generation of novel alleles. MSI can arise through various mechanisms, including point mutations in MMR genes, DNA polymerase slippage during replication, and insertion/deletion events within microsatellite regions [11]. Additionally, MSI may result from other molecular aberrations, such as hypermethylation of the MLH1 promoter [12], epigenetic silencing of MSH2 or MLH1 [13,14], microRNA-mediated downregulation of MMR genes [15], or slipped strand mispairing (SSM) [16]. Based on the number of altered microsatellite loci, MSI is classified into three categories, high-level MSI (MSI-H), low-level MSI (MSI-L), and microsatellite stability (MSS) [17]. MSI has been further subclassified into type A (variation <6 bp) and type B (variation >8 bp), while another categorization proposed a classification based on fragment size changes into type I (increases) and type II (decreases) [18].

Extensive research has demonstrated that MSI plays a critical role in the development of malignant tumours and is strongly associated with their initiation, progression, and clinical outcomes. Evidence indicates that patients exhibiting MSI-H tend to show enhanced anti-tumour immune responses, greater suppression of tumour cell proliferation, and more favourable prognoses compared to patients with MSI-L or MSS profiles [10,19-21]. According to these criteria, MSI-H is defined by mutations in two or more loci, MSI-L by a mutation in a single locus, and MSS by the absence of detectable mutations [19]. Compared with MSS, MSI status serves as a valuable predictor for therapeutic decision-making, particularly in MSI-H and MSI-L tumours [22]. Historically, the absence of standardized criteria for MSI detection limited progress in this field. To address this the American National Cancer Institute (ANCI), in 1997, proposed a group of five microsatellite markers, BAT25, BAT26, D2S123, D5S346, and D17S250, as reference loci for MSI analysis. Among these, BAT25 and BAT26 were mononucleotide repeats, whereas D2S123, D5S346, and D17S250 were dinucleotide repeats [23]. MSI occurring within the coding regions of genes is referred to as coding MSI (cMSI). This form of instability can result in the inactivation of proteins essential for tumour suppression, as well as the generation of frame shift peptides (FSPs). These FSPs are theoretically novel and tumour-specific antigens, as they arise exclusively from clonal tumour cells and are therefore unrecognized by the host immune system [10].

At present, MSI has been widely identified across a variety of cancers and has emerged as a prominent focus of oncological research. MSI was first identified in CRC cases [24] and subsequently described in other types of cancers. MSI has been associated with the biological behaviour of Colorectal (CR) and gastric carcinoma (GC), lymphoma/leukemia (L/L), and endometrial carcinoma (EMC). The MSI phenotype is frequently associated with Lynch (LS) and Turcot Syndrome (TS), two inherited cancer predisposition syndromes caused by germline mutations in MMR genes [Table1]. LS is most commonly linked to CR and EM cancers but is also associated with malignancies of the ovary, stomach, hepatobiliary tract, upper urinary tract, pancreas, brain, and skin [25-28] [Table 2].

MSI is rare in most primary brain tumours, such as Glioblastoma (GBM) and Anaplastic Astrocytoma (AA), whereas the estimated frequency is less than 5% in gliomas overall [29-33]. However, associations exist in case of genetic syndromes, as MSI is most relevant in brain tumours associated with LS [Table 2]. In these cases, patients may develop high-grade gliomas, whereas tumours often show MMR deficiency and MSI-high status [34]. More recently, MSI has also been detected, even though at lower frequencies, in non-small cell lung cancer (NSCLC), breast cancer (BC), prostate cancer (PC), bladder cancer, and melanoma [35-39] [Table 2].

Furthermore, MSI has been established as an important indicator of treatment response, prognosis, and recurrence in CRC, GC, and other malignancies, highlighting its significance in elucidating the molecular mechanisms underlying carcinogenesis [22,40-42]. Accordingly, MSI represents a promising biomarker for assessing tumour malignancy, therapeutic effectiveness, and patient prognosis. Moreover, characterization of MSI patterns may provide clinicians with valuable insights to support the development of personalized and targeted treatment strategies [40]. The current study presents a contemporary review of modern knowledge regarding the molecular biology of MSI in

the development of malignant tumours, and especially in malignant brain tumours in adults.

Syndrome	Inheritance Mode	Gene/Locus
Lynch Syndrome (Hereditary Non-Polyposis Colorectal Cancer-HNPCC)	Autosomal Dominant	MSH2, 2p21, MLH1, 3p21-23 MSH6, 2p21 PMS2, 7p22 (MLH3, 14q24.3)
Turcot's Syndrome	Autosomal Dominant or Autosomal Recessive	MLH1, MSH2, MSH6, PMS2
Muir-Torre Syndrome (subset of Lynch Syndrome)	Autosomal Dominant	MLH1, MSH2

Table 1: Genes causing predisposition to Lunch Syndrome and related Variants

[Modified by Wael M. Abdel-Rahman (2008). Genomic Instability and Carcinogenesis: An Update. Current Genomics; 9: 535-541].

Diseases	MSI characteristics
Lynch Syndrome (LS)	Normal adenocarcinoma, Villous adenoma, Adenoma (over 1.0 cm), Dysplastic adenoma [11]
Colorectal Cancer (CRC)	MSI-H tumors (infiltrated with dense cytotoxic T-cells, on the right side) [11]
Breast Cancer (BRC)	BRCA1 mutation can cause MSI-MSI related loci D351766 and D252739 can identify MSI related BRC [11]
Gastric Cancer (GC)	High expression of CD8 positive T-cell molecular marker, PD-L1 gene and IFN γ gene in patients with MSI-H [11]
Prostate Cancer (PC)	MSI frequency less than1.0%, is closely related to pathogenic embryonic mutants carrying Lynch syndrome-related genes [11]
Bladder Cancer (BC)	hMSH2 mutation can increase the risk, MSI related loci D9563, D95156, and D95283 can be used to screen patients with high micro-BC [11]
Leukemia	MSI frequency less than 1.0%, most are Chronic Myeloid Leukemia [11]
Cholangiocarcinoma	MSI frequency less than 1.0%, most are young patients with A typical tissue morphology [11]
Ovarian Cancer (OC)	An increased number of CD8+, PD-1, and TILS in MSI OC patients [11]
Pancreatic Ductal Adeno-carcinoma (PDAC)	HMLH1 and hMSH2, are mainly inactivated [11]
Endometrial Cancer (EC)	UCEC patients with MSI has higher immune com-ponents, CD3+ and CD8+TILS [11]
Adrenocortical Cancer (ACC)	MSI-H/dMMR patients with ACC have high variation load, ACC is closely associated with the deletion mutations of hMSH2 [11]
Follicular Thyroid Cancer (FTC)	Advanced FTC associated with MMR inactivation [11[
Malignant Brain Tumor	2.0-3.0% MSI in primary tumors [73,74], Astrocytic and non-Astrocytic CNS tumors showed incidence 0.0-8.0% [29-32], LS-associated account for 0.5-3.7% [147]-25.0% are Glioblastomas [180]
Non-Small Cell Lung Cancer (NSCLC)	0.8-40.0% [131-133]
Malignant Melanoma	Frequency 2.0-30.0% [160,161]
Urothelial Carcinoma (UC)	Frequency 1.0-28.0% [163-165], LS-associated Upper Tract UC 5.0% [166]

Table 2: MSI-H/dMMR associated diseases (modified by Li K, et al. (2020). Microsatellite.

Instability: A review of what the oncologist should know. Cancer CellInt; 20: 16)

Mismatch Repair (MMR) System

DNA is continually subjected to stress from both exogenous and endogenous sources. Exogenous factors include environmental and chemical agents such as cigarette smoking, asbestos exposure, and ionizing radiation, while endogenous sources include Reactive Oxygen Species (ROS) and Nitrogen Species (NOS). In addition, DNA sequence variations are able to arise during normal physiological processes such as replication and repair due to the incorrect incorporation of nucleotides. These replication errors are intrinsic to the activity of DNA polymerases [43]. To preserve genomic integrity and prevent the accumulation of deleterious mutations, cells have evolved multiple DNA surveillance and repair mechanisms, among which the MMR system plays a critical role. The MMR system comprises a set of conserved genes encoding proteins that are highly preserved across mammals and humans. Its origin can be traced to studies in Escherichia Coli, where the MutS and MutL genes

were first identified as key components of MMR [44]. In humans, the homologous genes implicated in this pathway are referred to as MSH (MutS homologs) and MLH (MutL homologs). The MMR process involves several sequential steps, including lesion recognition, initiation of repair, excision of the damaged DNA segment, and re-synthesis of the correct DNA strand. The MMR system primarily corrects base-base mismatches as well as insertion-deletion loops that occur during DNA replication and recombination. Functional MMR proteins operate as heterodimers, and the system involves multiple gene products, MSH family members such as, hMSH2, hMSH3, and hMSH6 and MLH/PMS family members such as, hMLH1, hPMS1, hMLH3, and hPMS2 [45,46] [Table 3].

In eukaryotic cells, the MMR machinery is primarily organized into two major hetero-dimeric complexes. The first involves hMSH2, which pairs with either hMSH6 or hMSH3 to form the MutSα and MutSβ complexes, respectively. The hMSH2-hMSH6 (MutSα) complex is responsible for recognizing single-base mismatches and small insertion-deletion loops involving dinucleotide repeats, whereas the hMSH2-hMSH3 (MutSβ) complex detects larger insertion-deletion loops, typically up to 13 nucleotides [47]. The MutL homologs in humans belong to the GHKL (gyrase/Hsp90/histidine kinase/ MutL) protein family and function as ATP-dependent molecular complexes capable of forming ring-like structures around the DNA helix. Among these, hMLH1 serves as a central component that forms heterodimers with other partners, including postmeiotic segregation increased (PMS) proteins such as PMS1 and PMS2, as well as MLH3. These complexes are recruited following mismatch recognition by MutSα or MutSβ and play a critical role in co-ordinating downstream repair events [48].

The nature of MSI

Microsatellites, also known as short tandem repeats (STRs) or simple sequence repeats (SSRs), are composed of repetitive DNA sequences consisting of one-six nucleotide motifs [49]. Their distribution differs from that of small satellite DNA, which typically comprises longer tandem repeats of approximately 15-65 nucleotides and is primarily localized near chromosomal termini. In contrast, microsatellites are widely dispersed throughout the genome and are predominantly found in proximity to coding regions, although they may also occur within introns and other non-coding regions. Each micro-satellite locus generally consists of a central repetitive core flanked by peripheral sequences, with its variability largely determined by changes in the number of repeat units with-in the core region [4].

The formation of microsatellites is commonly attributed to DNA polymerase slippage during replication, or to mismatches between the newly synthesized strand and the template strand during DNA replication and repair. These processes can lead to the insertion or deletion of one or more repeat units. Under normal conditions, the DNA MMR system corrects replication errors and maintains genomic stability. However, deficiencies or functional impairments in MMR genes within tumour cells can compromise this repair mechanism, thereby increasing the possibility of genetic mutations [50].

Consequently, MSI is considered a significant factor in tumour initiation and progression. Based on the frequency of instability, MSI is classified into three categories, as already mentioned, MSI-H, MSI-L, and MSS [51], as already mentioned. In current clinical practice, MSI-L is often grouped together with MSS due to their similar biological and clinical characteristics. In CRC, MSI can be further classified according to its underlying molecular mechanisms into sporadic CRC and LS-associated CRC. Most MSI cases are sporadic and arise from epigenetic silencing of gene expression, particularly through hypermethylation of the hMLH1 promoter, rather than direct gene mutations. In contrast, LS is an autosomal dominant hereditary condition caused by germline mutations in MMR genes and is associated with an increased risk of CRC as well as tumours in other regions of the colon and rectum [52].

MSI and Molecular Epidemiology across Cancer Types

The MSI phenotype has been identified across a broad spectrum of malignancies. In a large-scale study analysing over 11,000 tissue samples spanning 39 cancer types, MSI was detected in 27 tumour types, with an overall prevalence of approximately 3.8% [53]. Cancers in which MSI has been reported include CR, G, EM, ovarian, hepatobiliary, urinary tract, brain cancers, and skin malignancies. Among these, the highest prevalence of MSI was observed in CRC (approximately 10.2%, range 6.6-14.5%) [54-59], EMC, particularly the endometrioid subtype, (21.9%, range 15.1-29.6%) [56,60,61], GC (8.5%, range 6.4-10.9%) [55,56,60,62,63], and small bowel cancer (14.3%, range 5.4-26.3%) [56]. In GC, MSI prevalence varies considerably among histological subtypes, ranging from 0.9% in mixed-type tumours and 2.9% in diffuse-type tumours to 10.7% in intestinal-type tumours [63,64]. In contrast, MSI occurs less frequently in other malignancies, with reported rates of approximately 2-10% in ovarian cancer [55,65,66] and only 1-2% in pancreatic cancer [55,67-69]. Estimates of MSI prevalence in urothelial carcinoma remain highly variable, ranging from 1% to as high as 46% across different studies [70-72]. MSI has also been described in cancers not typically associated with LS, including GBM, cervical cancer, melanoma, sarcoma, and small intestinal tumours. However, its occurrence in these malignancies is relatively rare [55,73,74].

MSI is a hallmark of LS-associated cancers, where it is present in nearly all cases. It is also observed in sporadic cancers, accounting for approximately 10-15% of cases [59]. Nevertheless, LS itself represents a minority of MSI-associated cancers, contributing to no more than 19% of cases. The highest proportion of LS-related MSI is observed in CRC, followed by EMC (5-10%), small bowel cancer (approximately12%), and GC (4-15%) [64,74-77]. Overall, the majority of MSI cases (approximately 80-95%) arise sporadically [78]. The predominant mechanism underlying sporadic MSI is the epigenetic inactivation of the MLH1 gene through promoter hypermethylation, often affecting both alleles and resulting in loss of MLH1 protein expression. This mechanism accounts for approximately 90% of sporadic MSI cases [54,78,79] [Table 2].

Molecular profiling of MSI tumours, regardless of their origin (LS-associated or sporadic), reveals a range of recurrent oncogenic alterations. Frequently observed mutations involve genes such as BRAF, NRAS, KRAS, APC, PIK3CA, and TP53. KRAS mutations are detected in approximately 30-37% of MSI tumours in EM, small bowel, and CR cancers, and in 15-28% of GCs [64,80-82]. Notably, in CRC, the prevalence of KRAS mutations is lower in MSI tumours compared to MSS tutors, where it may reach up to 46% [83]. Furthermore, MSS tutors harbouring KRAS mutations are generally associated with more aggressive tumour behaviour and poorer clinical outcomes [84]. BRAF mutations are frequently observed in MSI CRC, with reported rates of up to 45%, predominantly involving the p.V600E variant [85,86]. Notably, BRAF mutations exhibit a strong association with sporadic cases and are

rarely detected in hereditary CRCs [86-89]. In a meta-analysis [90] was demonstrated that the BRAF V600E mutation was present in only approximately 1.4% of patients with LS, underscoring its limited relevance in hereditary MSI-associated tutors. In sporadic CRCs characterized by the MSI phenotype, BRAF p.V600E mutations frequently co-occur with MLH1 promoter hyper-methylation. This association suggests a potential mechanistic link between BRAF activation and epigenetic silencing of MLH1, contributing to the development of MSI in these tutors [91,92].

However, the direct relationship between MLH1 promoter hyper-methylation and the BRAFp.V600E mutation has been questioned by evidence indicating that not all CRCs harbouring BRAFp.V600E exhibit MLH1 silencing or develop the MSI phenotype. A sub-set of these tutors remains MSS, suggesting that additional molecular or epigenetic factors modulate the emergence of MSI in BRAF-mutated cancers [93]. Indeed, only approximately 20-30% of metastatic CRCs carrying the BRAFp. V600E mutation demonstrate MSI [94]. Furthermore, progression to an MSI phenotype through MLH1 hypermethylation is observed in roughly 75% of BRAF-mutated sessile serrated adenomas, while the remaining lesions evolve into MSS tutors. In contrast, among traditional serrated adenomas, BRAF mutations are present in approximately two-thirds of cases. However, MLH1 silencing and MSI are infrequently observed in this subtype [95,96]. Notably, in other cancer types, a consistent association between BRAF p.V 600E mutations and MSI or MMR deficiency (dMMR) has not been established [60-62,97,98].

In comparison, TP53 mutations are significantly less frequent in MSI tutors than in MSS ones. In CR and GC cancers, TP53 mutations are detected in approximately 20-30% of MSI cases, whereas their prevalence in MSS tutors ranges from 50-65% [62,99]. A similar trend is observed in EM, pancreatic, and ovarian cancers, where TP53 mutations are generally common but are rarely identified in MSI-associated tutors [61,67,68,100]. This distribution pattern suggests that TP53 alterations are unlikely to play a critical role in the tumorigenesis of MSI-driven cancers. PIK3CA mutations are more frequently observed in CR and GC cancers with MSI (30-45%) compared with MSS tutors (10-25%). In EMC, however, PIK3CA mutation rates are comparable between MSI and MSS subtypes, comprising approximately 45-60% of cases [61].

MSI tutors are also characterized by recurrent alterations in genes such as PTEN, ATM, RNF43, BRCA2, and ARID1A, all of which demonstrate markedly increased mutation frequencies relative to MSS CRCs [101]. Notably, approximately 20% of MSI tutors harbour therapeutically actionable gene fusions involving ALK, NTRK1/2/3, or RET [101]. In contrast, HER2 amplification does not appear to be significantly associated with MSI status [102].

The interplay between MSI and other oncogenic alterations, as well as the temporal role of dMMR in LS-associated CR carcinogenesis, can be conceptualized within the following distinct models [103]. In the classical model, dMMR arises as a secondary event following adenoma initiation driven by somatic mutations in KRAS and APC genes [104, 105]. Adenomas in this pathway retain MMR proficiency and exhibit MSS status and are most frequently identified in carriers of germline PMS2 or MSH6 mutations [106]. Partial preservation of MMR function in MSH6-deficient tumors, likely due to compensatory activity of MSH3, may underlie the comparatively reduced cancer risk in these individuals [107]. This model is estimated to account for approximately 25% of cases [108,109]. In contrast, the second and third models are characterized by early biallelic inactivation of MMR genes, leading to dMMR as a driver event and consequent MSI in all tumours [104,108]. To be more specific, the second model, predominantly identified in MSH2 and MLH1 mutation carriers, involves frame-shift-mediated inactivation of tumour suppressor genes within the WNT signalling pathway, particularly RNF43 and TGFBR2 [101,109]. The third model, accounting for approximately 10% of LS-associated CRCs and restricted to MLH1 mutation carriers, is defined by concurrent alterations in TP53 and CTNNB1 [104].

MSI Mechanisms

Slipped Strand Mispairing

In addition to point mutations, MSI can also arise through slipped strand mispairing (SSM) [110]. During DNA replication and synthesis, misalignment may occur between the newly synthesized strand and the template strand within microsatellite repeat regions. This mispairing can result in transient strand dissociation or the formation of stable looped structures implicating several repeat units. The rate of microsatellite slippage mutations increases exponentially with the number of repeat units [16]. Specifically, microsatellites with shorter repeat tracts tend to undergo expansions more frequently, whereas those with longer repeat tracts are more prone to contraction events.

MMR System Deficiency (dMMR)

MSI phenotype and/or loss of MMR protein expression, also known as deficient MMR (dMMR) phenotype may have tumorigenic potential when occurring in coding regions of key genes involved in several cellular functions and pathways. The MMR system is responsible for correcting errors that arise during DNA replication. In the context of the SSM mechanism mentioned above, aberrant loop structures generated during replication can be recognized and repaired by nucleases and the MMR machinery, restoring the DNA sequence to its pre-replication state. However, in cases of dMMR, these replication errors cannot be properly corrected. As a result, nucleotide substitutions accumulate, and the length of microsatellite sequences becomes altered [10, 111].

MSI-H Cancers and the Role of MSI in Tumorigenesis

A subset of human cancers is characterized by inactivating alterations in MMR genes, resulting in a failure to detect and correct errors that arise during DNA replication. These alterations may be inherited, as observed in LS, or may occur sporadically in approximately 10-15% of CR, G, and EM cancers. Due to their repetitive structure, microsatellite sequences are particularly susceptible to mutations in tumour's with dMMR function. Consequently, thousands of microsatellite alterations accumulate in the mentioned cancers, which are classified as MSI-H tumours. MSI-H tumours exhibit distinct clinicopathological characteristics compared to MSS cancers, and the spectrum of genetic events driving their progression is thought to differ significantly [112]. Notably, many of the genetic alterations identified in MSI-H tumours involve nucleotide repeat tracts within genes that are believed to have oncogenic potential. These alterations are considered to play a critical role in MSI-H tumorigenesis, as they may result in either gene inactivation or activation and are subject to selection through recessive or dominant mechanisms [113].

Mutation Characteristics in MSI-H Patients

Studies have recorded that MSI-H tumours exhibit certain shared mutational features. For instance, germline mutations in MMR genes, as

well as in genes such as POLE (DNA polymerase epsilon) and POLD1 (DNA polymerase delta), are more frequently observed in MSI-H patients compared to those with MSS tumours. Additionally, MSI-H tumours have been reported to enhance oncogene translation by shortening 3′ untranslated regions (3′-UTRs), which may disrupt microRNA (miRNA)-mediated regulatory mechanisms [60]. This phenomenon may help explain findings from a previous report [114], which suggested that certain non-coding RNA molecules resembling pathogenic elements can stimulate immune responses and contribute to tumour progression. These non-coding RNAs, transcribed from satellite DNA, do not encode proteins. However, their regulatory functions are closely associated with tumour development [115].

Association between MSI and tumour mutation burden

Another critical aspect to consider is the association between MSI and tumour mutation burden (TMB). dMMR induces an hypermutator phenotype, resulting in an elevated TMB, which is thought to enhance tumour immunogenicity. While the concurrent presence of MSI and TMB is relatively rare in solid tumours, occurring in only about 3-7% of cases [55,116], this overlap is more pronounced in LS-associated tumours. The incidence of high TMB (TMB-H ≥ 10 mutations / megabase) among MSI tumours is assessed at approximately 80-100% in CRC cases [56,117,118], 83-93% in EMC [56,119-121], and nearly 100% in G and small bowel cancers [56,80,122]. In CRC cases, tumours exhibiting both high TMB and MSI/dMMR correspond to the CMS1 subtype [123]. This subtype is characterized by hypermutation, hypermethylation, BRAF V600E mutations, and robust immune cell infiltration within the tumour microenvironment [124]. In CMS1tumors, MLH1 gene promoter hypermethylation result in gene silencing, DNA mutations accumulation, and the neoantigens expression that contribute to the tumour's heightened immunogenicity [125]. The TMB levels in MSI tumours may also depend on specific MMR complex loss and tumour histology or its primary site [126,127].

In a recent report which assessed CRC, EMC, and other tumours was found that the loss of mutSα (MSH2/MSH6) typically resulted in a more pronounced TMB than the loss of mutLα (MLH1/PMS2). However, certain tumour histologies, through secondary DNA repair mechanisms, may mitigate the effects of dMMR, leading to a less pronounced TMB despite similar immunohistochemistry (IHC) [Table 3] protein loss patterns. The mentioned findings underscore the gene-and histology-specific heterogeneity of MSI/ dMMR tumours [116]. Importantly, patients with MSI tumours exhibiting a high TMB tend to have a more favourable prognosis and are also considered optimal candidates for check-point inhibitor therapy [125].

MLH1 protein	MSH2 protein	MSH6 protein	PMS2 protein	Interpretation	Inactivated genes
+	+	+	+	MSS	None
-	+	+	-	MSI	MLH1
+	-	-	+	MSI	MSH2
+	+	-	+	MSI	MSH6
+	+	+	-	MSI	PMS2

Table 3: Immunohistochemical patterns of MSI.

(MSI: Microsatellite instability, MSS: Microsatellite Stability).

(Modified by Buecher B, et al. (2013). Role of microsatellite instability in the management of Colorectal cancers. Digest Liv Dis; 45: 441-449).

Mutational Characteristics Across Different Cancers

Analyses based on The Cancer Genome Atlas (TCGA) data indicated that MSI-H tumours shared common mutated loci while also exhibiting tumour-specific mutation standards [128]. For example, genes associated with transmembrane signaling/TGF-β pathways, cellular stress responses/DNA damage, and chromosome/M-phase regulation are frequently enriched among recurrent MSI-related mutations. Frame-shift mutations in TGFBR2 are more commonly observed in colon and gastric adenocarcinoma than in uterine corpus EMC, suggesting that the tumour microenvironment may influence the occurrence of MSI [60].

Furthermore, another study [129] demonstrated that the Promega MSI analysis system, which utilizes a group of five quasi-monomorphic markers (NR-21, BAT-25, MONO-27, NR-24, and BAT-26), can accurately detect MSI-H CRC without the need for matched normal DNA. Another similar report [130] further suggested that MSI tends to occur preferentially within functionally relevant genomic regions. To be more specific, in gastric adenocarcinoma, MSI is frequently associated with genes implicated in ion binding. In addition, tumour suppressor genes such as ACVR2A and RNF were among the most commonly and significantly mutated targets in MSI-H tumors, highlighting their relevance in MSI-driven tumorigenesis [11].

MSI in Other Malignancies

MSI has been identified across a range of malignancies, including non-small cell lung cancer (NSCLC), melanoma, breast cancer (BC), urothelial carcinoma (UC), thyroid cancer (TC), prostate cancer (PC), adrenocortical carcinoma (ACC), cholangiocarcinoma (CC), leukaemia, ovarian cancer (OC), pancreatic ductal adenocarcinoma (PDAC), and primary brain tumours. The expansion of MSI-focused clinical trials to these tumour types may further clarify the prognostic and predictive value of MSI beyond CRC. The reported frequency of MSI in NSCLC cases is highly variable, ranging from 0.8% to 40% [131-133], and its clinical significance in this setting remains incompletely defined. Another study [134] showed that MSI may be associated with poorer prognosis in NSCLC. Conversely, more recent studies indicate that MSI-positive NSCLC may exhibit improved responses to immunotherapy [135], while other clinical trials have demonstrated the efficacy of pembrolizumab in previously treated NSCLC patients harbouring MSI [136,137] [Table 2].

In BC, MSI is relatively rare, with reported frequencies ranging from 0.04% to 3% [138, 139]. However, higher rates have been observed in triple-negative BC (TNBC), where MSI prevalence has been reported to range from approximately 0.2% to 18.6% [140-142]. The clinical and biological significance of MSI in BC remains uncertain. While some studies have reported no significant impact of MSI on overall survival [131], others have suggested a favourable prognostic association, particularly in TNBC [140]. MSI has also been associated with negative expression of estragon and progesterone receptors, suggesting a potential link between microsatellite alterations and hormonal deregulation in BC progression [143]. Additionally, MSI has been associated with advanced clinical stage, larger tumour size, and higher tumour grade [144]. The KEYNOTE-028 and KEYNOTE-012 trials demonstrated the clinical activity of pembrolizumab in BC patients previously treated with CDK4/6 inhibitors [138,145] [Table 2].

PDAC exhibits MSI in approximately 1-2% of cases [146,147], with a subset of MSI-positive tumours associated with LS [148]. LS-associated pancreatic cancers, accounting for approximately 0.5-3.9% of cases, are often characterized by medullary histology and prominent lymphocytic infiltration [147]. Given the aggressive nature of PDAC and its general resistance to chemotherapy, immunotherapy represents a potential therapeutic avenue [149]. Prior studies have shown that patients with proficient (pMMR) PDAC treated with conventional chemotherapy have improved survival compared to those with dMMR tumours, suggesting that MSI status may serve as a predictor of therapeutic response [150-152]. In the KEYNOTE-016 trial, pembrolizumab demonstrated promising activity in MSI-positive PDAC, with complete responses observed in two patients and partial responses in three out of eight cases [73,153]. These findings provide preliminary evidence supporting the potential efficacy of immune checkpoint blockade in MSI-associated PDAC.

MSI has been reported in approximately 10-15% of thyroid cancers (TC) [154-156], and its presence has been associated with specific clinicopathological features. In particular, MSI-positive TCs are more frequently observed in papillary and anaplastic histological subtypes, as well as in poorly differentiated tumours. A recent study suggested that patients with MSI-positive TC may exhibit a more favourable prognosis compared to those with MSS disease [156]. A similar report showed that MSI-H can be detected in TC cases, especially in patients with follicular thyroid cancer (FTC), with a prolonged survival time [157]. It is also considered to be associated with delayed MMR inactivation in advanced TC cases. Although several clinical trials are currently evaluating the efficacy of pembrolizumab, nivolumab, and atezolizumab in MSI-positive TC, no immunotherapy has yet been formally approved for this indication [158,159]. Immune checkpoint inhibitors targeting the PD-1/PD-L1 axis may represent a potential therapeutic option in this context. However, further clinical investigation is required [156] [Table 2].

MSI has also been described in malignant melanoma, with reported frequencies ranging from 2% to 30% [160,161]. Kubeček et al. proposed that MSI may serve as a predictive biomarker in malignant melanoma [162]. Although the KEYNOTE-016 study demonstrated the efficacy of pembrolizumab in MSI-positive melanoma patients who had progressed following prior therapies, MSI-directed immunotherapy is not yet incorporated into routine clinical practice for melanoma [73] [Table 2].

In urothelial carcinoma (UC), MSI has been identified in approximately 1-28% of cases [163-165]. Upper tract UCs (UTUCs) occur in approximately 5% of patients with LS [166]. Loss of the MSH2/MSH6 heterodimer is frequently observed in UTUC, occurring in approximately 50-86% of cases [163,167]. Several studies have reported that MSI-positive UTUCs exhibit distinct morphological features compared to MSS counterparts, including increased intratumoral lymphocytic infiltration, reduced nuclear pleomorphism, and a pushing tumour border [147,168] [Table 2].

In prostate cancer (PC), MSI has been reported in approximately 1.2-12% of cases, and MSI-positive prostate tumours are generally associated with a more aggressive clinical phenotype [169]. Germline mutations in MMR genes are less frequently observed in localized PC, suggesting that MMR alterations may be more common in metastatic disease [170]. The KEYNOTE-016 study demonstrated improved responses to immune checkpoint inhibitors in MSI-positive PC [73]. Although MSI represents a potentially actionable biomarker in PC, immune checkpoint inhibitors are not yet routinely used in the treatment of metastatic disease [171] [Table 2]. Several studies have suggested an association between ACC and MSI. A recent article demonstrated that the occurrence of MSI in ACC is linked to deletion mutations in MSH2 [172]. Additionally, another study reported that MSI-H or dMMR ACC tumours exhibit a high mutational burden [53]. However, there is currently no substantial evidence in the literature regarding the impact of MSI status on the prognosis of ACC [Table 2].

Goeppert et al. [173] identified MSI-H in a small subset of CC cases, particularly in cases not associated with liver fluke infection. MSI-related CC can be detected through analysis of microsatellite loci such as BAT25, BAT26, and CAT25 [173]. Their findings further indicated that MSI-H cases were more frequently observed in younger patients and were associated with atypical histopathological features. Moreover, MSI-H/dMMR CC cases may demonstrate favourable responses to anti–PD-1/PD-L1 immunotherapy [Table 2].

Walker et al. [174] reported that MSI was not detectable in patients with acute myeloid leukaemia (AML). In contrast, Patel et al. [175] identified the presence of MSI in chronic myeloid leukaemia (CML), while no MSI was observed in healthy individuals, suggesting a potential association between MSI and CML pathogenesis. Their study also demonstrated that analysis of microsatellite loci D17S261 and D3S643 may aid in identifying MSI-positive cases of chronic leukaemia. Furthermore, MSI-H/dMMR status in CML cases may be associated with improved outcomes following anti–PD-1/PD-L1 immunotherapy.

A study by Howitt et al. [176] demonstrated that tumours with MSI exhibit increased infiltration of $CD8^+$ T cells, PD-1-positive cells, and tumour-infiltrating lymphocytes (TILs). Compared with MSS tumours, patients with clear cell OC characterized by MSI were more likely to benefit from immunotherapy. Furthermore, MSI testing, along with the evaluation of MMR proteins such as hMSH2 and hMSH6, can be utilized to identify MSI-associated OCs [177] [Table 2].

MSI in Brain Malignancies

MSI gliomas appear to occur in a small subset of dMMR extracolonic malignancies. Notably, MSI gliomas may arise in a subset of patients with the rare hereditary condition TS. In a proportion of these patients, germline mutations in MMR genes predispose affected individuals to the concurrent development of MSI-positive CRCs and GBMs [178,179]. The prevalence of MSI in primary brain tumours is relatively low, estimated at approximately 2-3% of cases [73,74]. Brain tumours are only rarely associated with LS, accounting for approximately 0.5-3.7% of cases, and limited data are available regarding the molecular and phenotypic characteristics of LS-associated brain tumours [147]. The MSI phenotype has been reported in approximately 25% of GBM [180] [Table 2]. Notably, MSI-positive GBM is characterized by low PD-L expression, suggesting that PD-L1 may not serve as a reliable predictive biomarker for response to immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway in this tumour type [181].

The MSI phenotype has also been identified in sporadic gliomas in both paediatric and adult populations, although reported frequencies vary considerably. A review of the current literature indicates that, in adult astrocytic and non-astrocytic CNS tumours, MSI was an uncommon event, with an incidence ranging from 0% to 8% [29-32] [Table 2]. However, a higher frequency of MSI has been reported in specific subsets of CNS tumours, particularly WHO grade III and grade IV paediatric astrocytoma's and gangliogliomas [29,30,182].

Conclusions

Tumour development is a multistep process involving a substantial number of genetic alterations, influenced by both host genetic background and environmental factors. A thorough understanding of these interactions holds significant clinical importance for elucidating tumorigenesis, disease progression, prognosis, and response to chemotherapy. The MMR system is a fundamental DNA repair mechanism responsible for maintaining genomic fidelity and stability. Its inactivation, whether due to germline, somatic, or epigenetic alterations, impairs error correction and promotes the development of MSI. MSI has been identified in multiple cancer types, where it serves both prognostic and predictive roles, particularly in relation to immunotherapy response. MSI is observed across a broad spectrum of cancers, including those associated with Lynch syndrome, such as colorectal, endometrial, small

intestinal, and gastric cancers, as well as sporadic tumours, albeit at lower frequencies, such as malignant brain tumours, leukaemias, etc. In this context, the investigation of MSI and frame-shift peptides (FSPs) provides valuable tools for the early molecular screening of high-risk patients and the optimization of therapeutic and personalized target strategies.

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