Review

Epigenetic mechanisms in the pathogenesis of Lynch syndrome


Inherited defects in the DNA mismatch repair (MMR) system, *MLH1*, *MSH2*, *MSH6*, and *PMS2* genes, underlie Lynch syndrome, one of the most prevalent cancer syndromes in man. The syndrome offers a model for cancers arising through MMR defects and microsatellite instability, which applies to ~15% of all colorectal, endometrial, and other cancers. Lynch syndrome also illustrates the significance of the epigenetic component in cancer development. Inactivation of tumor suppressor genes by epigenetic mechanisms is an acquired property of many tumors developing in Lynch syndrome. Furthermore, constitutional epimutations of MMR genes may explain a proportion of mutation-negative families lacking MLH1 or MSH2 protein expression in tumor tissue. This review provides an update of the molecular basis of Lynch syndrome by focusing on the role of epigenetic mechanisms in the pathogenesis of the disease.

Conflict of interest
Nothing to report.

Introduction to Lynch syndrome

Lynch syndrome (MIM No. 120435–6) is characterized by an autosomal dominant predisposition to colorectal carcinoma, endometrial carcinoma, and other cancers due to defective DNA mismatch repair (MMR). Clinically, the stringent Amsterdam criteria (1, 2), which require three or more family members diagnosed with a Lynch syndrome-associated cancer at an early age (below 50 years for one), and the less stringent Bethesda criteria (3) have been used to identify families with Lynch syndrome. Currently, the term Lynch syndrome is restricted to families with an identified pathogenic germline mutation in one of the DNA MMR genes.

The genetic definition of Lynch syndrome covers the Muir–Torre syndrome (MIM No. 158320), which shows an association of sebaceous gland tumors with Lynch syndrome-type internal malignancy (4). The predisposing mutation is present in a heterozygous state in constitutional tissues from Lynch syndrome mutation carriers, compatible with autosomal dominant inheritance. Rare individuals who inherit defective alleles from both parents in a recessive manner resulting in homozygosity or compound heterozygosity for predisposing mutation have a severe clinical presentation with childhood cancers (hematological malignancies and brain tumors) and early-onset colorectal cancer. This condition is referred to as constitutional MMR deficiency syndrome (CMMR-D, MIM No. 276300) to make a distinction from the conventional Lynch syndrome (5). Germline mutations in MMR genes may also be responsible for Turcot syndrome, in which primary brain tumors, usually glioblastomas, coexist with multiple colorectal adenomas (6). According to the predisposing gene and mode of inheritance, Turcot syndrome can represent Lynch syndrome or CMMR-D syndrome in MMR gene-associated cases and familial adenomatous polyposis (MIM No. 175100) in *APC*-associated cases.

Lynch syndrome is one of the most prevalent hereditary cancer syndromes in man. It accounts for 1–3% of unselected colorectal or endometrial carcinomas and up to 15% of those with microsatellite instability (MSI) or absent MMR protein (7–9). Extrapolating data derived from cancer patients have led to an estimate of 1:370 for the population incidence of Lynch syndrome (10).
Peltonäki

The history of Lynch syndrome can be divided into three main eras. Following the description of the first family with Lynch syndrome in 1913 (11), the syndrome was defined on the basis of clinical and family features for 80 years until the first susceptibility locus was identified (12). This started a genetic era leading to the discovery of some 3000 unique Lynch syndrome-associated mutations and variants to date (13). Finally, increased appreciation of epigenetic mechanisms in tumorigenesis during the last two decades and the identification of constitutional epimutation behind Lynch syndrome (14) have laid the foundation for an epigenetic era. Epigenetic mechanisms comprise DNA methylation, histone modifications, non-coding RNAs (including microRNAs), and chromatin remodeling (15, 16), which can underlie heritable alterations in gene expression in the absence of any changes in DNA sequence. Since the clinical and genetic characteristics of Lynch syndrome have been summarized in this journal recently (17), the present review focuses on epigenetic aspects.

Lynch syndrome genes

The protein products of Lynch syndrome genes play a key role in the correction of mismatches arising in DNA replication (18). Two different MutS-related heterodimeric complexes are responsible for mismatch recognition: MSH2-MSH3 and MSH2-MSH6 (Table 1). MSH2 in the complex is mandatory, whereas MSH3 can replace MSH6 in the correction of insertion–deletion mismatches, but not single-base mispairs. Mismatch binding is followed by the assembly and addition of a heterodimeric complex of MutL-related proteins, MLH1-PMS2, and possibly another alternative complex formed by MLH1-MLH3. This larger complex carries out MMR together with several other proteins.

Among nine human MMR genes, four, MLH1, MSH2, MSH6, and PMS2, are unequivocally linked to predisposition to Lynch syndrome (Table 1). Their approximate shares among all 3000 unique sequence variants of MMR genes deposited to the International Society for Gastrointestinal Hereditary Tumors (InSiGHT) database are 40%, 30%, 20%, and 10%, respectively (13; www.insight-group.org). Point mutations are the main types of mutation for all four MMR genes in most populations, and large rearrangements are not uncommon. Although most MSH2 and MLH1 mutations are truncating, up to one third are of the missense type and often require functional tests for the assessment of pathogenicity (19). A five-tiered system to classify MMR gene variants for pathogenicity has recently been incorporated in the InSiGHT database to assist clinicians in providing health care to their patients (13).

The observed functional redundancy among DNA MMR proteins may help explain why mutations in MSH2 and MLH1 predominate in Lynch syndrome families. Additional functions of MMR proteins may offer another possible explanation. Besides correcting replication errors, MMR proteins recognize lesions caused by exogenous mutagens and play an important role in DNA damage signaling (18). MSH2 and MLH1 are necessary for signaling damage-induced apoptosis and their inactivation would confer selective advantage on the cells in addition to hypermutability (20).

Features of Lynch syndrome that draw attention to epigenetic mechanisms

DNA MMR genes comply with Knudson’s two-hit hypothesis (21) in that both gene copies need to be inactivated for a phenotype. In hereditary cancer, one mutation, the first hit, in a tumor suppressor gene is inherited and the second hit occurs in (and is restricted to) the somatic cancer progenitor cell in a target tissue. In sporadic cancer, two inactivating hits, one in each allele, occur somatically prior to tumor initiation. The accumulating evidence suggests that either hit or both can be genetic or epigenetic. In Lynch syndrome-associated cancer, the two hits are usually genetic and consist of a point mutation or a large rearrangement for the first hit (see above) and loss of the wild-type allele (22) or gene conversion (23) for the second hit (Fig. 1). Recent observations of constitutional epimutations as the first hit (see below) and promoter methylation as the

<table>
<thead>
<tr>
<th>Escherichia coli</th>
<th>Saccharomyces cerevisiae</th>
<th>Share of all Lynch syndrome-associated mutations</th>
<th>Phenotype resulting from germline mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>MutS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Msh2</td>
<td>MSH2</td>
<td>30%</td>
<td>Typical Lynch syndrome, Muir–Torre syndrome</td>
</tr>
<tr>
<td>Msh6</td>
<td>MSH6</td>
<td>20%</td>
<td>Atypical or typical Lynch syndrome</td>
</tr>
<tr>
<td>Msh3</td>
<td>MSH3</td>
<td>0%</td>
<td>(No Lynch syndrome-associated mutations)</td>
</tr>
<tr>
<td>Msh1</td>
<td>Not identified</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Msh4</td>
<td>MSH4</td>
<td>0%</td>
<td>(No Lynch syndrome-associated mutations)</td>
</tr>
<tr>
<td>Msh5</td>
<td>MSH5</td>
<td>0%</td>
<td>(No Lynch syndrome-associated mutations)</td>
</tr>
<tr>
<td>MutL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mlh1</td>
<td>MLH1</td>
<td>40%</td>
<td>Typical Lynch syndrome</td>
</tr>
<tr>
<td>Pms1</td>
<td>PMS2</td>
<td>10%</td>
<td>Lynch syndrome with reduced penetrance, Turcot syndrome</td>
</tr>
<tr>
<td>Mlh2</td>
<td>PMS1</td>
<td>0%</td>
<td>(No Lynch syndrome-associated mutations)</td>
</tr>
<tr>
<td>Mlh3</td>
<td>MLH3</td>
<td>&lt; 2%</td>
<td>Atypical Lynch syndrome</td>
</tr>
</tbody>
</table>

N/A, not applicable.
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Fig. 1. (a) Molecular mechanisms of the first hit in Lynch syndrome-associated cancer compared to sporadic MSI colorectal cancer. The thickness of the arrows depicts the relative significance of the different mechanisms. M denotes the maternal and P the paternal chromosome (in this case, chromosome 3), and 1 and 2 indicate the two alleles of a predisposing gene (MLH1). A mutant locus is indicated by a filled circle and a normal unaffected locus by an open circle. The maternal chromosome was arbitrarily chosen as the target of the first hit in this diagram. (b) The corresponding mechanisms of the second hit (the first hit is marked with a black circle irrespective of the mutation type). No arrow points to mitotic non-disjunction, since this mechanism is typically associated with chromosomal instability and is rare in MSI cancers.

second hit (22, 24) in Lynch syndrome emphasize the increasing significance of epigenetic events, especially as methylation as the second hit is associated with a more generalized CpG island methylator phenotype (CIMP) in the tumors (22, 24). In sporadic colorectal cancer, epigenetic inactivation of MLH1 is much more common than mutational inactivation (25). Biallelic MLH1 inactivation by promoter methylation (Fig. 1) defines the subset of ~15% of sporadic colorectal cancers with MSI, which coincides with CIMP (26).

While tumor suppressor genes are typically recessive on cellular level, an increasing number exhibits haploinsufficiency with a single allele sufficient to initiate tumorigenesis (27). In Lynch syndrome, the dosage of MMR gene and protein clearly affects the clinical phenotype (constitutional heterozygosity for predisposing mutation is associated with Lynch syndrome whereas homozygosity gives rise to CMMR-D) and cellular phenotype (DNA damage signaling requires higher dosage of MMR protein compared to DNA MMR (28)).
Epigenetic mechanisms that regulate gene expression according to the prevailing cellular requirements are excellent candidates for factors capable of inducing subtle shifts in the dosage of gene product, thereby preventing or promoting tumor development. This is highly relevant to MMR genes and particularly MLH1, which is prone to frequent epigenetic inactivation.

In Lynch syndrome, genotype and phenotype are often poorly correlated leaving room for epigenetic determinants for phenotype. Apparent selectivity in tumor spectrum despite the fact that all tissues equally carry the predisposing mutation is a related but unsolved question. MMR gene mutation carriers have an elevated lifetime risk of colorectal carcinoma (10–53%), endometrial carcinoma (15–44%), and certain other cancers (below 15%). The predisposing gene and sex have turned out to be important factors of cancer risk (29–32). However, phenotype differences even in carriers of the same predisposing mutation (33) suggest the contribution of additional phenotype determinants. A number of common low-penetrance gene variants have been identified as possible modifiers of cancer risk in Lynch syndrome, including variants that are part of the epigenetic system (34). Environmental (35) and lifestyle factors (36) have been implicated in Lynch syndrome and provide an opportunity for the epigenetic system to serve as a link between genotype and environment as suggested (37).

Finally, epigenetic mechanisms need to be considered in clinical Lynch syndrome families that remain mutation negative after comprehensive strategies for mutation detection. While constant methodological developments (such as the adoption of targeted capture and next-generation sequencing (38)) are expected to reduce the fraction of mutation-negative Lynch syndrome families attributable to technical shortcomings, certain subsets of Lynch syndrome may still go undetected. Genetic mutations in MMR genes are identified in up to 88% of all classical Lynch syndrome families meeting the Amsterdam criteria and showing MSI in tumors (39) as opposed to less than 30% of kindreds not meeting the Amsterdam criteria (40, 41). Methodological approaches used for genetic mutations are not directly applicable to epimutations, which require special techniques for detection (42, 43). Epigenetic changes tend to be erased upon passage through the germline and result in non-Mendelian inheritance (see below). Hence, constitutional epimutations may have an important role to play in mutation-negative non-Amsterdam families in particular. Constitutional epimutations and the changing Lynch syndrome tumor spectrum will be discussed in more detail below as two specific examples of epigenetic mechanisms in the pathogenesis of Lynch syndrome.

**Constitutional epimutations in predisposition to Lynch syndrome**

Constitutional epimutation refers to constitutional hypermethylation at the promoter of one allele of a given (non-imprinted) gene leading to silencing of expression from that allele in all main somatic tissues. Epimutation is regarded secondary if induced by an adjacent genetic alteration and otherwise primary (44). Lynch syndrome offered one of the first examples of cancer-associated constitutional epimutations, namely primary epimutation of MLH1 (14, 45). Later, a number of cases of secondary epimutation of MLH1 have been reported as well, in association with a genomic deletion affecting the 5’ portion of MLH1 (46), a single nucleotide variant in the promoter area (47), and a large duplication encompassing MLH1 and flanking regions (48) (Table 2). To date, more than 50 index cases with primary (the most common type) or secondary constitutional epimutation of MLH1 are known with molecular and clinical characteristics summarized in a recent comprehensive review (49). In constitutional tissues of MLH1 epimutation carriers, the MLH1 promoter of the affected allele is often fully methylated resulting in complete silencing of expression from that allele in lymphoblastoid and other cells (46, 50). Mosaic methylation in blood accompanied by partial silencing can also occur (51). Tumors from MLH1 epimutation carriers show evidence of Knudson’s two-hit mechanism with epimutation as the first hit and loss of heterozygosity as a frequent second hit (46, 50).

The first case of MSH2 epimutation was reported in 2006 (52). It turned out to be a secondary epimutation caused by a deletion of the 3’ end of the EPCAM gene (53) (Table 2). Transcription of EPCAM lacking stop codon reads into the adjacent, structurally normal MSH2 gene inducing hypermethylation of its promoter. To date, several dozens of deletions of the 3’ end of EPCAM that differ in size and location have been described and are summarized in two recent reviews (54, 55). MSH2 promoter is methylated in tissues expressing EPCAM (mainly epithelial cells), but not in non-expressing normal tissues, causing somatic mosaicism (53). Since EPCAM is not highly expressed in blood, MSH2 promoter methylation may go undetected if determined from blood DNA alone. Tumors from carriers of EPCAM deletions, too, comply with Knudson’s two-hit mechanism. The constitutional EPCAM deletion inactivating one MSH2 allele represents the first hit, while the somatic hit inactivating the wild-type allele may be loss of heterozygosity of the EPCAM-MSH2 region (53), gene conversion of EPCAM (56), point mutation of MSH2 (53), and possibly MSH2 methylation (24). No MSH2 epimutations without EPCAM deletions have been reported.

Primary and secondary epimutations differ relative to their inheritance patterns in families. Primary epimutation of MLH1 shows non-Mendelian inheritance with patterns varying from apparent heritability to the reversion of the methylated allele to the normal active state (51, 57). In contrast, secondary epimutation of MLH1 (47, 58) and MSH2 (53) show classical Mendelian inheritance in pedigrees as dictated by the primary genetic defect. Nevertheless, secondary epimutation of MLH1 has been found to be subject to complete but transient reversion in the germline, being
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Table 2. Constitutional epimutations observed in Lynch syndrome

<table>
<thead>
<tr>
<th>Type of epimutation</th>
<th>MLH1</th>
<th>MSH2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene defect associated with secondary epimutation</td>
<td>Genomic deletion of MLH1 exons 1–2 (46)</td>
<td>Deletion of EPCAM removing stop codon (53, 55)</td>
</tr>
<tr>
<td>Tumor phenotype</td>
<td>MSI</td>
<td>MSI</td>
</tr>
<tr>
<td>Diagnosis of epimutation</td>
<td>Constitutional methylation at MLH1 promoter</td>
<td>Detection of constitutional EPCAM deletion combined with methylation at MSH2 promoter</td>
</tr>
<tr>
<td>Clinical phenotype</td>
<td>Age at onset and tumor spectrum typical of Lynch syndrome</td>
<td>Age at onset and tumor spectrum typical of Lynch syndrome (endometrial cancer risk depends on location of deletion)</td>
</tr>
<tr>
<td>Family features</td>
<td>Variable, from apparent sporadic cases (primary epimutation) to fulfillment of Amsterdam criteria (secondary epimutation)</td>
<td>Classical Lynch syndrome</td>
</tr>
<tr>
<td>Inheritance pattern</td>
<td>Variable, from apparent lack of heritability (primary epimutation) to autosomal dominant inheritance (secondary epimutation)</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Share of epimutations among mutation-negative families with MMR-deficient tumors</td>
<td>2–13% (shows population-specific variation)</td>
<td>0–40% (shows population-specific variation)</td>
</tr>
</tbody>
</table>

Constitutional epimutations of MLH1 and MSH2 give rise to typical Lynch syndrome phenotypes, including early age at onset (around 45 years) and elevated risk of colon and extracolonic cancers (49, 55; Table 2). In carriers of EPCAM deletion, colorectal cancer risk is comparable to that of MSH2 mutation carriers, whereas endometrial cancer risk is elevated in mainly those with deletions extending close to the MSH2 promoter. The differential cancer risk possibly reflects higher EPCAM expression (and consequently higher MSH2 methylation) in colon vs endometrial cells (59).

The prevalence of constitutional epimutations varies between populations and depends on the method of ascertainment of the cases and families. Constitutional epimutations of MLH1 have been reported to occur with frequencies ranging from ~2% (60) to 13% (51) in Lynch syndrome-suspected patients with absent MLH1 protein in tumor tissue and no germline mutations. The corresponding frequencies for EPCAM deletion-induced MSH2 epimutations (calculated for families/cases with extinct MSH2 expression and no germline mutations in MSH2) may vary between 0% (46) and 9% (61) and can rise to 40% in association with a founder effect (53).

The changing tumor spectrum of Lynch syndrome

The original Amsterdam I criteria for Lynch syndrome were based on colorectal cancer alone (1), whereas the Amsterdam II criteria additionally took extracolonic cancers into account (2). The inclusion of cancers of the endometrium, ureter, renal pelvis, and small bowel in the spectrum of Lynch syndrome tumors was based on available information, suggesting that these cancers had the highest relative risks among all cancers observed in Lynch syndrome (2). The Lynch syndrome tumor spectrum has markedly changed over time. For example, the incidence of stomach cancer has declined and that of colorectal cancer reciprocally increased in more recent generations of the progenitor Family G (62), reflecting temporal trends in the general population (63). The tumor spectrum may also vary depending on geographic location. Accordingly, Korean families show a higher incidence of stomach and pancreas cancer and a lower incidence of endometrial cancer compared to Dutch families (35). The exceptionally high frequency of breast cancer in clinically defined Lynch syndrome families from Brazil (64) compared to most other populations provides another illustrative example. These observations imply that the Lynch syndrome tumor spectrum is sensitive to environmental influences, whose effects in turn may be mediated by the epigenetic system as discussed above.

Molecular methods have become part of routine diagnostics of Lynch syndrome after the Amsterdam criteria were formulated, contributing to the definition of the Lynch syndrome tumor spectrum in two essential ways. First, it has become possible to distinguish (and exclude) those affected members (phenocopies) who do not carry the predisposing mutation of their families, which is important given that many cancers occurring in Lynch syndrome are also common in the general population. Second, molecular profiling has provided
new insights into the genetic and epigenetic events critical in the pathogenesis of the different Lynch syndrome-associated cancers.

MSI and/or absent MMR protein in tumor tissue are hallmarks of Lynch syndrome and widely used for pre-screening for the syndrome (10). MMR genes are ubiquitously expressed, but several mechanisms can contribute to tissue specificity for MMR-deficient carcinogenesis. These include the dosage of the MMR gene product, tissue-specific target genes, MMR-deficient carcinogenesis. The different mechanisms leading to MMR gene inactivation and MSI in sporadic colorectal cancers and colorectal cancers from Lynch syndrome (74). Inactivation of tumor suppressor genes by promoter methylation provides another example. Studies of sporadic and hereditary cancers have shown that tissue type (e.g. colorectal vs endometrial (75)), histological subtype (76, 77), and MSI status (26, 75) are important determinants of the tumor suppressor gene methylation pattern. Quantitative and/or qualitative differences in DNA methylation may occur in sporadic MSI vs Lynch syndrome-associated cancers even if the tumor type is the same (Fig. 2: 75, 77). Besides conventional tumor suppressor genes, methylation-mediated regulation applies to those microRNAs that are associated with a CpG island in the upstream region. Their differential methylation according to principles outlined above characterizes tumors from sporadic cases and Lynch syndrome, with the so-called ‘epi-microRNAs’ (microRNAs targeting the epigenetic machinery itself, such as DNA methyltransferase mRNAs) included (78).

Promoter methylation of various tumor suppressor genes occurs in a majority of Lynch syndrome tumors. Comparison of eight types of tumors from MMR gene mutation carriers showed, first, that the average fraction of methylated tumor suppressor loci was characteristic of tumor type and, second, that different tumor suppressor genes were methylated in tumors from different organs (66, 79). The findings are analogous to observations that coding microsatellite repeats are differentially affected by frameshift mutations in MSI-H.

BRAF-V600E mutation occurs in approximately half of sporadic MSI-H colorectal cancers but is totally absent in Lynch syndrome tumors (73) – a finding of diagnostic utility as will be discussed in the section on clinical implications below.

Distinct expression profiles of microRNAs illustrate epigenetic differences between sporadic MSI colorectal cancers and colorectal cancers from Lynch syndrome (74).

Promoter methylation at selected tumor suppressor gene loci in sporadic MSI colorectal carcinoma compared to colorectal and endometrial carcinomas from MMR gene (mostly MLH1) mutation carriers. The data are based on Joensuu et al. (75). Sporadic MSI colorectal cancer displays a high methylator phenotype. More or less the same loci are involved in colorectal carcinomas from Lynch syndrome, but the frequencies of tumors with methylation are lower. MLH1 is methylated in most sporadic MSI colorectal cancers as opposed to rare colorectal carcinoma) or absent methylation (endometrial carcinoma) in Lynch syndrome. In comparison with colorectal carcinomas from Lynch syndrome or sporadic cases, endometrial carcinomas from Lynch syndrome show an essentially different pattern of methylation (for example, RARB, CHFR, and ESR1 promoter methylation is typical of colorectal carcinoma and that of RASSF1A, a property of endometrial carcinomas). These data suggest that tumor suppressor promotor methylation primarily reflects the tissue of origin and secondarily origin as Lynch syndrome vs sporadic disease.
tumors from different organs, suggesting the existence of tissue-specific driver genes and mutations (80, 81). While plasticity, among other things, makes epigenetic driver alterations challenging to define (82), the concept of tissue-specific target genes differentially prone to inactivation by promoter methylation provides a possible mechanism for the epigenetic regulatory system to contribute to the Lynch syndrome tumor spectrum.

**Clinical implications of epigenetic changes associated with Lynch syndrome**

Among unselected colorectal cancers, 15% show MSI and/or loss of MMR protein(s), and distinction between sporadic cases due to acquired MLH1 methylation (constituting the majority of MMR-deficient cancers) and Lynch syndrome (constituting the minority) is highly important. BRAF-V600E mutation and MLH1 promoter methylation tests on tumors are recommended prior to germline testing in diagnostic algorithms (83, 84). Tumor BRAF-V600E mutation and MLH1 methylation (at C or D regions of the promoter (85)) are strong predictors of the absence of germline mutation and cost-effective in the selection of patients for germline mutation analysis (86, 87). However, exceptions exist; notably, acquired methylation of the MLH1 promoter may be present in a small proportion (less than 10%) of tumors from carriers of MMR gene germline mutations (22, 88). Furthermore, the possibility of constitutional epimutation should be kept in mind. Quantification of MLH1 methylation in tumor DNA has been proposed as a means to distinguish biallelic methylation typical of sporadic tumors from monoallelic methylation occasionally present in Lynch syndrome (89). Discrimination would, however, fail even by this method and other assays designed to determine the percentage of methylated DNA, if constitutional epimutation of MLH1 is accompanied by somatic loss of the wild-type allele, as often occurs in tumors from epimutation carriers (46, 50).

After a conventional MMR gene mutation is identified in the proband and deemed pathogenic, a gene test can be designed and predictive testing offered to the entire family. The status of the first-degree relatives, who had a 50% a priori risk of being carriers of the same mutation, then changes into proven carriers and non-carriers. Mutation carriers are counseled to have elevated lifetime risks for cancers typical of Lynch syndrome and are enrolled in lifelong surveillance (90), whereas non-carriers have cancer risks comparable to the average population and are exempted from regular surveillance. Based on available clinical data, carriers of constitutional epimutations should be offered cancer surveillance similar to that for any Lynch syndrome mutation carriers. As far as recurrence risks in family members are concerned, risk estimation is more complex in families with epimutation, due to variable inheritance patterns and incomplete understanding of the molecular mechanisms behind these. Primary epimutations are often permanently erased when the disease allele is transmitted from the parent to the offspring, resulting in non-Mendelian inheritance (51, 57), and transient erasure in gametes applies to secondary epimutations showing Mendelian inheritance (47). Uncertainty of the basic type (primary vs secondary) of a newly discovered epimutation, somatic mosaicism for methylation (51), and incomplete correlation between epimutation and transcriptional activity (for example, inherited disease haplotype without methylation can be transcriptionally silent (47)) may complicate predictive testing in families with epimutation. Considering a family with secondary epimutation, it seems obvious that an unaffected family member with a sequence change and methylation should undergo surveillance as per any Lynch syndrome family member; however, the absence of methylation in the individual would not justify exemption from surveillance, contrary to non-carriers of traditional Lynch syndrome mutations. It is safe to recommend that family members of epimutation carriers should generally remain under regular surveillance until the inheritance patterns of epimutations and their exact molecular basis are better understood (49, 51).

Epigenetic alterations occurring in cancer may qualify for markers of early diagnosis, prognosis, and treatment response (91). Changes observed in Lynch syndrome tumors provide multiple possibilities for clinical use. For example, tumor suppressor gene methylation in endometrial biopsy samples may distinguish lesions prone to malignant transformation and thereby aid endometrial cancer surveillance (92). Molecular biomarkers, such as MMR defects and CIMP, may predict sensitivity to chemotherapeutic agents and be used to guide decisions on adjuvant therapy in colorectal cancer (93–95). For Lynch syndrome patients, tailored treatment and prevention are increasingly offered based on the unique clinical and molecular features of the disease (96). Examples...
given in this review highlight the role of the epigenetic system as a connector between genetic and environmental influences (Fig. 3). Being involved at all stages of multistep tumorigenesis, capable of functionally substituting for genetic changes, and reversible, epigenetic changes are likely to provide targets for a growing number of clinical applications for both Lynch syndrome and sporadic cancers in the future.

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