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An Update on the Pathogenesis of Lynch Syndrome: Recently Described Novel Molecular Mechanisms

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Abstract

Lynch syndrome, originally described in 1913 and previously known as hereditary nonpolyposis colorectal carcinoma syndrome, is the most common hereditary cancer syndrome. This syndrome is classically due to germline mutations in the mismatch repair genes MLH1, MSH2, MSH6, or PMS2. The cancer risk for patients with Lynch syndrome is not limited to the colorectum; women with Lynch syndrome are at risk for endometrial cancer, and Lynch patients of both genders are at risk for other cancers as well. There are cases of cancers in families that meet the clinical criteria (Amsterdam and Bethesda criteria) for Lynch syndrome but do not have a mutation in the one of the four classic mismatch repair genes. For some time, there has been speculation that other mutations or mechanisms were responsible for a subset of Lynch syndrome patients; much research has gone into identifying those alternative mutations and mechanisms. Recently, EPCAM deletion, CHEK2 mutations, and germline MLH1 hypermethylation have been identified as alternative mutations that cause Lynch syndrome in mismatch repair-negative patients. This article reviews these novel mechanisms and mutations, their clinical significance, and the pathogenesis of these Lynch causing mutations.

Keywords: Lynch syndrome; Pathogenesis; Cancers; Muttions

Introduction

In 1913 Warthin described a family in Michigan with a propensity to develop gastrointestinal and gynecologic cancers without colorectal polyps [1,2]. In 1966, Lynch et al. published data on two other Midwestern families with a clustering of similar types of cancer [1,2]. This syndrome, Lynch syndrome (formerly known as hereditary non-polyposis colorectal cancer), is the most common hereditary cancer syndrome and is inherited in an autosomal dominant fashion [1-3]. Typically, Lynch syndrome is the result of germline mutations in the mismatch repair (MMR) genes *MSH2*, *MSH6*, *PMS2*, or *MLH1* with subsequent heterozygous loss of function [1-5]. While Lynch syndrome accounts for approximately 1-7% of all colorectal carcinomas [2-9], there is also an elevated risk of extracolonic malignancies including carcinomas of the small bowel, upper genitourinary tract, stomach, pancreas, ovary, and endometrium [1-3,5-14]. In women, endometrial cancer and colon cancer are equally likely to be the sentinel tumor event [5].

The MMR proteins are responsible for the repair of DNA base-pair errors or "mismatches" that develop during DNA replication [1]. When these errors occur, they are most commonly in long, repetitive DNA sequences commonly seen in microsatellites [1]. Microsatellites are short mono, di, or trinucleotide repeats in noncoding regions throughout the human genome [1]. When there is a mutation in one of these MMR genes the abnormal protein is unable to correct the transcriptional errors or "mismatches," and the length of the microsatellite regions (which are usually fixed in a given individual) become variable, leading to microsatellite instability [1]. Abnormal MMR proteins can be detected using immunohistochemistry and microsatellite instability can be assessed for using molecular methods, though definitive diagnosis of Lynch syndrome requires germline sequencing of MMR genes. Historically patients with Lynch syndrome have been identified based on family history, first by the Amsterdam criteria and more recently by the modified Bethesda criteria [4-6]. A subset of approximately 40% of patients with Lynch syndrome that meet clinical criteria and have a microsatellite instability-high colorectal cancer do not have an identifiable mutation in one of the four mismatch repair genes [2,3,5,6,7,13]. Recently, several novel genetic abnormalities have been identified which lead to the Lynch syndrome phenotype and may explain differences in the rates and risk of extracolonic malignancies [1-3,5-18]. We subsequently outline newly identified abnormalities, including *EPCAM* deletions, germline promoter hypermethylation of the *MLH1* gene, and *CHEK2* mutations, and their role in Lynch syndrome.

Epithelial Cellular Adhesion Molecule (EPCAM) Mutations

The *EPCAM* gene, formerly known as *TACSTD1* (tumor associated calcium signal transducer 1), codes for epithelial cellular adhesion molecule CD326 and is located on the short arm of chromosome 2 [1,6-9]. *EPCAM* is expressed in nearly all epithelial cells as well as some epithelial malignancies, including colorectal carcinomas [1,6,8,9]. Fairly recently, a germline deletion in the 3' exon of *EPCAM*, which is directly upstream from *MSH2*, was discovered in Dutch, German, and Chinese populations that results in *MSH2* promoter hypermethylation, inactivation of the *MSH2* gene, and development of Lynch syndrome [1,3,5-12]. It is estimated that this deletion may be present in up to1-2.8% of those with Lynch syndrome [6,14]. Concomitant lack of *MSH2* and *EPCAM* expression, as determined by immunohistochemistry, is characteristic of these tumors; however, *EPCAM* expression can be retained in some cancers and may not be expressed by all cells limiting the utility of immunohistochemistry in diagnosis [1,6]. The cumulative risk of colorectal cancer at age 70 years for carriers of an *EPCAM* deletion is similar to those that are carriers of *EPCAM-MSH2*, *MSH2*, or *MLH1* mutations; however, it is higher than carriers of *MSH6* mutations [10].

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Gene (s)	Mutation (s)	Mechanism	Phenotype
Mismatch Repair (*MLH1*, *MSH6*, *PMS2*, *MSH2*)	Germline deletions, point, truncation, missense, or frame shift	Abnormal MMR protein expression leading to faulty repair of DNA replication errors	Early-onset colorectal cancer; increased risk of endometrial, ovarian, gastric, urinary tract, renal, biliary tract, brain, and small bowel cancers
Epithelial Cellular Adhesion Molecule (*EPCAM*)	Germline deletion involving 3´ exon	Epigenetic silencing of neighboring *MSH2*	Early-onset colorectal cancer; increased risk of endometrial, bladder, small bowel, and appendiceal cancers
MLH1	Germline promoter hypermethylation	Loss of *MLH1* expression	Tumor spectrum, phenotype, and incidence are under investigation
Cell Cycle Check Point Kinase 2 (*CHEK2*)	1100delC and I157T	Inactivation of *CHEK2*: a serine/threonine kinase with mutliple regulatory functions (cell cycle progression, apoptosis, DNA damage repair)	1100delC: increased risk of breast, colon, and ovarian cancers; and various other Lynch-related malignancies I157T: increased risk of breast, colon, kidney, prostate, and thyroid cancers

Table 1: Molecular Mechanisms Responsible for Lynch Syndrome.

Germline Promoter Hypermethylation of *MLH1*

Approximately 10% of sporadic colorectal cancers demonstrate the microsatellite instability-high (MSI-H) phenotype with loss of *MLH1* protein expression by immunohistochemistry as a consequence of somatic hypermethylation of the promoter region of the *MLH1* gene and transcriptional silencing [1-3,9,13,14]. Another novel mechanism leading to a Lynch syndrome phenotype is germline promoter hypermethylation of the *MLH1* gene [1,13,14]. Both germline and somatic hypermethylation result in loss of expression of the *MLH1* protein by immunohistochemistry and a microsatellite instability-high phenotype. The presence of hypermethylation of the *MLH1* promoter does not exclude Lynch syndrome [1,13,14]. The main factor differentiating the two is that sporadic tumors demonstrate somatic hypermethylation and tumors of Lynch syndrome show germline hypermethylation [1,13,14]. In one study, 9.4% of patients with Lynch syndrome (MMR mutation negative; fulfilled Amsterdam criteria) were due to germline hypermethylation of *MLH1* [1,13]. Methylation analysis can be carried out by extracting DNA from peripheral blood lymphocytes, treating the DNA with bisulfite, amplifying the *MLH1* promoter region by polymerase chain reaction, and separating the methylated and unmethylated products by gel electrophoresis [13]. Currently, the exact phenotype regarding cancer risk, cancer types, and cancer incidence in this group is still being studied [1].

Cell Cycle Checkpoint Kinase 2 (*CHEK2*) Mutations

Mutation in cell cycle checkpoint kinase 2 (*CHEK2*) is a recently described mechanism for the development of Lynch syndrome [1,2,15-19]. *CHEK2* is a multiorgan cancer susceptibility gene that codes for a serine/threonine kinase that serves a regulatory function in processes such as cell cycle progression, apoptosis, DNA damage repair, and may be a genetic modifier for other susceptibility genes [1,15,17,18]. *CHEK2* mutations have been associated with elevated risk of breast cancer in some northern and central/eastern European populations (Poland, Finland, Germany, and the Czech republic) and are second only to *BRCA* mutations in hereditary breast cancer gene incidence [1,2,15-19]. There are four known *Ck2* mutations; two of them, I157T and 1100delC, may be associated with increased risk of multiple malignancies including breast, colon, kidney, prostate, and thyroid cancer [1,2,15-19]. Initial studies demonstrated that carriers of the 1100delC mutation had significantly higher rates of breast cancer, colon cancer, ovarian cancer, and other malignancies seen in Lynch syndrome; it was identified in approximately 3% of families with clinically diagnosed Lynch syndrome [1,16,19]. *CHEK2* mutations may be responsible for some cases of Lynch syndrome without a MMR mutation, though the possibility that the 1100delC is modifying an unidentified susceptibility gene that causes a syndrome similar to Lynch cannot be excluded [1,16].

Studies of the I157T mutation found that this mutation is strongly associated with Lynch-related malignancies, both colorectal and extracolonic, in Finnish and Polish populations [1,2,15,17,18]. The missense I157T allele seems to be the mutation most associated with colorectal cancer and was seen in 7.7% of Lynch syndrome families and 4.8% of control subjects [17]. All of these studies are limited by the small number of cases but there is evidence to suggest that the 1100delC and I157T *CHEK2* mutations may be responsible for the Lynch phenotype.

Conclusion

Lynch syndrome is a common hereditary cancer syndrome which is most classically due to germline mutations in the mismatch repair genes *MLH1, MSH2, MSH6, or PMS2*. Now, 100 years after Lynch syndrome was first described, several novel mechanisms involved in the pathogenesis of this syndrome, other than mismatch repair gene mutations, are being discovered. Among these novel mechanisms, *EPCAM* deletions, *CHEK2* mutations, and germline promoter hypermethylation of *MLH1* have been described with evidence that these are responsible for some of the MMR-negative cases (Table 1). Other genetic pathways that are linked to the Lynch syndrome phenotype maybe discovered, helping to identify those individuals with Lynch syndrome, allowing for appropriate preventative screening in these patients and their family members.

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