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Mismatch repair defects and Lynch syndrome: the role of the basic scientist in the battle against cancer

Christopher D. Heinen*

Center for Molecular Medicine and Neag Comprehensive Cancer Center, University of Connecticut Health, Farmington, CT 06030, USA

Abstract

We have currently entered a genomic era of cancer research which may soon lead to a genomic era of cancer treatment. Patient DNA sequencing information may lead to a personalized approach to managing an individual's cancer as well as future cancer risk. The success of this approach, however, begins not necessarily in the clinician's office, but rather at the laboratory bench of the basic scientist. The basic scientist plays a critical role since the DNA sequencing information is of limited use unless one knows the function of the gene that is altered and the manner by which a sequence alteration affects that function. The role of basic science research in aiding the clinical management of a disease is perhaps best exemplified by considering the case of Lynch syndrome, a hereditary disease that predisposes patients to colorectal and other cancers. This review will examine how the diagnosis, treatment and even prevention of Lynch syndrome-associated cancers has benefitted from extensive basic science research on the DNA mismatch repair genes whose alteration underlies this condition.

Keywords

Lynch syndrome; mismatch repair; colorectal cancer; personalized medicine; microsatellite instability; chemotherapy

1. Introduction

Lynch syndrome (LS) is the most prevalent hereditary colorectal cancer (CRC)-predisposition syndrome resulting in approximately 30,000 cases of CRC per year (1). This syndrome has also been referred to as hereditary non-polyposis colon cancer (HNPCC), however, the recognition that numerous extracolonic cancers can develop in these patients, such as endometrial, ovarian, stomach, pancreatic and multiple other cancers, has led many to discontinue using this nomenclature (2). Successful management of LS patients begins with a proper diagnosis of the condition, and includes often times aggressive cancer prevention approaches and appropriate decisions about cancer treatment. Understanding the

*Corresponding author. Tel: +1 860 679 8859; fax: +1 860 679 7639.

molecular changes underlying tumor etiology aides the clinical decision-making process at each step. The discovery that LS is caused by inherited mutations in genes of the DNA mismatch repair (MMR) pathway has been tremendously important for the management of this disease. Basic science research on the MMR pathway predated its link to human cancer and only accelerated after the connection was established. The information learned in the laboratory has had implications for LS diagnosis, prevention and treatment. Whereas many of the minireviews in this special issue will deal with specific aspects of MMR molecular mechanism, this review will highlight examples of how this mechanistic information has been put to use in the clinic (Fig. 1). In addition, minireviews by Peña-Diaz & Rasmussen; Li, Pearlman & Hsieh; Sijmons & Hofstra; and Begum & Martin will further elaborate on some of the connections between basic science research and clinical advances highlighted here.

2. History of Lynch syndrome

The first patient that we now recognize as likely having LS was a German immigrant who settled in Michigan in the mid 1800's (3). Before dying of cancer at the age of 60, the man fathered 10 children, 6 of whom also died of cancer. One of his descendants was a young seamstress who reported to her employer, Aldred Warthin, then Chairman of the Department of Pathology at the University of Michigan, that she was very worried that she might die of cancer since so many members of her family had previously died of cancer. This conversation led Warthin to collect information on her family history and create a pedigree describing the multiple cancers that affected successive generations in her family. Warthin further examined the cancer cases that came through his pathology laboratory and noted that around 15% of those cases had some family history of cancer (4). He concluded that there must be a hereditary effect on some cancers.

In 1962, Henry Lynch, an internal medicine resident in Nebraska with an interest in genetics, similarly met a patient recovering from delirium tremens who blamed his heavy drinking on fears of dying from colorectal cancer due to the many family members who died of cancer (2). As did Warthin, Lynch proceeded to develop a family history of this patient, which showed multiple cases of CRC which lacked the distinct polyposis phenotype of familial adenomatous polyposis (FAP), a known CRC-predisposition syndrome at that time. Soon after, Lynch was made aware of the work at the University of Michigan describing similar families and began to argue for the recognition of a new syndrome of clustered cancers in families, referred to at the time as cancer family syndrome (CFS). That this syndrome had a genetic basis was a contentious issue for many years as the accepted dogma was that environmental factors, commonly shared within families, was the main cause of cancer.

3. Into The Molecular Era of LS Diagnosis

3.1 The Molecular Genetics of LS

As Lynch and other researchers accumulated information data on CFS families around the world accumulated over the next 30 years, acknowledgement of this condition, eventually to be referred to as LS, became more common. The diagnosis of LS depended on knowledge of

family history to determine the extent of cancer clustering in the family (see the minireview of Sijmons and Hofstra in this issue). The presence of a family history of cancer and/or an early age of cancer diagnosis remains the first clue that leads to a clinical suspicion of LS. The average LS patient develops cancer by the age of 45, two decades earlier than in the general population. To aid the diagnosis of LS, an International Collaborative Group on HNPCC devised clinical criteria known as the Amsterdam Criteria (5) that established rules based on age of diagnosis and number of cancers across multiple generations in a family. Those criteria were expanded in 1999 to account for the extracolonic cancers frequently observed in LS families (6). However, a leap forward in LS diagnosis emerged from the discovery in 1993 that almost all LS tumors displayed a form of nucleotide-level genomic instability called microsatellite instability (MSI) (7–9). While using polymorphic microsatellite markers to identify regions of loss of heterozygosity, it was observed that LS-associated tumors contained additional expansions or contractions in these repeat sequences. The significance of these findings was not immediately obvious to clinicians and even cancer researchers. However, some basic scientists did recognize this phenotype as one they had observed in lower organisms with defects in DNA repair and recombination pathways.

MSI, or the increased tendency of tandem repeat sequences to undergo small insertion or deletion loop (IDL) mutations, was first noted in the 1970s in bacteriophage (10) and was proposed to occur when denatured repeats reannealed out of register leading to a bulge of bases from the duplex DNA (11). This instability was enhanced when repeat-containing sequences were introduced into *mutS* or *mutL Escherichia coli* strains defective for MMR, a pathway already recognized to be involved in repairing mispaired bases (12). Similarly, studies in *Saccharomyces cerevisiae* showed that mutations in MSH2, MLH1 or PMS1 resulted in a several hundred fold increase in tandem repeat instability, further linking the MMR pathway with MSI (13). Upon report of increased MSI in LS cancers, basic scientists studying MMR in lower organisms turned their attention to discovering a homologous pathway in human cells. One of the first reports by Parsons et al. (14), showed that cancer cell lines derived from LS patients failed to repair small IDLs as well as single basepair mismatches. This report suggested that LS was a disease of defective MMR. During the same time period, Fishel et al., identified the human *MutS* homolog *MSH2* and suggested that mutations in this gene were causative for LS (15) as did Leach et al., who identified deleterious mutations within the human *MSH2* gene (16). The following year, two groups cloned the human MutL homolog *MLH1* and found deleterious mutations within LS families (17,18). In addition to these two genes, another human *MutS* homolog *MSH6* was later discovered and reported to be altered in the germline of LS patients (19). Finally, a small subset of LS patients was shown to have mutations in the *MutL* homolog *PMS2* (20,21). Thus, basic science research on DNA repair in yeast and bacteria provided the crucial insights necessary to determine the genetic basis for LS, establishing it as a genetic disease and vindicating the work of Warthin, Lynch and others. Importantly, this discovery also sparked a new field of cancer research that elucidates the role of DNA repair and genome stability in preventing tumorigenesis.

In addition to establishing a genetic basis for LS, linking defective MMR with the disease led to the current molecular era of LS diagnosis. While the Amsterdam criteria assisted in

identifying LS patients, their use depended on the patient having accurate knowledge of their family history, and even then may not capture all cases (22). However, the ability to now assess a tumor for molecular markers of defective MMR can provide a diagnostic clue. MSI detection, via a simple PCR screen, is commonly used as a first screen for defective MMR in suspected LS patients (23,24). In addition, as the majority of germline mutations in MMR genes in LS patients result in loss of stable protein, immunohistochemistry (IHC) analysis of the tumors is also performed using antibodies against the four major MMR proteins (25). Guidelines, similar to the Amsterdam criteria, though less stringent, were developed to identify those patients who should undergo these molecular tests (24). Termed the Bethesda Guidelines, they use personal history and clinical features to identify suspected LS patients. Today, given the relatively inexpensive nature of the MSI and IHC molecular screens, many health centers have moved to a universal screening approach, testing all new CRC patients for MMR defects to identify possible LS cases, regardless of age or family history (22,26–30).

3.2 MMR-defective sporadic colorectal cancer

The detection of MSI in a tumor does not necessarily mean the patient suffers from LS. Between 10–40% of sporadic colon, endometrial, ovarian and other cancers display MSI as well indicating that MMR can be disrupted in sporadic cancers. The loss of MMR function in sporadic tumors was shown in multiple laboratories to result primarily from hypermethylation of the *MLH1* promoter, leading to its reduced expression (31–33). Thus, to distinguish LS patients from sporadic cancer patients, the next step in the diagnostic process is to sequence the four major MMR genes using genomic DNA usually from a blood sample of the affected individual. Detection of a deleterious, germline mutation in one of the four major MMR genes often serves as the ultimate confirmation of an LS diagnosis. Thus, the use of DNA sequencing for personalized medicine has already been occurring in the LS field for over a decade.

3.3 Variants of Uncertain Significance

A publically available database of all known cancer-causing mutations in LS curated by the International Society for Gastrointestinal and Hereditary Tumors shows that 42% of LS cases are caused by mutations in *MLH1*, 33% in *MSH2*, 18% in *MSH6* and 7.5% in *PMS2* (34). While a clearly deleterious mutation such as a deletion or frameshift can confirm an LS diagnosis, about 20–30% of the mutations detected are missense variants (35,36). The pathogenic significance of these missense variants cannot necessarily be assumed preventing the clinician or genetic counselor from making a definitive diagnosis. These missense variants, termed variants of uncertain significance (VUS), have been a source of intensive investigation in the MMR field (for more in depth discussion of this topic, please refer to Peña-Diaz & Rasmussen in this issue). Recently, a group of clinicians, genetic counselors and basic scientists came together to devise a classification scheme for assessing the clinical significance of MMR VUS (37). This classification scheme relies on an accumulation of clinical and genetic data about the patient such as whether the variant segregates with the affected family members in a suspected LS family and whether it associates with a tumor that displays features of defective MMR such as MSI. In addition to these clinical and genetic data, classification also depends on a functional assessment of the variant-containing

MMR protein performed in a basic science laboratory. Due to the extensive basic science research performed over the last few decades, much is known about the molecular mechanism of the MMR pathway. This information has been useful for developing functional assays for testing VUS.

The most common assays have been *in vitro* biochemical assays. The ability to reconstitute the entire repair of a single basepair mismatch in the test tube using cell extracts (38) or recombinant proteins (39,40) has allowed researchers to isolate the effects of individual variants in the MMR process (41–45). In addition, assays that isolate individual steps in this pathway such as DNA mismatch binding, MMR protein-protein interactions or ATP processing have been used (35,45–48). While *in vitro* assays may detect specific defects caused by a VUS, normal activity in these assays does not necessarily mean the variant is neutral. Not all functional aspects by which a variant can cause a defect in MMR are captured in these assays. Cellular localization, chromatin interaction and other protein-protein interactions which may be important for MMR function *in vivo* are not assessed. Thus, testing the effects of VUS function in a cellular model may be necessary to examine variants with no phenotype in *in vitro* studies. Early attempts to study VUS in cells involved transient transfections in transformed human cell lines (49–51). These early studies demonstrated that certain variants had effects on MMR protein stability which could affect MMR function. Transfection of GFP-tagged MMR variants into NIH-3T3 primary cells was used to identify variants that affected the nuclear localization of the MMR protein complexes, providing another functional assay that cannot be assessed in the test tube (48,52,53). As the ability to carefully control expression levels of the variant-containing protein via transient transfection is limited, more recent studies have examined other means of introducing the variant transgenes such as the use of lentiviral vectors (54) or direct variant knock-in into the endogenous gene in mouse embryonic stem cells (55–57). The significance of the VUS problem in LS underscores the challenges that await the broader clinical community as the use of genome sequencing information for guiding diagnosis and clinical management increases. For there to still exist so much uncertainty for a disease like LS whose genetic basis is so well understood involving a pathway whose function is so well understood causes one to pause when contemplating the disease significance of a sequence variant in a gene that is not as well understood as the MMR genes. However, the strategies applied in classifying MMR VUS in LS may serve as a guide for meeting those challenges.

4. Mechanistic lessons applied to treatment of MMR-defective cancers

4.1 The MMR-dependent damage response

Information about the MMR pathway from the basic science laboratory has been essential for guiding the diagnosis of LS, however, the current challenge for many laboratories is learning information that will help guide treatment and even prevention of MMR-defective cancers. The observation that MMR-deficient cells are more resistant to the cytotoxic effects of certain DNA damaging agents used in conventional chemotherapy was a major discovery in this respect (58–61). The first evidence of a MMR-dependent damage response was demonstrated in MMR-deficient *E. coli* that were shown to be resistant to the cytotoxic effects of the DNA alkylating agent *N*-methyl-*N*’-nitro-*N*-nitrosoguanidine (MNNG) (62).

This finding was later confirmed in human cells (63) and has become the best characterized MMR-dependent damage response (for an in depth review, refer to Li, Pearlman & Hsieh in this issue). The major cytotoxic lesion created by MNNG is the O^6-methylguanine (^{Me}G) which is commonly mispaired with thymine during replication resulting in a potentially mutagenic ^{Me}G-T mispair. The MMR pathway recognizes these lesions and removes the mismatched thymine in the daughter strand. However, if the ^{Me}G lesion in the parental strand is not removed, usually by the direct-repair protein methylguanine methyltransferase (MGMT) (64), the polymerase will likely misincorporate a thymine again upon resynthesis. This has been proposed to lead to repeated futile cycles of MMR recognition and excision and the ultimate generation of an unreplicated gap opposite the ^{Me}G (65–67). When the cell enters the next cell cycle, a new replication fork will encounter this gap and convert it into a lethal double strand break. Thus, processing of a ^{Me}G-T mispair by the MMR pathway creates secondary DNA damage that ultimately causes cell death. In addition to the futile cycle model, researchers have demonstrated protein-protein interactions between the MMR proteins and key DNA damage signaling molecules such as ATR, ATM, CHK1 and CHK2 (68–72) suggesting a more direct role for the MMR proteins in triggering a damage response. It is proposed that the MMR proteins, following lesion recognition, can recruit damage signaling kinases to sites of damaged DNA. Both mechanisms indicate that MMR plays a protective role in removing damaged cells to reduce the risk of mutation accumulation. In addition to alkylating agents, the MMR pathway may also induce a response to other agents such as 6-thioguanine (73,74), 5-fluorouracil (75–77), and the intrastrand crosslinker cisplatin (78–81), though the mechanism of response to these drugs is less well understood.

4.2 Response of MMR-defective cancers to chemotherapy

The discovery of the MMR-dependent damage response is clinically relevant as it pertains to tumor response to chemotherapy. Studies examining the benefits of 5-fluorouracil (5-FU) in patients with MSI+ colorectal cancer concluded that the therapy had no effect on overall survival or disease free survival, while benefits were observed in patients with microsatellite stable tumors (82–87) (also see Li, Pearlman & Hsieh in this issue). This clinical result is consistent with cellular studies observing enhanced drug resistance in MMR-defective cells. For 5-FU specifically, laboratory studies of human cancer cell lines demonstrated that 5-FU was more effective in MMR-proficient cells as treatment leads to an incorporation of 5-fluoro-2’-deoxyuridine into DNA. These lesions are commonly mispaired with guanine (75–77) and serve as a substrate for the MMR proteins likely resulting in a similar damage response mechanism as observed with ^{Me}G-T mismatches (77). 5-FU also increases levels of deoxyuridine by decreasing thymidine nucleotide pools. Deoxyuridine misincorporation into DNA results in formation of U-G mispairs that also stimulate MMR activity (77). Thus, treatment of cancer cells with 5-FU may cause multiple lesions that activate a MMR-dependent damage response.

Preclinical studies have also demonstrated increased resistance to cisplatin and carboplatin in MMR-defective cells (78–81) (also see Li, Pearlman & Hsieh and Begum & Martin in this issue). The MMR pathway recognizes primarily GpG intrastrand crosslinks that are generated by platinum-containing agents. These studies may explain clinical observations of

MMR loss in recurrent ovarian tumors following treatment with cisplatin (79,88–92). Treatment of the primary tumor with cisplatin may lead to selection for a subset of cancer cells that have lost MMR function. A similar observation was made in gliomas following treatment with the alkylating agent temozolomide as increased mutations in *MSH6* were found in recurrent tumors that were not present in the primary cancer (93,94).

As noted earlier, MMR-defective sporadic cancers mostly arise due to hypermethylation of the *MLH1* promoter, thus basic science studies have examined the effects of demethylating agents such as 2'deoxy-5-azacytidine (decitabine) on the ability to restore *MLH1* expression, and therefore function. Decitabine treatment of an ovarian cancer cell line was shown to restore MLH1 expression as well as increase sensitivity to cisplatin, carboplatin and temozolomide (95,96). This effect was enhanced in cells treated with decitabine and the histone deacetylase inhibitor belinostat (97). These studies spurred clinical trials examining combinations of decitabine and other chemotherapies. A phase II clinical trial examining decitabine pretreatment followed by carboplatin suggests that the combination improves response rate and progression free survival (98). Similarly, chemotherapeutic resistance of metastatic melanoma to temozolomide appears improved by treatment with decitabine (99).

5. A peek into the lab to see what is next

5.1 Synthetic lethality and cancer treatment

An emerging area of cancer research that holds promise for new therapeutic approaches involves the exploitation of synthetic lethal interactions between DNA damage response pathways, including MMR (100,101) (also see Begum & Martin in this issue). Synthetic lethal interactions occur between two genes or pathways when the loss of both leads to cell death, whereas the loss of either one alone is tolerated. The best characterized synthetic lethal relationship involving a DNA damage response pathway involves the chemical inhibition of poly(ADP-ribose) polymerase 1 (PARP1) in cells deficient for the homologous recombination repair (HRR) proteins BRCA1 or BRCA2 (102,103). PARP1 responds to single-stranded DNA breaks and prevents their degradation into toxic double strand breaks by either stabilizing the lesion or recruiting other DNA proteins to repair the break (104). Increased conversion of these lesions into double strand breaks in the absence of PARP1 activity would be particularly toxic to cells defective in homologous recombination repair. Recently, the PARP1 inhibitor olaparib has been approved by the US Food and Drug Administration for use in cancers with defects in the *BRCA* genes and is being explored for use in cancers with other defects in the HRR pathway (100).

Synthetic lethal interactions involving the MMR pathway were first described in yeast with mutants in *pol3* that affect its proofreading exonuclease activity (105–107). Cell death may occur due to a possible mutational overload resulting from loss of both error correction functions. Synthetic lethal interactions with MMR in human cells were identified through small interfering RNA (siRNA) screens in MSH2 or MLH1 defective cell lines (108). As described in more detail in the review by Begum & Martin in this issue, the knockdown of DNA polymerase β in MSH2 deficient cells results in increased cell death. Likewise, MLH1 defective cells were sensitive to knockdown of DNA polymerase γ, both polymerases thought to be involved in the repair of 8-oxo-guanine lesions. One rationale for these

findings comes from earlier studies that showed that MMR proteins can bind to 8-oxo-guanine-adenine mispairs *in vitro* (109,110) and that MSH2 deficient cells are more sensitive to treatment with the oxidizing agent methotrexate (111) (also see review by Crouse in this issue). Thus, the MMR pathway may play an important back-up role in the repair of oxidative damage in DNA, a function that can be exploited in MMR-defective cells. A similar siRNA screen against an array of cellular kinases and associated proteins determined that MSH2, MLH1 and MSH6 were also synthetically lethal with the PTEN-induced putative kinase 1 (*PINK1*) gene (112). A corresponding accumulation of 8-oxo-guanine lesions in these cells suggested that loss of PINK1, a mitochondrial kinase that regulates cytochrome c release from the mitochondria, may affect mitochondrial membrane potential leading to increased oxidative stress. Therefore, therapeutic strategies that increase the levels of 8-oxo-guanine lesions in MMR-defective cancers cells may exploit the lack of a MMRdependent clearing of these lesions, resulting in tumor specific cell death. From these studies, one may hypothesize that another potential target for synthetic lethality with MMR is MTH1 which plays a key role in removing oxidized dNTPs from cells to prevent their incorporation into DNA. Recent studies have shown that cancer cells are addicted to the activity of MTH1 and that inhibitors of this enzyme can selectively kill cancer cells (113). MMR defective cancers may be particularly susceptible to MTH1 inhibitors.

5.2 Mutated genes in MMR-defective cancers

Understanding the mechanism by which defects in MMR cause cancer may guide new treatment or prevention strategies. Loss of MMR has been shown to increase mutation frequency several hundred fold and this mutator phenotype has been proposed to increase the chances of acquiring mutation in other important growth control or survival genes (114). In particular, loss of MMR has been associated with an increase of frameshift mutations in small sequence repeats within the coding regions of genes (115–118). The first observation of this mutator phenotype at work involved the detection of a frameshift mutation in a run of adenines within the coding region of the TGFβ type II receptor gene in MMR-defective cancer cells (116). The frameshift leads to a premature stop codon and production of a truncated protein product which abrogates the TGFβ signaling pathway. Since that first discovery, a number of other genes have been identified that display increased mutation within intra-genic repeats. Many of these genes had not been previously implicated in colorectal tumorigenesis suggesting that the pathway to tumor development may differ in MMR-defective cancers. Consistent with this idea, exome sequencing of colorectal carcinomas has revealed a subset of cancers that display a hypermutator phenotype marked by a set of commonly mutated genes that differ from those altered in non-hypermutated tumors (119). Of the hypermutated tumors, 77% were marked by MSI with the majority of those containing a hypermethylated MLH1. Thus, basic science studies, particularly increased genome sequencing studies of MMR-defective cancers, may identify new targets for therapeutic intervention in these tumors. One cautionary note, however, is that due to the hypermutability of these tumors, many of the mutations identified may merely be passenger mutations that do not directly contribute to tumor phenotype. Also, it is not entirely clear how similar the development of sporadic MMR-deficient tumors is to LS cancers. Sporadic MMR-deficient tumors are more commonly marked by enhanced CpG island methylation which may lead to downregulation of subsets of genes not affected in LS (120–122).

Sporadic MSI+ tumors are also associated with oncogenic *BRAF* mutations, which are rarely found in LS tumors (122,123). Due to this fact, testing for *BRAF* mutations is sometimes used clinically to distinguish whether a cancer is likely sporadic versus LS-associated (124–126) (also see Sijmons and Hofstra in this issue).

6. Conclusions

The buzzwords *personalized* medicine, *precision* medicine and *genomic* medicine are frequently used these days by researchers and clinicians to describe a new world where medical treatment will be more tailored to individuals based on specific genetic or molecular biomarkers. However, this approach has already been utilized in the LS field for over a decade. The combination of a well-defined disease caused by mutations in a well-researched cellular pathway has led to a wealth of information that has aided patients and family members suffering from this condition. The story of LS provides a hopeful model for the use of molecular and genetic information to precisely diagnose and treat other diseases. At the same time, the story of LS underscores the absolute necessity of continued investment in basic science research – from bacteria to humans – if this vision of improved personalized medical care is to become a reality.

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Abbreviations

LS	Lynch syndrome
CRC	colorectal cancer
HNPCC	hereditary non-polyposis colon cancer
MMR	mismatch repair
FAP	familial adenomatous polyposis
CFS	cancer family syndrome
MSI	microsatellite instability
IDL	insertion/deletion loop
MSH2	human mutS homolog 2
MLH1	human mutL homolog 1
MSH6	human mutS homolog 6
PMS2	post meiotic segregation increased 2
IHC	immunohistochemistry
VUS	variants of uncertain significance
MNNG	*N*-methyl-*N*’-nitro-*N*-nitrosoguanidine

^{Me}G	O^6-methylguanine
MGMT	O^6-methylguanine-DNA methyltransferase
5-FU	5-fluorouracil
PARP1	poly(ADP-ribose) polymerase 1
BRCA1	breast cancer 1 early onset
BRCA2	breast cancer 2 early onset
HRR	homologous recombination repair
siRNA	small interfering RNA
PINK1	PTEN-induced putative kinase 1
MTH1	human mutT homolog 1
TGFβ1	transforming growth factor beta 1
BRAF	v-raf murine sarcoma viral oncogene homolog B

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Highlights

- The history of LS and its association with MMR is discussed
- Basic science research has greatly informed the clinical management of LS
- Diagnosis has been aided by understanding the molecular biology of faulty MMR
- Laboratory studies have also offered clues about tumor response to therapy
- Strong basic science research will drive the success of precision medicine efforts

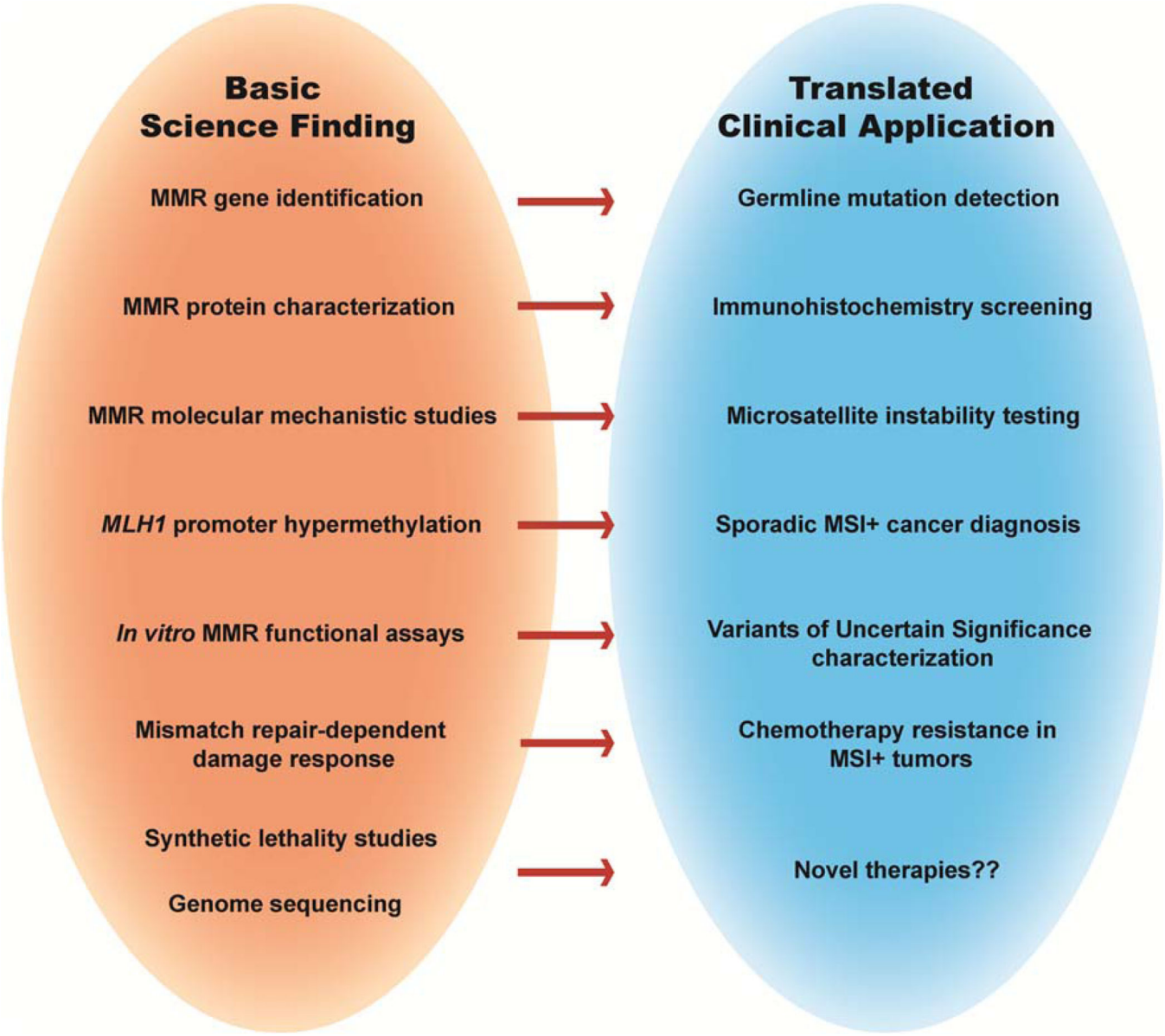

Fig. 1.

Some of the major basic science research breakthroughs in the DNA mismatch repair field and the clinical application that resulted directly or indirectly.