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

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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.

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 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 [127–129].

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 1800s [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

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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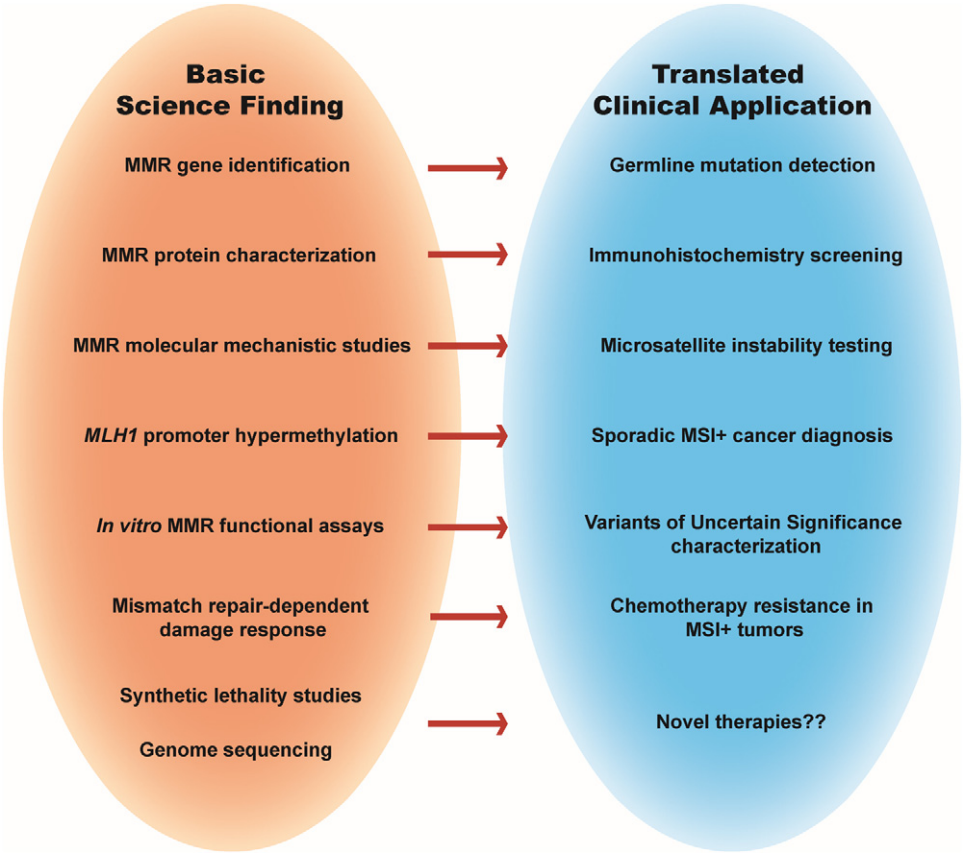

Fig. 1. Some of the major basic science research breakthroughs in the DNA mismatch repair field and the clinical application that resulted directly or indirectly.

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 data on CFS families around the world 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 [129]). 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