Chapter 25. The DNA mismatch repair story 220911bg3

Drugs Against Cancer: Stories of Discovery and the Quest for a Cure

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CHAPTER 25

The DNA Mismatch Repair Story: fixing base-pairs that don't match.

Replicating a cell's genome is a challenge: all 6.4 billion base-pairs of the human genome must be copied correctly. The DNA polymerases that carry out this function are highly accurate: they make only one copying mistake every 10,000 to 100,000 nucleotides. But that leaves nearly 100,000 errors each time a cell divides, and each uncorrected error is apt to result in a mutation. These polymerases however have evolved a proofreading capability that allows them to detect and correct about 99% of the errors they have made. But that still leaves about 1,000 errors uncorrected. Those remaining errors still would have to be corrected to avoid accumulating mutations. Quite remarkably, almost all organisms from bacteria to mammals have evolved a backup system. This "DNA mismatch repair" system works similarly in all organisms and is carried out by variations of some of the same genes. It is the topic of this chapter, as shown in Figure 25.1 in relation to other DNA repair mechanisms.

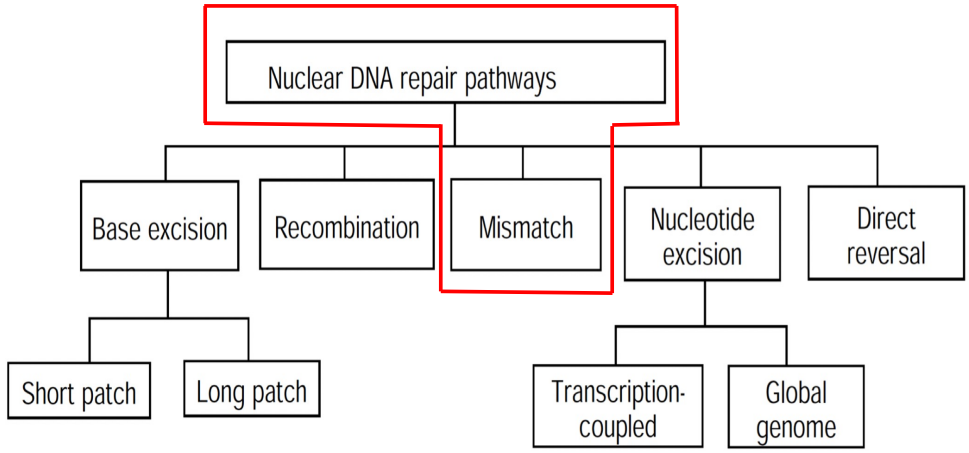

Figure 25.1. The topic of this chapter, DNA mismatch repair (MMR) outlined in red, in relation to the other DNA repair pathways in the cell nucleus. *From (Kohn and Bohr, 2001)*.

Cancer-prone families that have DNA mismatch repair defects.

The story begins in 1895 when a seamstress who worked for Aldred Scott Warthin (Figure 25.2 *left*), Chairman of the Department of Pathology at the University of Michigan, said she was distressed that 5 of her 9 siblings had died of cancer, and she feared the same would happen to her, which unfortunately it did (Boland and Lynch, 2013). A family tree over 3 generations showed 33 of 70 family members having died of cancer of the uterus, stomach or colon. The first cancer-prone family tree, published by Warthin in 1913, is reproduced in Figure 25.3. Warthin traced the cancer tendency back to a German family who immigrated before the Civil War (Figure 25.2 *right*). Warthin's report indicated that cancer could have a familial origin, which was a new idea not readily accepted at the time and remained dormant until Henry T. Lynch (Figure 25.2 *center*) revived it many years later.

The case for inherited factors disposing to cancer was eventually revived in 1970, when Henry T. Lynch of Creighton School of Medicine in Omaha, Nebraska, started compiling evidence from family histories. But, even then, his research grants were rejected, because of bias against the idea, and because his reported cancer frequencies were thought statistically coincidental. It was another 20 years of persistence that finally yielded evidence that could not be denied (Kunkel and Erie, 2005, 2015). With some justification Lynch became noted as "the father of cancer genetics," although he himself said that the designation rightfully belonged to Alfred Warthin. The most decisive case was "non-polyposis colon cancer," also known as Lynch syndrome, which was later found to be caused by an inherited mutation in a DNA mismatch repair gene.

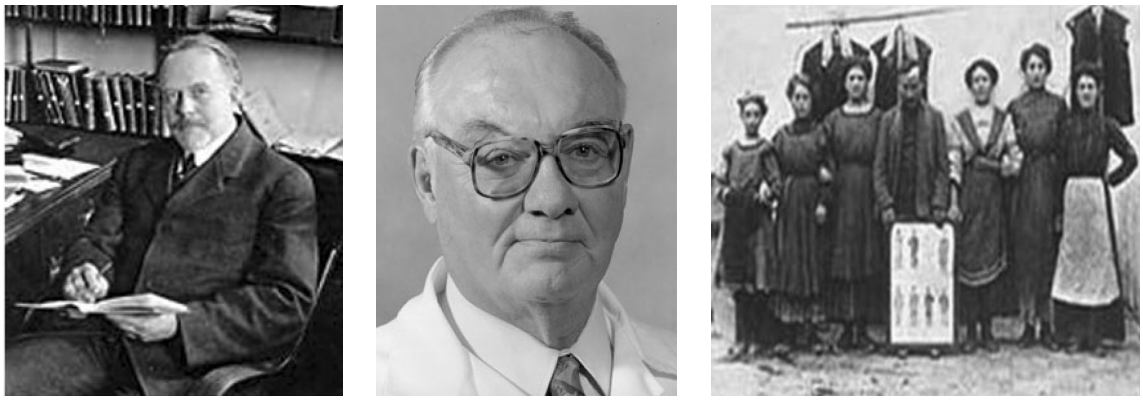

Figure 25.2. (*Left*) Aldred Scott Warthin, MD, PhD, (1866-1931) Chairman of the Department of Pathology at the University of Michigan in Ann Arbor was first to report a cancer-prone family. (*Center*) Henry T. Lynch (1928-2019) compiled family trees to show that susceptibility to cancer is sometimes inherited. He defined hereditary non-polyposis colon cancer (HNPCC), also known as Lynch syndrome. Warthin and Lynch could share the designation "fathers of cancer genetics." (*Right*) The German family, who immigrated before the Civil War, to whom Aldred Warthin traced the first familial cancer disease (Boland and Lynch, 2013).

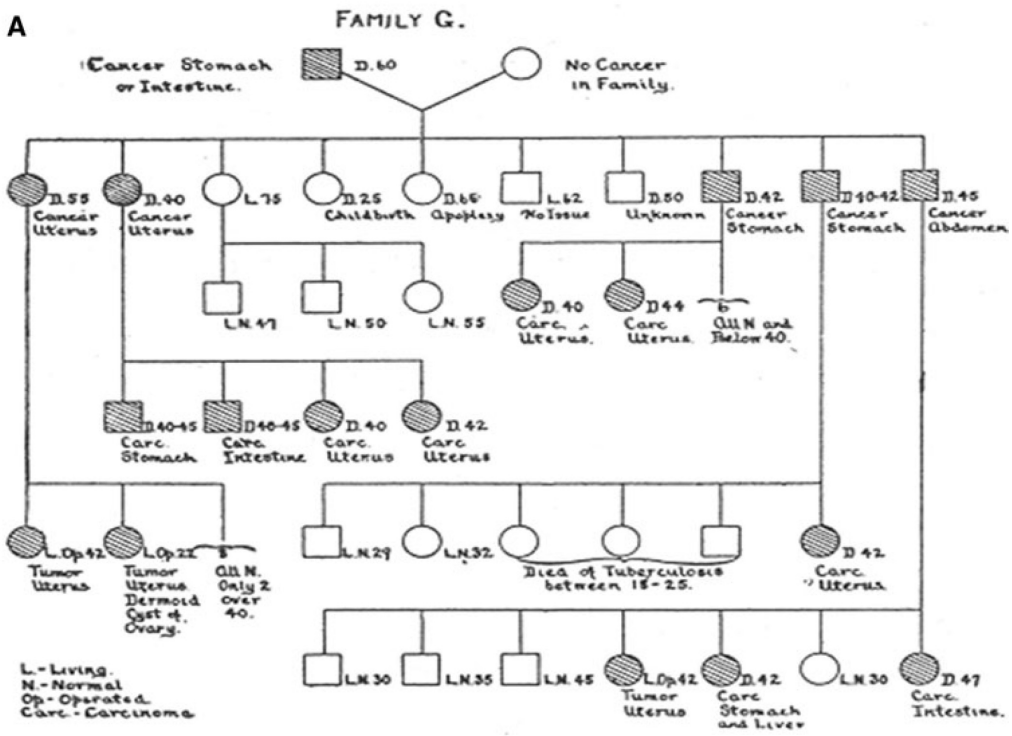

Figure 25.3. The first reported cancer-prone family, published in 1913 by Aldred Scott Warthin. The history traced back to a male founder (top of diagram) who died in 1856 at age 60 of cancer of stomach or intestine. (Squares, male; circles, female; hatched, died of cancer.) (Boland and Lynch, 2013).

Discovery of DNA mismatch repair.

> *Perhaps the most telling lesson of the past forty years has been the recognition that very different forms of life are built around essentially similar mechanisms. All species are discovered to have more in common with each other than their differences would suggest.*
>
> (John Maddox in 'News and Views'
> Nature, Lond. 1993 363, 13.)

DNA mismatch repair is a prime example of a system that exists in nearly all organisms from bacteria to mammals. Indeed, some of the genes of the bacterial system resembled the corresponding mammalian genes sufficiently to help find the mammalian genes once the bacterial ones were known (Radman et al., 1995).

DNA base-pair mismatches (other than the normal A-T of G-C matches) can happen due to replication errors or to chemical DNA damage. An early question was whether such mismatches could be repaired. Studies of DNA damage in bacterial viruses in the early

1970's suggested that bacteria could do that. This was confirmed in 1975 by Wildenberg and Meselson, who prepared a bacterial virus bearing mismatched base-pairs. Upon infecting bacteria with this defective virus, the bacterial host was able to repair the mismatch and allowed the virus to multiply normally (Wildenberg and Meselson, 1975). Analogous experiments in mammalian cells infected with viruses inactivated by a base-base mismatch showed that the cells were able to reactivate these viruses. All of the possible mismatches were found to be repairable (Brown and Jiricny, 1988). This method: ability of a cell to rescue a virus having DNA damage, became a common way to detect the repair of various kinds of DNA damage, both in bacteria and in mammalian cells.

Although known to exist in bacteria, much about mismatch repair remained a mystery in 1982, when Tom Lindahl reviewed what was then known about DNA repair (Lindahl, 1982). Mismatch repair would have to distinguish and repair the newly synthesized DNA strand, which is the strand that would incur errors during replication, but how the repair system did that was not clear. When Paul Modrich reviewed what was known about mismatch repair in 1991, the enzymes and pathways were already well worked out in bacteria, but the details of how it worked in higher cells remained fuzzy (Modrich, 1991). Remarkably, however, a defect in mismatch repair resulted in high mutation rates in bacteria (Modrich and Lahue, 1996). This was likely true also in mammalian cells because the repair systems functioned similarly.

The genes and mechanisms of DNA mismatch repair (MMR).

DNA damage sometimes alters or deletes bases in DNA, so that they cannot associate with their complementary bases. This causes problems when the cell tries to replicate through such mismatches in its DNA. The replicative DNA polymerases rarely make mistakes, and can self-correct most of them, but rare errors inevitably get through. When that happens, the base added to the end of the growing DNA chain does not match (A-T or G-C) the corresponding base on the opposite DNA strand. Virtually all organisms have molecular machinery to repair such mismatches. When mismatch repair was defective, cancer was likely to ensue. Anticancer drugs also can result in base-pair mismatch, which impacts on the clinical outcome. In particular, and contrary to what one might have expected, the mismatch machinery sometimes made a drug more instead of less toxic to the cell. This chapter aims to clarify these mechanisms, and to review how all of this knowledge came to be uncovered.

The human versions of the MMR genes were found by the albeit modest DNA sequence similarity with the bacterial versions (Radman et al., 1995). Six human MMR genes were discovered, whose proteins products interacted as shown in Figure 25.4. The six proteins were found to come together to recognize and repair two types of defects in DNA: mismatch of a single base-pair and loops formed by inserted or deleted base-pairs, which I will describe in turn. Defects in any of these genes (or of a gene called EPCAM that is located near the MSH2 gene) caused high mutation rates all over the genome, making people vulnerable to developing cancer (Baretti and Le, 2018).

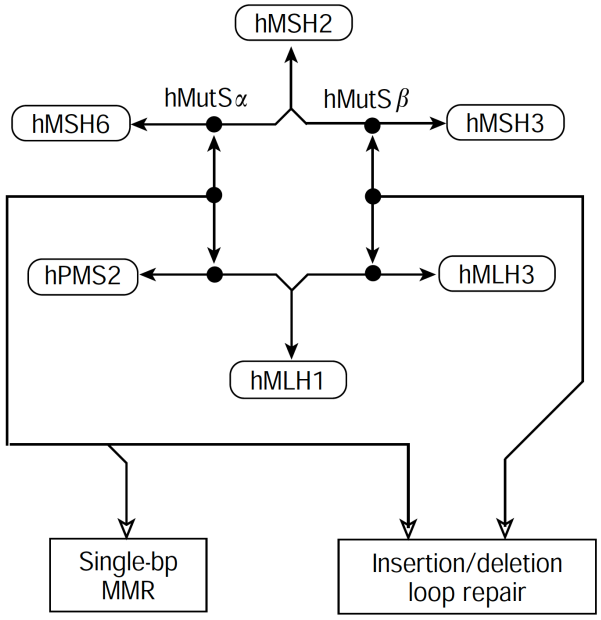

Figure 25.4. Molecular interactions and functional capabilities of the six human proteins implicated in DNA mismatch repair (MMR). hMSH2 combines with hMSH6 or with hMSH3, and hMLH1 combines with hPMS2 or hMLH3. These pairs then come together to form the functional units (Kohn and Bohr, 2001). (The solid circles on the lines represent the species formed by the bindings – for example, the circle labeled hMUTSα, represents the hMUTS2-hMUTS6 dimer.)

How MMR repairs mismatch of a single base-pair.

How the MMR repair process works in mammalian cell was still not completely understood at the time of this writing. A detailed model of how a mismatch is repaired was proposed by (Hsieh and Zhang, 2017). A simplified version of their model is presented in Figure 25.5.

The repair begins with a MSH2-MSH6 (or a MSH2-MSH3) dimer forming a clamp around the DNA. With the aid of PCNA, the clamp diffuses along the DNA in search of a base-base mismatch (**C** in Figure 25.5) (Pluciennik et al., 2010). It is somehow able to distinguish the newly replicated strand, which has the misincorporated base, but how it did that remained unknown at the time of the review by (Hsieh and Zhang, 2017).

Then, with the aid of MLH1-PMS2, a break is created in the newly synthesized strand on one side or other of the mismatch (**D** in Figure 25.5). The segment of newly synthesized DNA that has the mismatch in it is then digested away by Exo1, leaving a single-strand segment of template strand that becomes coated with the single-strand binding protein, RPA (**E** in Figure 25.5) (Kadyrov et al., 2009; Kunkel and Erie, 2015). Finally, a DNA polymerase that

specializes in DNA repair fills in the gap in the newly synthesized strand, inserting the correct base (**F** in Figure 25.5).

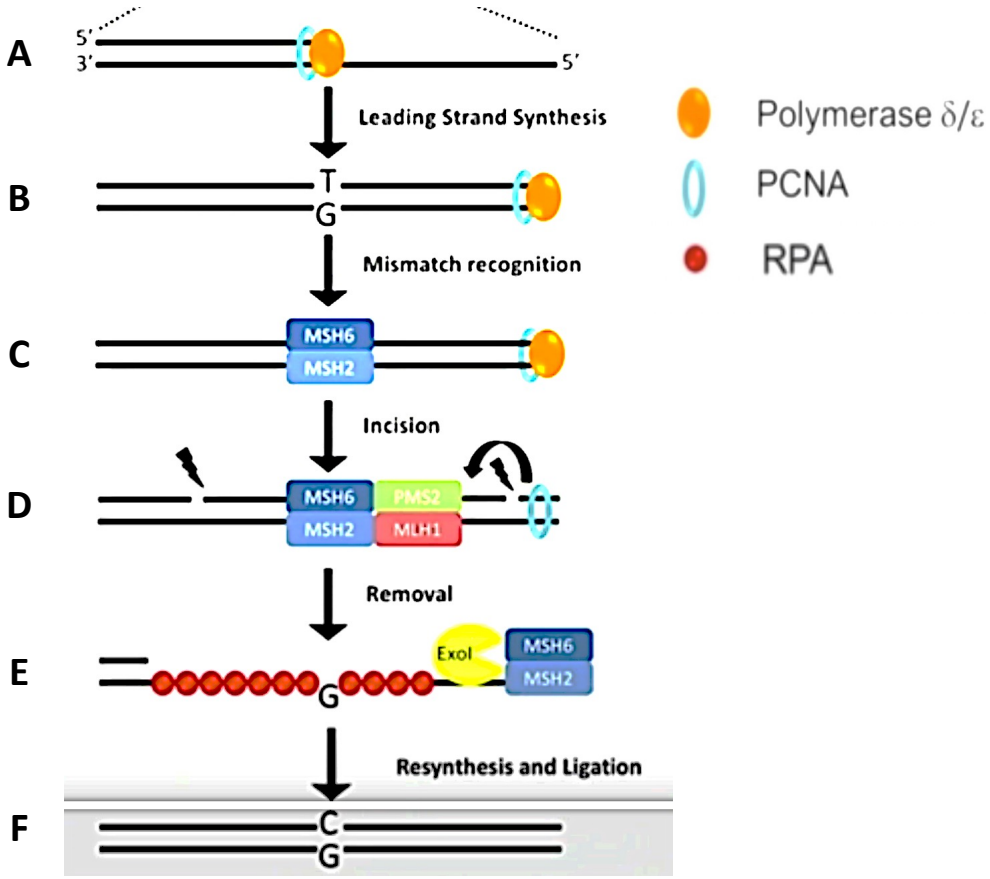

Figure 25.5. Simplified scheme of how MMR was thought to repair single mismatches in DNA (Brandon D'Arcy, adapted and from (Hsieh and Zhang, 2017).)
Starting from the top:
A shows the replicative synthesis of a DNA strand by a DNA polymerase (assisted by donut-shaped PCNA) progressing from left to right.
B shows a G:T mismatch in the DNA.
In **C**, a MSH2:MSH6 (or MSH2:MSH3) dimer recognizes and binds to the mismatched base-pair.
In **D**, a MSH1:PMS2 dimer is recruited and diffuses along the DNA; it induces a break on either side of the newly replicated DNA.
In **E**, an exonuclease (Exo1) has digested away the segment between the breaks, and the DNA single-strand segment left behind becomes stabilized by binding an array of RPA molecules.
In **F**, the repair is completed by a DNA-repair polymerase.

Microsatellite instability indicates defective mismatch repair (MMR).

Microsatellite instability is caused by and is a common feature in mismatch repair deficient cancers, especially cancers of colon, stomach, and ovary. To begin with, however, what is microsatellite DNA? Before answering that, however, I would like to digress briefly by mentioning how the jargon "satellite DNA" arose. Colleagues in Paul Doty's laboratory, when I was there in1960, were banding mammalian DNA by CsCl equilibrium ultracentrifugation when they noticed a bump in the otherwise symmetrical peak, which indicated that a small fraction of the DNA had an unusually low GC/AT ratio. They called it satellite DNA because it showed itself as a small component adjacent to the bulk of the DNA (Figure 25.6). It turned out to be the largest repetitive DNA component in mammalian cells, alphoid DNA, which is associated with the centromeres of all chromosomes. "Satellite DNA" eventually came to mean any set of repeated sequences in the genome. "Microsatellite DNA" came to refer to any relatively short DNA segment consisting of repeats of one or two (or rarely up to six) nucleotides.

A major discovery about microsatellite DNA came in 1993 from researchers in Southern California (Ionov et al., 1993). They discovered that many colon cancer patients had reduced numbers base-pair repeats in the microsatellite DNA in their tumors (Figure 25.7). They thought that the changes in the microsatellite DNA might be the cause of the cancer. Later investigations however revealed that the microsatellite changes were not the cause of the cancers, but rather were caused by a defect in a DNA repair mechanism: DNA mismatch repair, that was in fact a main cause of the cancers (Kunkel and Erie, 2015).

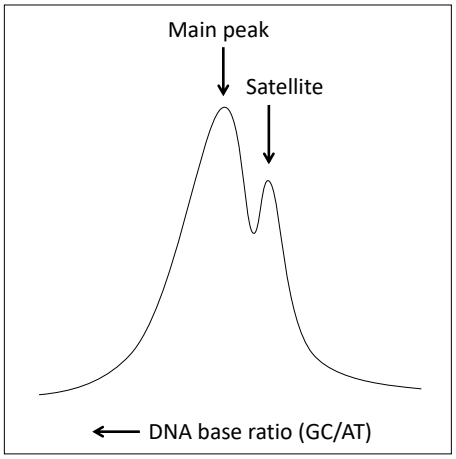

Figure 25.6. Origin of the term "satellite DNA". It was first noted as a small sideband in the DNA of mammalian cells that was banded on the basis GC/AT ratio by ultracentrifugation to equilibrium in a concentrated CsCl gradient. The AT-rich satellite was later found to have a monomer length of a few hundred base-pairs in arrays of up to 100 million bases in the centromeres of chromosomes.

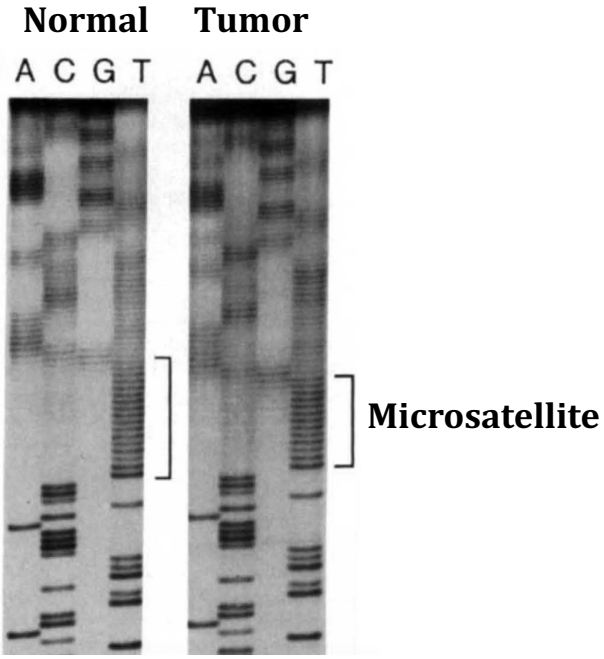

Figure 25.7. Reduced number of A:T base-pair repeats in a microsatellite DNA in the tumors of a patient with colon cancer (Ionov et al., 1993).

How microsatellite instability arises.

The replicative DNA polymerases, in addition to mispairing errors, sometimes produced a different type of error. While copying a string of repeated nucleotides (or nucleotide pairs), the polymerase could slip forward or backward, causing deletion or insertion of one or more nucleotides in the newly replicated strand (Figure 25.8). Sequence repeats of say 6 to 20 nucleotides were found all over the genome. If a sequence repeat was in or near a gene, an insertion or deletion of one or two nucleotides in the repeated sequence was apt to cause a frame-shift mutation – that is when the triplet code that defines the amino acid sequence of the gene's protein product gets to be out of synch so that a subsequent triplet may code for nonsense or STOP (Bhattacharyya et al., 1995; Eshleman and Markowitz, 1996).

The mismatch repair (MMR) system was found to recognize and repair insertions and deletions, thereby preventing those kinds of mutations. People who had frequent changes in the lengths of their sequence repeats – a condition called microsatellite instability – were found to have defects in their mismatch MMR genes. If a MMR defect was in one of their chromosomes, it predisposed them to developing cancer when a MMR mutation occurred in the sister chromosome (Baretti and Le, 2018). As long as the MMR genes in one chromosome were ok, adequate MMR function remained. But if MMR mutations existed in both sister chromosomes, then MMR was defective.

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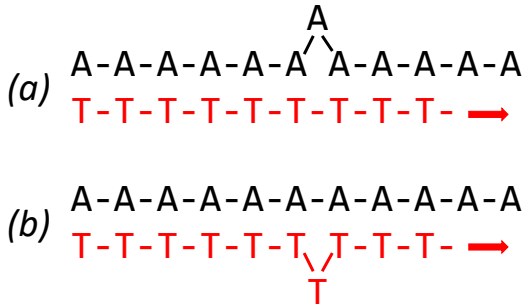

Figure 25.8. Deletion (*a*) or insertion (*b*) of a nucleotide – such as A or T in a string of repeats of the same nucleotide. This happens when the DNA polymerase slips forward or backward as it copies. In this example, the polymerase is copying a string of A's to produce a sting of the complementary nucleotide T (red).

Hereditary non-polyposis colon cancer (HNPCC).

Did colon cancer sometimes run in families? This was clearly the case for a type of cancer where family members developed hundreds of pre-cancerous polyps in the colon. The gene responsible for this type of cancer – *APC*, familial adenopolypsis coli – was identified in 1991. However, in 1993, another type of colon cancer that did not arise in polyps was shown to have a genetic origin. This type of familial disposition for colon cancer (Lynch syndrome) was several times less frequent than the *APC* type and was found to be caused by a defect in DNA mismatch repair (Nicolaides et al., 1994; Papadopoulos et al., 1994; Peltomaki et al., 1993).

Although the most common colon cancer arises in polyps in the descending (left side) colon, HNPCC is quite different. It does not arise in polyps and it occurs in the ascending colon which is on the right side of the body. The cancers arising in that part of the intestine, the HNPCC cancers, were usually caused by a defect in one of the genes that carry out DNA mismatch repair (MMR) – mismatch is when there are base-pairs in DNA that don't have the usual A-T or G-C match. MMR gene defects are often inherited, as in Lynch syndrome, but also can sometimes happen when a DNA polymerase inserts the wrong base or when there is chemical damage to a base. If a mismatch is not repaired, then replication of the mismatch will cause mutation and may eventually lead to cancer (Kunkel and Erie, 2005, 2015). Expression of MMR genes is coupled to DNA replication – the genes are most active during S and G2 phases of the cell cycle, which is when they would be most needed (Kunkel and Erie, 2015).

The MMR gene story had already begun in 1993, when Bert Vogelstein, Richard Kolodner and their colleagues isolated a gene in chromosome 2 that was mutated in patients who

had HNPCC or microsatellite instability. They found that the nucleotide sequence of the gene resembled the sequence of a MMR gene, namely MSH2, of microorganisms. They inferred that the mutation and the microsatellite instability were causally related to the disease (Fishel et al., 1993; Leach et al., 1993).

A defective MMR gene in a single chromosome would not by itself cause trouble, provided that the corresponding gene in the other chromosome was normal. However, the defect in one chromosome made people vulnerable to develop cancer later if DNA damage or a replication error resulted in the MMR defect in both chromosomes. That is why people with Lynch syndrome did not develop cancer until later in life.

The MMR defect in colon cancers of the HNPCC type were most often caused by mutation of MLH1 or MSH2 – which conferred a lifetime risk of colon cancer by as much as 80%. Germline mutations in MSH2 and MLH1 accounted for approximately 60% of HNPCC, although nearly one-third of HNPCC patients had a MMR gene that was silenced epigenetically, for example by DNA methylation of the promoter region of the gene. Non-inherited inactivation of the mismatch-repair gene MLH1 happened in approximately 15% of patients by suppression of the gene by epigenetic methylation of DNA.

Mutations of microsatellite repeat length were extraordinarily common in MMR-deficient cancers. Such cancer cells had thousands of microsatellite mutations, and the presence of this microsatellite instability strongly indicated that the cells were cancerous (Modrich and Lahue, 1996).

Treatment of metastatic colon cancer

Once colon cancer has spread to distant metastases, surgery was no longer an option. Chemotherapy was then able to extend the survival of many of the patients. Particularly effective were 5-fluorouracil combined with oxaliplatin, irinotecan and/or capecitabine. Further progress then used monoclonal antibodies to target epidermal growth factors in patients whose cancers were driven by overexpression of these receptors. The first effective monoclonal antibody was cetuximab (see Chapter 17), and the responses of many of the patients was enhanced by adding irinotecan to the treatment (Figure 25.9.). Cetuximab, however, combined a human antibody chain with a mouse-derived antigen-recognition part. The mouse part sometimes produced toxicity by causing an immune response. That problem was solved by creating a fully humanized monoclonal antibody, panitumumab, which replaced cetuximab (Xie et al., 2020).

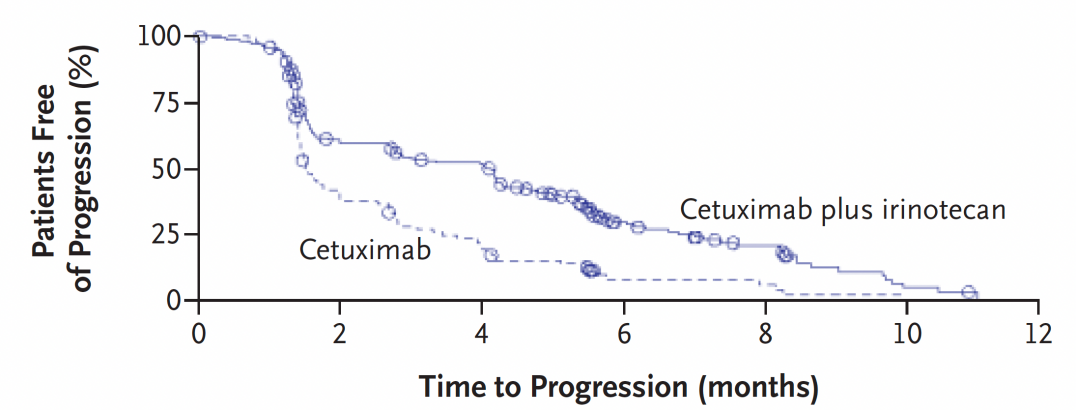

Figure 25.9. A monoclonal antibody, cetuximab, produced responses in about half of colon cancer patients who had previously failed to respond to chemotherapy that included irinotecan, a camptothecin-related drug. Adding irinotecan to cetuximab produced even better responses (Cunningham et al., 2004).

Immunotherapy of mismatch repair-deficient cancers.

Mismatch repair-deficient cancers, such as many cancers of the ascending colon, acquired exceptionally large numbers of mutations due to microsatellite instability that often caused frameshift mutations. These cancers therefore produced many structurally abnormal proteins, which the protein-degrading machinery in the cell would break down into fragments that the cell displayed on the cell surface. Cells of the immune system recognized the abnormal protein fragments and acted to kill the cells that produce them. Mismatch repair-deficient cancer cells were particularly vulnerable to attack by the immune system because of the large number of abnormal protein fragments they displayed.

Cells however have a protective system that limits the immune process so that it does not kill too many normal cells. This is a delicate balance between a cell killing system and a protective system. Immunotherapy was developed to push the balance in favor of killing cancer cells. For that purpose, monoclonal antibodies were developed that blocked the molecules that inhibited the cell killing action of the immune system's killer T-cells.

The first discovered natural inhibitor of the cell-killing action of the immune system's killer T-cells was PD-1, although its action was at first misunderstood. PD-1 was initially isolated as an immunoglobulin-related gene whose production was increased in cells undergoing programmed cell death, which was how it derived its name (Ishida et al., 1992).

Before the action of PD-1 was understood, a monoclonal antibody targeting a related T-cell inhibitor, CTLA-4, was found to produce a few good responses in metastatic melanoma (Phan et al., 2003). Monoclonal antibodies targeting PD-1 were then tested in patients who had several types of metastatic cancer, and there were some good responses (Brahmer et al., 2010; Brahmer et al., 2012).

Since mismatch repair deficiency produced large amounts of abnormal protein fragments that the immune system would recognize, a large group of researchers from several cancer centers conducted a phase-2 study to evaluate the clinical activity of pembrolizumab, a monoclonal antibody targeting PD-1 (Le et al., 2015). The idea was that mismatch repair deficient cancers would potentially engender a strong immune response that would kill the cancer cells, but that PD-1 would block this potentially therapeutic action. PD-1 was known to bind receptor molecules, PD-L1, on the cancer cell surface and thereby to inhibit the immune response. Moreover, the cancer cells produce lots of PD-L1 to evade the immune system. The monoclonal antibody would bind PD-1 so that it could not bind PD-L1. The immune system would then be more free to act against the cancer.

The researchers focused their attention on colon cancer, because cancers of the ascending colon often were notably deficient in mismatch repair. They cited a study in which 1 of 33 colon cancer patients had a good response to the PD-1 monoclonal antibody and asked what was different about that one responding patient. They thought that patient might have been the only one in the group that had a mismatch repair deficient cancer. The 33 patients would have included the most common colon cancers that arise in polyps in the descending colon and rarely have mismatch repair deficiency. That would explain why there was only one responding patient out of 33: the responding patient might have had a mismatch repair deficient cancer in the *ascending* colon.

They therefore investigated whether mismatch repair deficiency would make cancers more responsive to a monoclonal antibody, pembrolizumab, that binds PD-1 on T-cells and blocks its binding to its ligands, PD-L1 or PD-L2, on the cancer cells (Le et al., 2015). The expected response of mismatch repair-deficient colorectal cancers was indeed clearly seen (Figure 25.10). Good responses were also seen in other mismatch repair-deficient cancers.

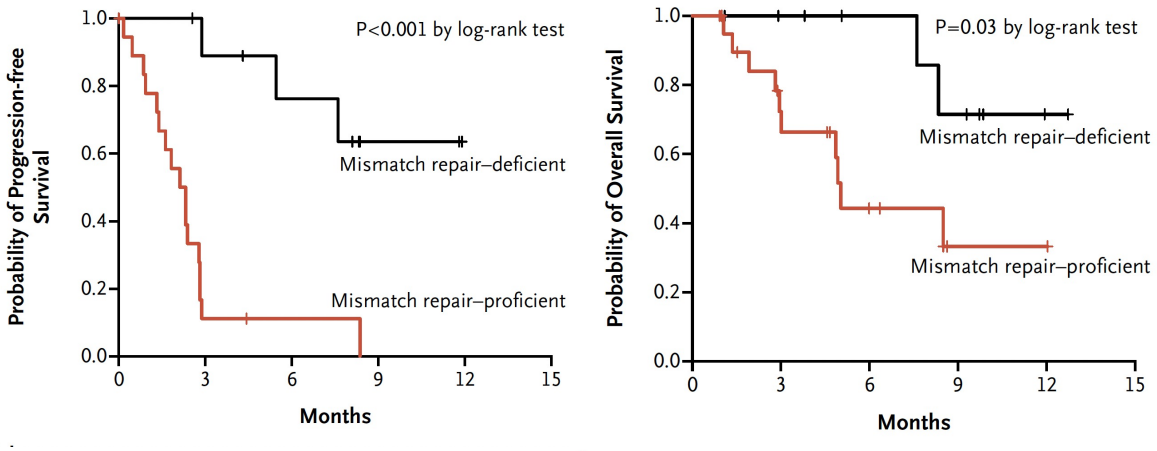

Figure 25.10. Patients with progressive metastatic colorectal cancer were treated with pembrolizumab, a monoclonal antibody that binds PD-1 and prevents its binding to PD-L1 or PD-L2. Deficiency in mismatch repair was associated with much longer progression-free survival (*left*) and better overall survival (*right*) (Le et al., 2015).

In addition to PD-1, another natural inhibitor, CTLA-4, was discovered that T-cells display on their surface to limit their own cell-killing function. CTLA-4 interacts with and inhibits cells of the immune system that activate the T-cell's cell-killing function. To enhance the T-cell's capacity to kill cancer cells, CTLA-4 inhibiting monoclonal antibodies were developed as potential therapeutics in addition to the monoclonal antibodies directed against PD-1 and PD-L1/2.

A next step was to test whether adding a CTLA-4 directed monoclonal antibody, ipilimumab, to a PD-1 directed monoclonal antibody, nivolumab, would enhance the therapeutic effect of the latter against mismatch repair-deficient metastatic colon cancer (Overman et al., 2018; Overman et al., 2017). The combination of these monoclonal antibodies had already been approved for treatment of metastatic melanoma. The results showed that the combination indeed gave better clinical results than nivolumab alone against mismatch repair-deficient metastatic colon cancers (Figure 25.11).

The monoclonal antibodies offered promising new treatments for patients with DNA mismatch repair-deficient cancers. However, the cancers sometimes developed resistance to the treatments, and this problem remained to be solved (Thomas et al., 2020).

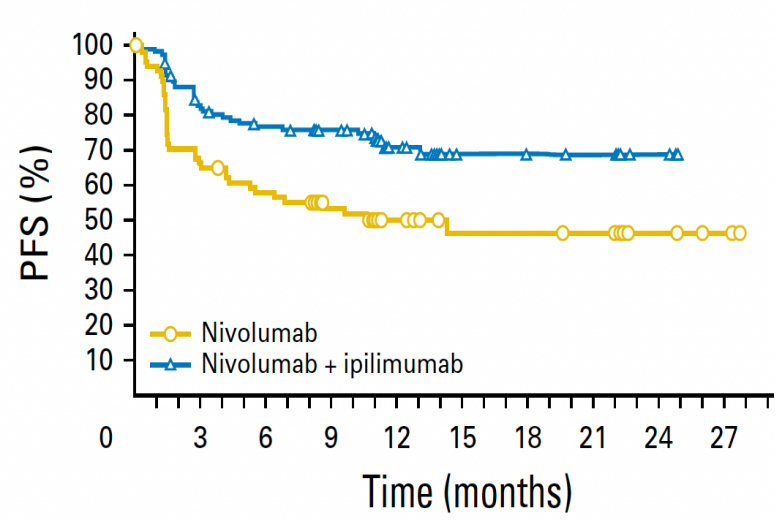

Figure 25.11. Durable responses of metastatic colon cancers to treatment with monoclonal antibodies. The cancers were mismatch repair-deficient and had high microsatellite instability. Adding ipilimumab, a CTLA-4 monoclonal antibody, to nivolumab, a PD-1 monoclonal antibody, improved the progression-free survival (PFS) of the patients (Overman et al., 2018; Overman et al., 2017).

From the European Society for Medical Oncology in Medscape Oncology of a remarkable success in a clinical trial, reported in 2022, of ipimumab plus nivolumab before surgery in patients with DNA-mismatch-repair-deficient colon cancer:

PARIS — "Unprecedented" pathologic responses were seen after a neoadjuvant 4-week course of ipilimumab (Yervoy) plus nivolumab (Opdivo) was given before surgery to patients with DNA mismatch repair deficient (dMMR) colon cancer, say researchers reporting new results from the NICHE-2 trial.

The trial involved 112 patients with dMMR colon cancer who were given one cycle of low-dose ipilimumab and two cycles of nivolumab followed by surgery. The results show that 95% of patients had a major pathologic response (MPR) and 67% had a pathologic complete response (pCR) to immunotherapy. To date, none of these patients have had disease recurrence after a median follow-up of 13.1 months.

Study presenter Myriam Chalabi, MD, an oncologist at the Netherlands Cancer Institute, Amsterdam, described the findings as "unprecedented," especially as many of the patients had stage 3 and high-risk disease, and the expected disease recurrence rate with standard-of-care adjuvant chemotherapy in these patients would usually have been around 15%.

"Importantly, this treatment was very well-tolerated," she added. Chalabi presented the new results here during a presidential session at the European Society for Medical Oncology (ESMO) Annual Meeting 2022, held in Paris, France. Neoadjuvant immunotherapy "has the potential to become standard of care" in these patients, she said, adding that the "future has never been brighter" for dMMR colon cancer.

Around 10%-15% of colon cancers are dMMR, and around 33% of these are associated with Lynch syndrome, she noted. She also urged pharmaceutical companies to seek approval for immunotherapy in this patient population, to warm applause from the audience.

Commenting on the results, Andrés Cervantes, MD, PhD, professor of medicine at the University of Valencia, Spain, said in an ESMO press release that the "innovative" study "questions the need for surgery and postoperative chemotherapy in all patients in whom the primary tumor has disappeared."

He observed that adjuvant chemotherapy has remained standard of care, "despite the fact that chemotherapy is not so active and a complete disappearance of the tumor in the surgical specimen is not observed.

Overall, Cervantes said that dMMR status is a "strong predictor of the positive effect observed with this short-course immunotherapy," adding that "determining dMMR can be easily done by immunohistochemistry in the conventional pathology lab, without the need for complex molecular testing."

The "minimal toxicity" seen in the study "may also facilitate the implementation of this strategy, potentially sparing patients from surgery."

-- Reported by Liam Davenport on September 11, 2022.

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